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EDITORIAL

Surgeon's perspective on short bowel syndrome: Where are we?

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Abstract

Short bowel syndrome (SBS) is due to a massive loss of small bowel: the reduction of gut function is below the minimum necessary to maintain health (in adults) and growth (in children) so intravenous supplementation is required. Parenteral nutrition represents the milestone of treatment and surgical attempts should be limited only when the residual bowel is sufficient to increase absorption, reducing diarrhea and slowing the transit time of nutrients, water and electrolytes. The surgical techniques lengthen the bowel (tapering it) or reverse a segment of it: developed in children, nowadays are popular also among adults. The issue is mainly represented by the residual length of the small bowel where ileum has shown increased adaptive function than jejunum, but colon should be considered because of its importance in the digestive process. These concepts have been translated also in intestinal transplantation, where a colonic graft is nowadays widely used and the terminal ileum is the selected segment for a living-related donation. The whole replacement by a bowel or multivisceral transplant is still affected by poor long term outcome and must be reserved to a select population of SBS patients, affected by intestinal failure associated with irreversible complications of parenteral nutrition.

Key words: Parenteral nutrition; Bowel rehabilitation; Surgical rescue; Intestinal transplantation; Short bowel syndrome

Core tip: Short bowel syndrome represents a surgical dilemma: parenteral nutrition is considered the gold standard of care and any surgical attempt must be limited by the universal principle "first do not harm." The surgical rehabilitation should be pursued when there are enough residual intestines to obtain a better bowel function: lengthening the intestine or reversing a loop of it with different techniques should have the only aim of slowing the transit while increasing the absorptive surface. When intestinal failure is associated to life-threating parenteral nutrition complications, bowel transplantation should be considered as an option.

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INTRODUCTION

Short bowel syndrome (SBS) results from a reduced length of the small intestine. A "normal small bowel length," measured from the duodeno-jejunal flexure to ileocolic valve, is estimated at 250 cm ± 40 cm at birth, and the growth is maximal during the first year of life[1]. In adults, the small bowel length varies from 275 cm to 850 cm, with a mean of 350 cm ± 60 cm, depending on the method used, radiologic, surgical, or per autopsy[2]. The massive loss of small bowel represents the most frequent mechanism of intestinal failure, defined by the European Society for Clinical Nutrition and Metabolism as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth"[3]. Among children "the minimum necessary for the absorption" is a residual small bowel length of more than 25% of the expected for gestational age[3], in adults SBS usually appears when the small bowel length is less than 200 cm (67% of the normal length)[4]. Malabsorption and diarrhea represent the classical symptoms, associated to deficit of growth in the pediatric population. Wilmore *et al*[5] first demonstrated long-term survival with parenteral nutrition (PN) in a child affected by SBS. Nowadays home PN represents the standard of care in patients affected by massive loss of small bowel with excellent long term results[6-12]. PN does not replace physiologically the bowel function because uses the intravenous route to supplement nutrients and it could be affected by several life-threating complications. Under this perspective, a surgical rehabilitation in case of SBS should be represented by: (1) the possibility to slow the transit and obtain an adequate absorptive surface of the remnant intestine through lengthening procedures and (2) whole replacement of the massive intestinal loss with a bowel transplant. It is worthwhile to analyze briefly the main reported studies on the issue in international literature, in order to develop an updated perspective under the surgical point of view.

OVERVIEW OF THE LITERATURE

SBS is mainly, but not only, a matter of length. In children, the massive resection of the small bowel could lead to a "very short bowel syndrome" (≤ 40 cm)[13,14], "ultra-short bowel syndrome" (between < 30 and < 10 cm)[15-17] or "no gut syndrome" (only the duodenum is left)[18-20]. Adults with less than 200 cm but more than 75 cm of small bowel[21] have a potentially functional intestine especially if the colon (and specifically the ileocolic valve) is preserved in continuity. Among SBS patients, the role of the colon in the process of digestion has been demonstrated since the '90s[22-25]. The presence of remaining colon is associated with a lower dependency on PN[26,27] and there is agreement that the remaining small bowel after massive intestinal loss is supported by the colon (if in continuity) for completion of the digestion process. On the other hand, jejunum and ileum have different roles in digestion and ileum has probably a greater adaptive potential than jejunum[28]. A remnant ileum (especially in continuity with the colon) could probably guarantee a faster weaning from PN. Clinical experience shows that patients with a jejuno-colonic anastomosis (SBS type II), even better with a jejuno-ileo-colonic anastomosis (SBS type III), have an improved absorption with time after a period of intestinal rehabilitation, whereas patients with end-terminal jejunostomy without colon (SBS type I) do not show that. When the colon is missing, among adults 115 cm of small bowel with an end enterostomy are considered the limit before SBS.

SURGEON'S PERSPECTIVE

In SBS the remaining small bowel may dilate. This is important for surgeons in order to lengthen the intestine, tapering it. It has been shown that the extent of dilation is associated with the bowel length, and both are related to enteral autonomy[29]. Two surgical procedures are popular in order to lengthen the bowel: Bianchi and Serial Transverse Enteroplasty Procedure (STEP). The Bianchi procedure, summarized by Bianchi in 1997[30], is also known as longitudinal lengthening and tailoring (LILT). The small bowel mesentery is separated as two leaves with a GI anastomosis stapler to create a tunnel, and then the two resulting small bowel segments of smaller diameter are connected with an end-to-end anastomosis in an iso-peristaltic fashion. In the STEP, first described by Kim in 2003[31], the dilated small bowel is narrowed by serial transverse applications of the GI stapler from opposite directions, creating a new lengthened small intestine (zig-zag channel). This procedure does not require an intestinal anastomosis and the mesenteric vascular supply is untouched. Since its first description, STEP has become a widespread procedure, sometimes repeated on the same patient (re-STEP) to obtain a longer intestinal segment. Bianchi and STEP procedures have been performed at first in children and more recently also in adults[32-35]. Most of the studies are on STEP: while enteral autonomy (median time: 21 mo) is eventually possible in some patients[36], improved enteral tolerance can be achieved in a majority[37,38]. STEP can be performed on shorter intestinal segments or intricate segments such as the duodenum, which is technically not feasible for Bianchi procedure, and it seems to have a lower mortality but an overall progression to transplantation[39]. The spiral intestinal lengthening and tailoring procedure is a new

surgical technique based on a spiral shape incision of the dilated intestine (at 45°-60° to its longitudinal axis), and re-tubularization in a longer but narrower fashion. It does not alter the orientation of the muscle fibers like STEP, offering minimal mesenteric handling compared to Bianchi procedure. It has been reported in a 3-year-old girl[40] where, 6 mo after the procedure, PN was weaned off. Another manuscript described the technique in a 10-month-old child[41] showing at 1-year follow-up a growth on the 15-25th centile on 82% oral calories and 18% PN, passing 2-3 daily stools. Three children with "no gut" syndrome and dilated duodenum underwent a novel surgical procedure of "duodenal lengthening" combined with a technical modification of STEP[18]: duodenal tapering was performed with sequential transverse applications of an endoscopic stapler on the anterior and posterior wall of the duodenum, avoiding bilio-pancreatic injury. Two patients weaned PN off at 12 mo post-surgery and the last one's PN caloric requirements decreased by 60%. The surgical rescue of "no gut" syndrome has been reported in adults as well. Bueno *et al*[20] demonstrated the feasibility of lengthening a dilated duodenum in a patient where his mega-duodenal stump was tapered by STEP, restoring his digestive continuity through an end-to-side duodeno-colonic anastomosis. After 24 mo of follow-up, the time on daily PN was shortened from 24 to 9 h and the volume and calorie requirements were reduced by half.

Since lengthening procedures slow the bowel transit time, a "reversed anti-peristaltic segmental bowel loop" has been proposed with the same aim: this procedure can be indicated in patients with an adequate remnant bowel length. Median oral autonomy was described up to 100% ± 38% with a lower amount of parenteral calories, as well as PN dependence[42]. In another report[43] 56% of patients improved their enteral autonomy.

The different graft types used in intestinal transplantation are the isolated small bowel, combined liver-intestine, multivisceral and modified multivisceral ones[44]: liver-containing grafts have shown the longest survivals. Apart from cadaveric donation, living-related intestinal transplantation has been pursued especially in a pediatric setting[45]: terminal ileum represents the used graft, because of technical feasibility and its greater adaptive potential than jejunum[28]. Short term results of intestinal transplantation have recently improved in terms of survival and digestive autonomy, due to advances in surgery and immunosuppression. Immunosuppressive therapy has evolved significantly over the past 20 years: the tacrolimus-based therapy as maintenance, preceded by induction with anti-thymocyte globulin or an interleukin-2 blocker, is the main used protocol worldwide. A "secondary" agent like steroids, azathioprine, mycophenolate mofetil or an mTOR inhibitor is recommended after an episode of rejection. Innovative cross match strategies and optimizing organ allocation could improve the long-term outcome, but the main causes of death and graft loss remain sepsis and rejection. Challenges for long-term results are chronic rejection and immunosuppressant-related complications[46,47]. According to Intestinal Transplant Registry reports[44], 1611 children were transplanted worldwide between 1985 and 2013, with an overall patient survival rate of 51%. In the 2014-2016 Scientific Registry of Transplant Recipients[48], the 6 American centers that in 2016 performed 10 or more intestinal transplants in adults reported a 1-year graft survival from 61% to 83% and a 3-year graft survival from 29% to 73%. In an earlier report from 2008 to 2010, the 1-year graft survival in adults was 71%, illustrating the relatively modest gains achieved[47]. Intestinal transplantation should be suggested to a very select subset of SBS patients with severe and irreversible complications of PN and no hope of intestinal rehabilitation. In conclusion, among SBS patients the surgical rehabilitation (Table 1) of the remnant bowel must be performed to slow the intestinal transit time increasing at the same time the absorptive surface: only in cases of irreversible intestinal failure with PN life-threating complications, intestinal transplantation could represent a therapeutic option even if still encumbered by suboptimal long term results.

Table 1 Surgical rehabilitation of short bowel syndrome

SBS surgical rehabilitation
Lengthening procedures
Bianchi
STEP
SILT
Duodenal lengthening
Reversed anti-peristaltic segmental bowel loop
Intestinal transplantation

SBS: Short bowel syndrome; STEP: Serial transverse enteroplasty procedure; SILT: Spiral intestinal lengthening and tailoring.

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REVIEW

Complement-mediated renal diseases after kidney transplantation - current diagnostic and therapeutic options in *de novo* and recurrent diseases

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Abstract

For decades, kidney diseases related to inappropriate complement activity, such as atypical hemolytic uremic syndrome and C3 glomerulopathy (a subtype of membranoproliferative glomerulonephritis), have mostly been complicated by worsened prognoses and rapid progression to end-stage renal failure. Alternative complement pathway dysregulation, whether congenital or acquired, is well-recognized as the main driver of the disease process in these patients. The list of triggers include: surgery, infection, immunologic factors, pregnancy and medications. The advent of complement activation blockade, however, revolutionized the clinical course and outcome of these diseases, rendering transplantation a viable option for patients who were previously considered as non-transplantable cases.

Several less-costly therapeutic lines and likely better efficacy and safety profiles are currently underway. In view of the challenging nature of diagnosing these diseases and the long-term cost implications, a multidisciplinary approach including the nephrologist, renal pathologist and the genetic laboratory is required to help improve overall care of these patients and draw the optimum therapeutic plan.

Key words: Complement-related diseases; Kidney transplantation; *De novo*; Recurrent diseases

Core tip: The recent progress in our understanding of the pathophysiology of complement-mediated diseases is gaining considerable popularity. Complement dysregulation due to inherited or acquired factors is currently the culprit mechanism. Several constitutional abnormalities usually trigger the process of recurrence, with a subsequent high rate of graft loss. The development of the terminal complement inhibitor "eculizumab" is a breakthrough in controlling abnormal complement activation. While diagnosing complement abnormalities is one challenge, treatment cost with this new agent is another major hurdle in any health care system. New lines of promising therapies are currently in the pipeline.

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INTRODUCTION

The complement components can be seen in biopsies of almost all types of glomerulonephritis, which can be broadly divided into two main groups: (1) "complement over-activation" includes IgA nephropathy (IgAN) and immune complex membranoproliferative glomerulonephritis (MPGN); and (2) "complement dysregulation" that encompasses atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G)[1]. While complement activation is triggered by immune complex formation in the former group, genetic mutations are the driver of complement over-activation in the latter one. This explains why the disease process in the former class is potentially modifiable by immunosuppression in the post-transplantation period, which is not the case in the latter class. Our understanding of the biogenetic causes of C3G and aHUS/thrombotic microangiopathy (TMA) has been expanding. The mechanisms of these diseases not only affect their clinical history, but also affect the recurrence rate[2]. The role of complement in C3G evolution is now well-recognized[3]. Recent progress in understanding the pathophysiology of MPGN led to newer classifications of MPGN into immune complex-mediated and complement-mediated subtypes. The hallmark of complement-mediated MPGN is the deposition of C3 and other complement products in glomerular tissues[4]. This is caused by dysregulation and loss of control of the AP complement pathway[5]. The AP is tightly regulated under physiological conditions. It can be disrupted through either inherited (mutations/polymorphisms) or acquired (autoantibodies) interferences to the regulating components. Histological staining using immunofluorescence (IF) is currently the best determinant technique, and C3G is defined by dominant C3 with dispersed, reduced or absent immunoglobulin (Ig). Based on electron microscopy (EM) examination, C3G subdivides into complement three glomerulonephritis (C3GN) and dense deposit disease (DDD). In C3GN, discrete deposits can be seen in the mesangium and capillary walls (subendothelial and subepithelial regions). On the contrary, DDD deposits are large in size, extremely dense (osmiophilic) and intramembranous, which leads to a characteristic thickening of the glomerular basement membrane (GBM)[5]. The term aHUS is applied to a heterogenous group of diseases (Figure 1) that share TMA manifestations with an associated decline in renal function (classically, no IF staining of C3 or any other complement components). In aHUS, complement abnormalities (either genetic mutations or acquired autoantibodies) are well-recognized mechanisms with a clearly associated complement-mediated TMA[1]. In this article, we will discuss various types of complement-mediated renal diseases after kidney transplantation and their current therapeutic options.

Methodology

In view of the lack of prospective controlled trials concerned with complement-mediated diseases post-kidney transplant, we tried to shed the light in this review on the most recent expert opinions, with regard to the best tools of management for these devastating diseases.

CLINICAL PRESENTATION

Salient features of C3G

DDD and C3GN share some salient features that include proteinuria, hematuria and increased serum creatinine concentration[6,7]. Recurrence of C3G is typically encountered one to two years after transplant[7]. C3G comprises a spectrum of diseases that result from aberrant control of complement activation, deposition and dysregulation, leading to C3 glomerular deposition with characteristic electron-dense deposits (EDD) in EM (Table 1).

Table 1 Morphological features of C3 glomerulopathy

	Morphological features of C3G
Light microscopy	Active lesions
	Mesangial expansion with or without hypercellularity
	Endocapillary hypercellularity including monocytes and/or neutrophils
	Capillary wall thickening with double contours (combination of capillary wall thickening + mesangial increase is referred to as a membranoproliferative pattern)
	Fibrinoid necrosis
	Cellular/fibrocellular crescents
	Chronic lesions
	Segmental or global glomerulosclerosis
	Fibrous crescents
IF microscopy	Typically dominant C3 staining
Electron microscopy	DDD: Dense osmiophilic mesangial and intramembranous electron dense deposits.
	C3GN: Amorphous mesangial with or without capillary wall deposits including subendothelial, intramembranous and subepithelial EDD
	Subepithelial "humps" may be seen in both DDD and C3GN

Adapted from Goodship *et al*[12]. C3G: C3 glomerulopathy; DDD: Dense deposit disease; C3GN: C3 glomerulonephritis; EDD: Electron dense deposits, fibrinoid necrosis.

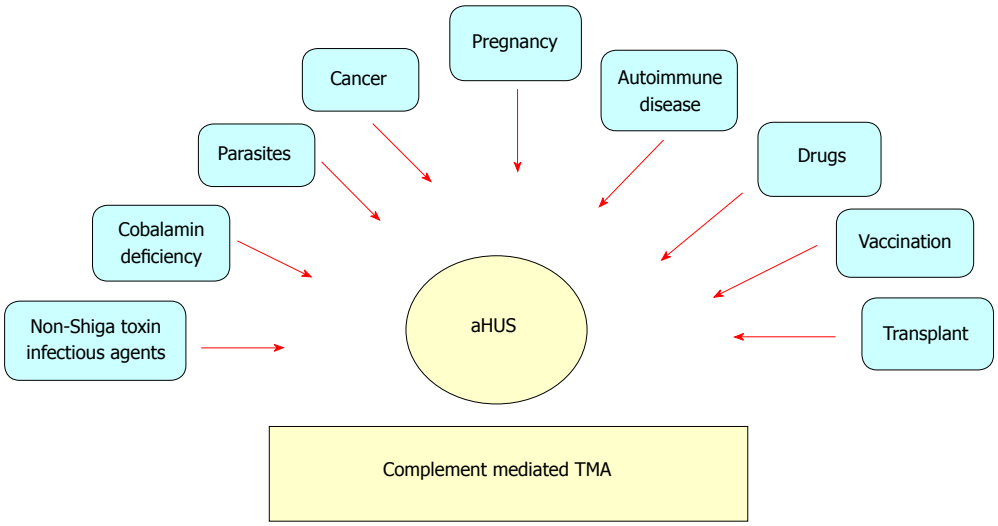

Figure 1 Heterogeneity of atypical hemolytic uremic syndrome. Adapted from Salvadori *et al*[1]. TMA: Thrombotic microangiopathy; aHUS: Atypical hemolytic uremic syndrome.

Pathology

Renal biopsy is crucial for C3G diagnosis. LM is not helpful, due to its extremely diverse appearance. IF is the mainstay for diagnosis. A unique criterion in IF studies is the presence of dominant C3 staining, which is twice as intense as any other immunoreactant (IgG, IgM, IgA, and C1q)[8]. Ninety percent of DDD patients, but fewer C3GN patients, can be diagnosed through applying this criterion[8]. Repeated biopsy may be required to confirm the diagnosis. As C3G may present in acute infection, C3 can be observed with post-infectious GN. Humps are no longer pathognomonic criteria of post-infectious GN, however they can also be encountered in C3G. However, the presence of double contours in the GBM raises the possibility of C3G diagnosis. To differentiate DDD from C3GN, EM studies should be accomplished, as it has pivotal clinical implications. Moreover, staining for IgG as well as light chains on pronase-digested paraffin should be applied for all cases of C3GN on standard IF, particularly in adults (Figure 2 and Table 1)[9,10].

Salient features of TMA

TMA is mostly presented 3-6 mo post-transplant, but it can occur at any time after renal transplantation[13]. Presentation of TMA is not universal, ranging from the renal-limited form up to a complete systemic picture with its classic triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and decline in renal function[14]. MAHA is defined as increased LDH, decline in HB and haptoglobin, and appearance of schistocytes in peripheral blood smears. On the other hand, localized (renal-limited) TMA usually presents later in the post-transplant course. In the acute stage, evidence of endothelial injury with platelet aggregation (thrombosis), fibrinoid necrosis, as well as

Table 2 Morphological features in microangiopathy

Active lesions	Chronic lesions
Glomeruli: Thrombi - Endothelial swelling or denudation - Fragmented RBCs - Subendothelial flocculent material. EM: Mesangiolysis - Microaneurysms	Glomeruli: LM: Double contours of peripheral capillary walls, with variable mesangial interposition - EM: New subendothelial basement membrane - Widening of the subendothelial zone
Arterioles: Thrombi - Endothelial swelling or denudation - Intramural fibrin - Fragmented red blood cells - Intimal swelling - Myocyte necrosis	Arterioles: Hyaline deposits
Arteries: Thrombi - Myxoid intimal swelling - Intramural fibrin - Fragmented red blood cells	Arteries: Fibrous intimal thickening with concentric lamination (onion skin)

Adapted from Goodship *et al*[12]. EM: Electron microscopy; LM: Light microscopy.

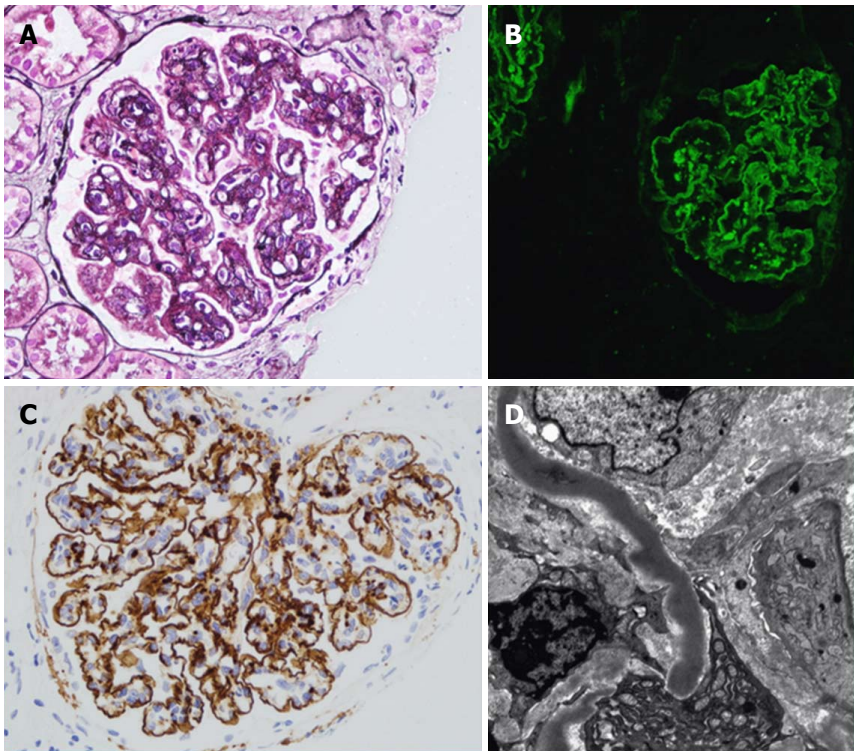

Figure 2 Renal histology in individuals with dense deposit disease. A: Light microscopy with silver stain showing a membranoproliferative glomerulonephritis pattern with double contours of the glomerular basement membrane; B: Immunofluorescence; C: Immunohistochemistry with immunoperoxidase showing strong capillary wall staining of C3 and some granular mesangial C3; D: Characteristic sausage-like, intramembranous, osmiophilic deposits on electron microscopy. Adapted from Barbour *et al*[11].

glomerular ischemia can be seen. On the other hand, chronic lesions show duplication and multilayering of the GBM, with clustering of the matrix layers and vessel wall cells leading to the characteristic onion skin shape appearance (Table 2)[15]. As TMA is not always present with full-blown systemic pictures, genetic studies to unmask the underlying complement defect are ultimately mandated, particularly if no other clear cause has been associated (*e.g.*, AMR-associated TMA). AMR can give a TMA-like picture, as it is an antibody interaction with the endothelium. This is also a fundamental maneuver to differentiate *de novo* from recurrent disease (positive genetic testing), with consequent clinical therapeutic implications[16].

Extrarenal manifestations of aHUS and C3G

Twenty percent of aHUS patients express extrarenal manifestations. Their relation to complement activation and TMA evolution is unclear. Drusen is rarely seen in TMA[17]. Drusen formation, which represents an accumulation of lipids and complement-rich proteins between Bruch's membrane and the retinal pigmentary epithelium, is commonly reported in age-related macular degeneration but present at a much earlier age with C3G[18]. In C3G, retinal drusen and acquired partial lipodystrophy have been commonly reported. The latter is most commonly encountered with C3 nephritic factors. Factor D, an essential agent for C3 convertase formation, is highly concentrated in adipocytes that undergo C3 nephritic factor-induced complement-dependent lysis[19] (Table 3).

Pathogenesis and classification of C3G

The new classification of MPGN encompasses two

Table 3 Extrarenal manifestations reported in atypical hemolytic uremic syndrome, dense deposit disease, and C3 glomerulonephritis

aHUS	DDD/C3GN
Digital gangrene, skin	Retinal drusen
Cerebral artery thrombosis/stenosis	Acquired partial lipodystrophy
Extracerebral artery stenosis	
Cardiac involvement/myocardial infarction	
Ocular involvement	
Neurologic involvement	
Pancreatic, gastrointestinal involvement	
Pulmonary involvement	
Intestinal involvement	

Adapted from Goodship *et al*[12]. aHUS: Atypical hemolytic uremic syndrome; C3GN: C3 glomerulonephritis; DDD: Dense deposit disease.

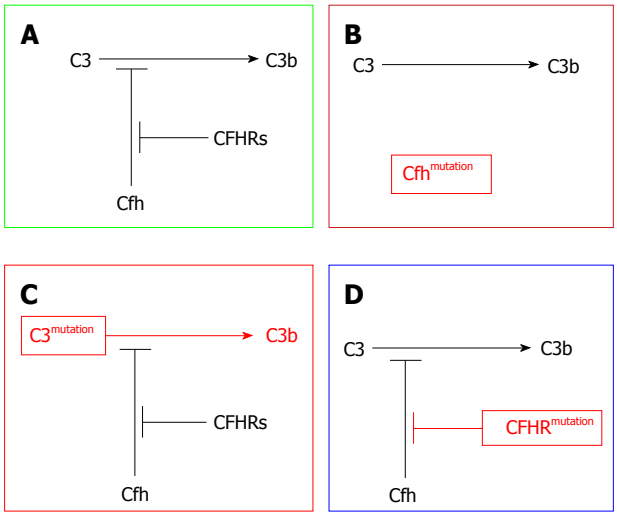

Figure 3 Disease mechanisms in C3 glomerulopathy, based on genetic defects identified in family studies. A: Physiological regulation of C3 activation to C3b *via* the alternative pathway is mediated by complement factor H (CFH) (Cfh). Competitive inhibition of CFH by CFHR proteins is termed CFH deregulation; B: Homozygous deficiency or dysfunction of CFH results in excessive C3 activation; C: Hyper-functional C3 produces excessive C3 activation despite normal CFH activity; D: Abnormal CFHR proteins enhance CFH deregulation, leading to excessive C3 activation. Adapted from Barbour *et al*[11].

subtypes: the immune complex-mediated GN (ICGN) and complement-mediated GN (CGN), recently named (C3G). The former is characterized by both Ig as well as complement component deposition in kidney tissues as recognized by IF studies. The latter is characterized by dominant complement deposition with smaller amounts of Ig deposition. Further subdivision of C3G into C3GN and DDD can be attained through EM studies[20]. Both subtypes are triggered through dysregulation of any part of the AP. For example, patients may develop the C3 convertase-stabilizing factor called C3NeF, which leads to uncontrolled complement activation. Loss-of-function mutations in complement regulatory proteins (CFH or CFI)[20-23] or gain-of-function mutations in C3 leads to CFH resistance, which has been postulated as an underlying mechanism (Figure 3).

Pathophysiology and recurrence of C3G

Pathophysiology of AP activation in DDD and C3GN is nearly the same. In both disorders, disturbance of the fluid phase is triggered as a result of aberrant gene mutations or the presence of autoantibodies. However, the presence of C3 nephritic factor (C3NeF) is by far the most commonly acquired complement defect. C3NeF has the ability to block CFH-mediated decay by stabilizing C3 convertase[5,24]. By binding to C3 convertase, C3NeF has the ability to trigger it approximately ten times[25,26]. C3 convertase can also block the action of CFH, CR1, as well as decay-accelerating factor (DAF).

C3NeF is prevalent in 50%-80% C3G patients[27]. Other autoantibodies have also been found (*e.g.*, autoantibodies against factor B[28], CFH[29,30] and C3 convertase)[28]. In C3G, CFH mutations have been frequently reported. Different forms of mutations can be presented as defective or completely absent protein H. These mutations can be seen in homozygous or heterozygous forms[31,32]. C3NeF can also be encountered, which denotes the clustering of different risk factor varieties. More recently, genetic mutations involving the CFHR gene have been reported in the C3G cohort of patients[33]. CFHR group genetic mutations[34], deletions[35], duplications[36], as well as hybrid genes[37] have also been observed in C3G patients, either in an isolated manner or in a familial cohort. Malik and his associates[38] reported that members of one family can develop C3G as an result of aberrant copies of CFHR3 and CFHR1 loci. The presence of familial C3G underscores the genetic basis of several C3G varieties and their relation to AP dysregulation.

To summarize, complement dysregulation is the specific etiology of C3G, which could be genetic or acquired. While genetic causes encompasse complement gene mutations, acquired causes include the C3NeFs, which have the ability to impede normal complement regulation[1]. Moreover, genetic varieties constitute the pathophysiologic basis of C3G and aHUS evolution (Table 4). Recently, a robust correlation between CFH-related proteins and a variety of complement-mediated diseases have been documented. Functional parameters (*e.g.*, complement regulators and CFH competitors) have recently attained significant popularity[39].

TMA or C3G?

Both TMA and C3G have a common underlying

Table 4 Overview of mutations in complement factor H-related protein genes

Genetic defect	Phenotypical expression
Duplication in *CFHR5* gene	C3 glomerulopathy (CFHR5 nephropathy)
Duplication in *CFHR1* gene	C3 glomerulopathy
Hybrid *CFHR3/CFHR1*	C3 glomerulopathy
Hybrid *CFHR2/CFHR5*	C3 glomerulopathy
Hybrid *CFH/CFHR1*	aHUS
Hybrid *CFH/CFHR3*	aHUS

Adapted from Salvadori *et al*[1]. aHUS: Atypical hemolytic uremic syndrome; CFH: Complement factor H.

causation: AP dysregulation. However, the question that arises is "which factors influence the evolution of one disease rather than the other?"[40]. The prevalence of the fluid phase complement activation dysregulation in animal models suggests that C3G is the responsible factor. On the other hand, complement activation involving capillary walls can result in TMA evolution[41]. Furthermore, absolute CFH deficiency is in favor of an activation of the fluid phase complement with subsequent C3G evolution, while the lack of an aberrant CFH binding region is in favor of TMA evolution[41]. It has also been postulated that CFH and CFH/CFHR mutations induce aHUS to inhibit CFH-binding to many cell surfaces, while C3G-associated mutations in CFHRs cannot inhibit CFH binding to endothelial cell surfaces[42]. The prevalence of familial C3G mutations serves as a robust indicator of the genetic base of C3G recurrence[1].

Risk of DDD recurrence

Despite the well-known DDD variants of C3, its pathogenesis has only recently been recognized. The five-year graft survival rate was only 50% in one retrospective study of 75 children[6]. In adults, a majority of the recipients developed recurrence in post-transplant periods, with 25% of them losing their allografts[43]. In another broader cohort that included eighty adults and children with C3G, Medjeral-Thomas *et al*[44], reported histological recurrence in all six DDD recipients. Graft loss had resulted in 50% of his cases. For recipients who developed DDD recurrence, the ten-year graft survival rate has been reported to be up to 57.5% in an UNOS review[45]. Risk factors for DDD recurrent disease and graft loss are not well-recognized. However, the histological recurrence rate was reported to be more than 70%[46,47]. Recurrence may present spontaneously in post-transplant periods, though it may take several years to manifest[47]. This discrepancy raises some questions, such as the impact of the longevity of follow-ups, the need for tissue diagnosis, and the real rate of DDD recurrence.

Risk of C3GN recurrence

There is no documented relation between mode of presentation, C3 serum levels, or C3NeF levels and C3GN recurrence[48]. The only trustworthy risk factor correlated with C3 recurrence is the presence of heavy proteinuria, with two thirds of C3 patients showing vulnerability to recurrence and a high incidence of graft loss[5,7,27]. All the available data about recurrence are based on case series, with the largest by Zand *et al*[7] that failed to reveal robust evidence of recurrence risk. This observation is partially explained by the heterogeneity of complement defects implicated in C3GN evolution. Early reports postulated HLA-B8 DR3 and living related donation as possible risk factors for recurrence[49]. However, the more recent reports suggested the following: (1) history of graft loss owing to recurrence[50]; (2) aggressive histopathological alterations in native kidney biopsy; and (3) hybrid CFHR3 1 gene-related C3GN. Wong *et al*[51] have recently reported a high rate of C3G recurrence (five patients received a total of eight kidney transplants). Four (50%) renal allografts had disease recurrence, of which three had biopsy-proven recurrence, with time to recurrence ranging from as early as 2 wk following living-related donor transplantation, to 93 and 101 mo for the two remaining allografts, respectively[51].

Diagnosis of C3G recurrence

The declining appearance of proteinuria, hematuria or eGFR is a strong indicator of C3G recurrence. Final diagnosis is usually made through LM, IF, and EM studies of kidney biopsy. After histopathological examination, a thorough evaluation of any genetic mutation in the AP should be accomplished, especially if these studies were not previously fulfilled with the native kidney disease.

Diagnosis of C3G/TMA recurrence

A robust work-up of analytic studies including genetic, biochemical and pathological evaluation should be instituted, including the following: (1) complement components and complement regulatory protein levels; (2) peripheral WBC MCP levels; (3) screening for antibodies to CFH and C3NeFs; and (4) mutation screening of CFH, CFI, CFB, C3, and MCP. Furthermore, recombination in the CFHR region should be tested[52].

Prognosis of DDD/C3GN

In both DDD and C3GN, recurrent disease is usually associated with allograft loss[6,44,53]. The one-year allograft survival was reported to be 94%, with 69% at five years, and 28% at ten years. Three predictive criteria for progression to ESRD were recognized: (1) crescentic GN; (2) severe arteriolar sclerosis by LM; and (3) decline of renal function at the time of first biopsy[44].

Prognosis of TMA

Compared to recurrent TMA, the prognosis of *de novo* TMA is quite poor. Fifty percent of patients may lose their graft within a couple of years after diagnosis[54,55]. Many reports were in favor of this attitude[54-56]. Before

Table 5 Recommended therapy approach for C3 glomerulopathy based on small prospective trial, case reports, and expert opinion

All patients	Moderate disease	Severe disease
Lipid control	Urine protein > 500 mg/24 h despite supportive therapy, or	Urine protein > 2000 mg/24 h despite immunosuppression and supportive therapy or
Optimal BP control (< 90% in children and ≤ 120/80 mm Hg in adults)	Moderate inflammation on renal biopsy or	Severe inflammation represented by marked endo- or extracapillary proliferation with/without crescent formation despite immunosuppression and supportive therapy or
Optimal nutrition for both normal growth in children and healthy weight in adults	Recent increase in serum creatinine suggesting risk for progressive disease	Increased S. Cr suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy
	Recommendation	Recommendations
	Prednisone	Methylprednisolone pulse-dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease
	Mycophenolate mofetil	Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease

Adapted from Goodship *et al*[12].

the era of eculizumab (EZ), Schwimmer *et al*[54] reported that 54% of systemic TMA can develop dialysis requiring AKI, and about 38% lost their allograft. However, no one patient with localized TMA has complicated with TMA-related allograft loss or a need for dialysis. Nevertheless, both systemic and localized forms may experience unfavorable long-term graft survival[54,57].

THERAPY OF COMPLEMENT DYSREGULATION-RELATED DISEASES

Treatment of de novo C3G

The therapeutic approach for *de novo* C3G therapy is similar to that of recurrent disease. Very minimal information is available regarding *de novo* C3G[58].

Treatment of recurrent C3G

In light of the paucity of data from controlled studies, some experts have suggested an approach that depends on disease severity (*i.e.,* mild, moderate and severe) based on the degree of proteinuria and the magnitude of allograft dysfunction (Table 5): (1) conservative measures, as with other glomerulotides, including RAS blockade and lipid-lowering agents; (2) glucocorticoids, MMF, rituximab and PE have been used with variable success[59,60]. In selected patients, MMF has been reported to be effective in C3GN controls in a retrospective study[12,61]; and (3) EZ was firstly reported by Bomback *et al*[62], in treating six patients with C3G (three with DDD and three with C3GN) in an open-labelled trial. EZ dose is guided by previous experience in aHUS and used for one year. Improved kidney function was observed in two patients; one patient showed partially improved proteinuria, while another patient showed better histological and laboratory findings[62]. Notably, elevated serum membrane attack complex (MAC) levels were associated with clinical improvement[63]. Duration of therapy is not yet defined. The beneficial effects of EZ in DDD recurrence[46] and C3GN recurrence[64] have been shown in case reports[65]. However, histopathological evidence of disease progression has been observed in subsequent biopsies. This highlights the fact that there is no standard accepted biomarker for disease monitoring, which can be used to assess the patient's response to treatment and predict better renal function.

In 2018, Garg *et al*[66] described the spectrum of C3 pathophysiology and its clinical implications. The observed variability of the degrees of upstream (site of C3 convertase) and downstream (site of C5 convertase) complement dysregulation may result in variable phenotypic differences[67,68]. Consequently, the nature of this spectrum will be reflected clinically on disease progress in two ways: firstly, the variability in response to EZ therapy (Figure 4)[66]. In C3G, if the dominant process focused on activation of C5 convertase (resulting in increased soluble C5b-9 levels), EZ will be of therapeutic benefit. On the other hand, patients with the dominant process focused on dysregulation at the level of C3 convertase (increased C3 split product levels), the impact of EZ therapy will be less impressive, and the process of uncontrolled complement dysregulation will persist with consequent ongoing renal injury. Secondly, future application of "soluble C5b-9" as well as "C3 degradation product" measurements will be feasible in monitoring EZ therapy (and other newly introduced C3 convertase inhibitors agents) and, thereby, will help in predicting its response[66]: (1) compstatin is a C3 inhibitory peptide that can block C3 and its convertase interaction, so that all of the three complement pathways are activated; (2) CP40 is a compstatin analog with a selective C3 inhibitor property. CP40 can prevent *in vitro* complement-mediated hemolysis induced by C3GN patient sera. Moreover, it can abort dysregulated AP activation induced by autoantibodies and genetic

A

Underlying defect	Lab response		Tissue response (histopathology)	Reference
	SCr	PCR		
None	○	●	●	Bomback *et al*, 2012[62]
C3Nef	●	●	Not performed	McCaughan *et al*, 2012[46]
C3Nef	●	●	●	Sa'nchez-Moreno *et al*, 2014[85]
None	●	●	●	Le Quintrec *et al*, 2015[80]

B

Underlying defect	Lab response		Tissue response (histopathology)	Reference
	SCr	PCR		
C3Nef	○	○	●	Bomback *et al*, 2012[62]
C3Nef, CD46 mutation	●	Non-proteinuric throughout	○	Bomback *et al*, 2012[62]
C3Nef, CFH mutations	○	● > ●	● (Increased fibrosis and continuously active C3GN)	Gurkan *et al*, 2013[64]
CFH and CFI mutations	●	●	● Improved tubulointerstitial injury, recovered ischemic injury; presistent 2-3 C3 deposition	Garg N *et al*, 2018[66]

● = Improved ○ = No change ● = Worsened ● > ● = Improved, then worsened

Figure 4 Response of complement 3 glomerulopathy subtypes to eculizumab therapy based on laboratory parameters and tissue (histopathological) response. A: Dense deposit disease response to eculizumab therapy[66]; B: Complement 3 glomerulonephritis response to eculizumab therapy[66]. CFH: Complement factor H; CFI: Complement factor I; C3Nef: C3 nephritic factor.

mutations[63]. Since C3d is the major complement fragment deposited in C3GN and DDD, CP40 represents a promising therapeutic agent. CP40 has been evaluated in paroxysmal nocturnal hemoglobinuria and hemodialysis-induced inflammation[69,70]. If CP40 is able to offer a disease-specific targeted therapy, this agent may represent a breakthrough in C3G control; (3) other novel therapeutics: antibody-based agents targeting complement function by blocking particular components of C3 convertase to hamper its formation and/or function (*e.g.*, anti-C3b monoclonal antibodies reported by Paixao-Cavalcante *et al*[71], anti-FB antibodies as described by Subias[72], and anti-properdin antibodies as professed by Pauly *et al*[73] targeting complement blockade are all under thorough evaluation[74]). Soluble complement receptor1 (CR1): a robust regulator of complement activity *in vitro,* soluble CR1 can prevent dysregulation of the AP C3 convertase. The safety and efficacy of the soluble CR1 in normalizing complement activity in pediatric patients with ESRD have been reported. With its ability to breakdown active C3b, soluble CR1 infusion can induce clinical improvement in C3GN as well as in the serum levels of MAC in patients with DDD recurrence[37].

Methods of achieving C3GN control are summarized in Table 5[34,75-86]. Until enough data from randomized control trials become available, the guidelines related to complement blockade therapy of C3GN should be based on those applied in aHUS (Table 6)[12].

Renal transplantation for C3G

Minimal data is available concerning renal transplantation for C3G. The available recommendations (Table 7) are currently based on expert opinion. Recurrence post-transplant is common, with about half of the patients with C3G at risk of losing their grafts[12].

TREATMENT OF POST-TRANSPLANT TMA

For cases of TMA secondary to medication, switching of the culprit drug to another agent (mTOR or CNI) is associated with a better response[88-90]. The first line of therapy of *de novo* TMA should encompass withdrawal of the offending drug, an essential step that is usually associated with correction of the hematological profile[57].

Plasmapheresis (PE) and intravenous immunoglobulins (IVIG) (particularly with AMR-associated TMA):

Table 6 Monitoring eculizumab therapy

CH50 (total complement activity)	AH50 (alternative pathway hemolytic activity)	Eculizumab trough	Alternative assays
Measures the combined activity of all of the complement pathways	Measures combined activity of alternative and terminal complement pathways	May be a free or bound level	The following assays are under investigation
Tests the functional capability of serum complement components to lyse 50 % of sheep erythrocytes in a reaction mixture	Tests functional capability of alternate or terminal pathway complement components to lyse 50% of rabbit erythrocytes in a Mg^{2+}-EGTA buffer	ELISA: using C5-coated plates, patient sera, and an anti-human IgG detection system	Free C5
Low in congenital complement deficiency (C1-8) or during complement blockade	Will be low in congenital C3, FI, FB, properdin, FH, and FD deficiencies or during terminal complement blockade	Not affected by complement deficiencies	*In vitro* human microvascular endothelial cell test
Normal range: Assay dependent	Normal range is assay-dependent.	Recommended trough level during complement blockade: 50-100 μg/mL	SC5b-9 (also referred to as sMAC and TCC) remain detectable in aHUS remission, so not recommended as a monitoring tool
Recommended goal during therapeutic complement blockade: < 10% of normal	Recommended goal during complement blockade: < 10% of normal		

Adapted from Goodship *et al*[12]. aHUS: Atypical hemolytic uremic syndrome; C3: Complement component 3; C5: Complement component 5; EGTA: Ethyleneglycol tetraacetic acid; ELISA: Enzyme-linked immunosorbent assay; FB: Complement factor B; FD: Complement factor D; FH: Complement factor H; FI: Complement factor I; sC5b-9: Soluble C5b-9; sMAC: Soluble membrane attack complex; TCC: Terminal complement complex.

Table 7 Transplant considerations in C3 glomerulopathy[1]

Timing	Donor selection	Risk reduction
Avoid transplantation during acute period of renal loss	No specific recommendation can be made on donor choice. When considering living donors, high risk of recurrence should be weighed against presumed risk of waiting on cadaveric donor list	C3G histological recurrence is as high as 90%[7,87]
Avoid transplantation during acute inflammation		Limited data suggest: rapid progression to ESRD in native kidneys increases recurrence risk[87]
No data supporting whether specific complement abnormalities (*e.g.*, high titer C3Nef, low C3 or high soluble C5b-9) predict increased risk for relapse		There are no known strategies to reduce recurrence risk of C3G
		Clinical recurrence should drive decision to treat[7]
		In absence of clinical trials, use of anti-complement therapy is based solely on a small open-label trial and positive case reports[62] (the impact of publication bias is unknown)
		C3G associated with monoclonal gammopathy has a high rate of recurrence[7]

[1]Based on limited retrospective cohort data. Adapted from Goodship *et al*[12]. C3: Complement component 3; C3G: C3 glomerulopathy; C3Nef: C3 nephritic factor; ESRD: End-stage renal disease.

fresh-frozen plasma (FFP) is advised as a reposition fluid, which must be type-specific, ordered in advance and thawed before use, despite the high risk of reactions; however, it replaces all plasma constituents and is appropriate for patients with TMA[91]. Before the era of EZ, the following supportive explanations have been provided: (1) proven efficacy in TTP[92]; (2) a graft salvage rate of more than 80%, as reported by Karthikeyan *et al*[13]. He addressed two possible benefits for this type of therapy: clearance of the platelet aggregation factors (*e.g.*, thromboxane A2) and replenishment of the deficient agents (*e.g.*, PGI2-stimulating factor)[13]; (3) with frequent possibility of the presence of underlying complement dysregulation, commencing PE therapy will also be beneficial in two ways: clearance of the aberrant complement components, and replacement with normally functioning complement proteins[93]; (4) clearance of the anti-HLA antibodies in AMR-associated aHUS improved patient outcome[55,94]; (5) PE/IVIG therapy was successfully associated with a 100% response rate in five solid organ transplants complicated by a systemic form of TMA. There was no evidence of relapse after cessation of the culprit drug (*e.g.*, tacrolimus) in a recent report[57].

Belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), selectively inhibits T cell activation through a co-stimulatory blockade[95].

EZ, an anti-C5 agent that blocks lytic C5b-9 MAC generation, not only revolutionized aHUS therapy but was also effective in preventing its recurrence[96]. The role of complement activation in TMA evolution has been recognized in a majority of *de novo* TMA patients. Chua *et al*[97], for example, reported deposition of C4d in all biopsies of post-transplant TMA. Efficacy of this

Table 8 Eculizumab dosing in atypical hemolytic uremic syndrome based on dosing goal

Minimal dose	Discontinuation
Desire to continue dosing with the minimal dose required to achieve a pre-identified level of complement blockade[1]	Desire to discontinue complement blockade
Dose reduction or interval extension Goal CH50 < 10% (recommended) Goal AH50 < 10% (recommended) Goal eculizumab trough >100 μg/mL	No consensus exists regarding tapering of dose

[1]Additional monitoring may be required during intercurrent events (*e.g.*, infection, surgery, vaccination) to detect unblocked complement activity. Adapted from Goodship *et al*[12]. AH50: Alternative pathway hemolytic activity; CH50: Total complement activity.

agent has also been documented in the management of resistant cases of medication-associated *de novo* TMA, including those with unidentified genetic mutations[98-103]. Moreover, efficacy of EZ has been also shown in some cases of resistant AMR-associated TMA[103-111]. However, Loupy *et al*[112] reported a similar graft survival (95.8% *vs* 89.7% at two years post-transplant, respectively) and estimated GFR (52.6 mL/min *vs* 46.7 mL/min) in comparing PE-treated recipients with the EZ-treated group. Considering the high cost of this drug, utilization of this agent is better confined to PE-dependent patients, AMR-associated TMA and to cases with refractory hemolysis.

Treatment of recurrent TMA

Minimal work-up of genetic studies should include: CFH, CFI, CFHR, CFB, MCP and C3[113]. All cases with suspected TMA should be screened for all complement components and its related proteins. Cases with isolated membrane cofactor protein (MCP) mutations (not combined with other gene defects) may be safe for kidney donation. Cases with documented TMA and with a lack of definitive genetic defects may proceed with kidney transplantation under the umbrella of intensive PE therapy[114]. Polygenic patterns of TMA should be dealt with cautiously in case of living donation[115].

Prevention of aHUS

Avoid trigger factors that stimulate complement activity (*e.g.*, ischemia-reperfusion injury, viral infection and culprit medications)[52]. Immunosuppressive regimens devoid of medications related to TMA evolution[116] are advised. PE therapy alone is not sufficient for TMA cure and prevention, with the following explanations postulated: (1) PE alone frequently failed to prevent TMA recurrence[117]; (2) TMA regression cannot be preserved after cessation of therapy; and (3) recipients treated with PE showed an evidence of "subclinical" disease[118], which declares that PE has no influence on complement activity. Prophylactic use of rituximab proved to be beneficial as an anti-CFH-antibody[119], and this effect can be augmented with the addition of PE therapy[120,121]. The anti-C5 monoclonal antibody EZ has been reported to be successful in preventing TMA recurrence in recipients with CFH, CFH/CFHR1 hybrid gene mutations as well as in C3 gene mutations[122-125].

Prophylactic complement blockade

Eighty percent of kidney transplantation recipients with TMA proved to be associated with genetic mutations[126]. Based on the fact that a TMA episode is suspected with trigger factor (*e.g.*, surgery), a robust suggestion is to protect the patient with complement blockade, if not already instituted[127]. Unfortunately, this suggestion lacks appropriate evidence[12].

Therapeutic protocols for aHUS recurrence

Given a clear role of complement blockade in the management of TMA, two regimens have been suggested: (1) minimal dosage to achieve complement blockade; and (2) a dose withdrawal scheme (Table 8)[84]. EZ monitoring, however, is mandated for better response (Table 6)[128-131].

HOW TO MONITOR COMPLEMENT BLOCKADE - TABLE 6 DESCRIBES EZ THERAPY MONITORING

Duration of therapy

There is not enough data supporting life-long therapy. However, sustaining EZ seems to be reasonable in certain situations. Figure 5 represents a small guide, meanwhile early biomarkers of disease recurrence and complement activation became available.

Unanswered questions

The lacunae in satisfactory data still present as proper dosage, dose intervals, and duration of therapy[132], as well as the impact of this type of therapy on transplant spectrum[133].

Cessation of therapy

Figure 5 represents a guiding scheme suggested for EZ withdrawal[12].

Is EZ therapy the end of the road?

In 2013, Verhave *et al*[118] reported the feasibility of successful kidney transplantation without EZ therapy in four patients with high-risk aHUS. Patients received living donor kidneys with a therapeutic regimen consisting of: Basiliximab for induction, tacrolimus in low dosage, prednisone, and MMF for maintenance

Table 9 Risk of atypical hemolytic uremic syndrome recurrence according to the implicated genetic abnormalities

Gene mutation	Location	Functional Impact	Mutation frequency in aHUS (%)	Recurrence after transplantation (%)
CFH	Plasma	Loss	20-30	75-90
CFI	Plasma	Loss	2-12	45-80
CFB	Plasma	Gain	1-2	100
C3	Plasma	Gain	5-10	40-70
MCP	Membrane	Loss	10-15	15-20
THBD	Membrane	Loss	5	One case
Homozygous *CFHR1* del (3%-8%)	Circulating	Undetermined	14-23 (> 90% with anti-CHF AB)	NA

Adapted from Salvadori *et al*[1]. aHUS: Atypical hemolytic uremic syndrome; NA: Not available; CFH: Complement factor H; CFI: Complement factor I; CFB: Complement factor B; C3: Complement 3; MCP: Membrane cofactor protein; THBD: Thrombomodulin.

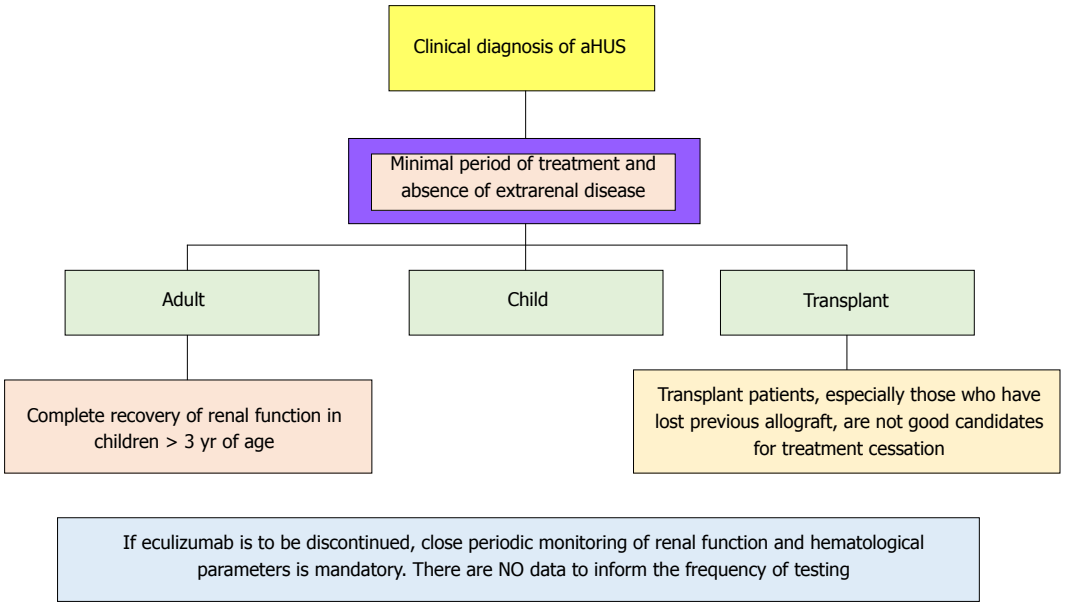

Figure 5 Recommendations for cessation of treatment with complement inhibitors. There are no prospective controlled studies in patients with atypical hemolytic uremic syndrome (aHUS) to define criteria for discontinuation of eculizumab therapy. This flow diagram is based on expert opinion[134-137]. Discontinuation can be considered on a case-by-case basis in patients after at least 6-12 mo of treatment and at least 3 mo of normalization (or stabilization in the case of residual chronic kidney disease) of kidney function. Earlier cessation (at 3 mo) may be considered in patients (especially children) with pathogenic variants in membrane cofactor protein if there has been rapid remission and recovery of renal function. Patients on dialysis or eculizumab should be maintained for at least 4 to 6 mo before discontinuation. In this setting, assessment of fibrotic changes in kidney biopsy may be helpful. In transplant patients, especially patients who have lost previous allografts, discontinuation is not recommended. Adapted from Goodship *et al*[12].

immunosuppression. A statin has also been added. Further precautions include: lowering BP as much as tolerable and minimizing the cold ischemic time. For the next 16-21 mo, no recurrence or rejection events have been reported[118]. The following conclusion has been addressed: successful kidney transplantation in recurrent aHUS patients can be achieved with an EZ-free regimen through: (1) decreasing cold ischemic time; (2) minimizing the risk of rejection; and (3) preserving endothelial integrity[118].

Renal transplantation in TMA

Timing of transplant: six months after commencing, dialysis should elapse before proceeding in transplant, as renal recovery can be observed several months after initiation of EZ therapy[137,138]. Two prerequisites should be fulfilled before commencing renal transplantation: (1) resolution of the extrarenal manifestations of TMA; and (2) recovery of TMA hematological parameters. The magnitude of recurrence risk may be used to evaluate the recipient's need for complement blockade (Table 9)[1].

CONCLUSION

The role of complement cascade in the evolution of kidney diseases either in the native kidney or post-transplant is well recognized. The prognosis of aHUS and, in some cases, C3G is greatly improved after commencing complement blockade. These agents are not only curative, but also successful in preventing post-transplant disease recurrence. Owing to the inherited nature of most of these diseases, the maintenance of this therapy is recommended despite cost burden. Consequently, the need for regimens allowing safe withdrawal of these agents is urgently required. However, newer therapies (*e.g.*, new monoclonal

antibodies, recombinant proteins, and small interfering RNA (siRNA) agents) hold promise for the near future[139,140].

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SYSTEMATIC REVIEW

Impact of machine perfusion of the liver on post-transplant biliary complications: A systematic review

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Abstract

AIM

To review the clinical impact of machine perfusion (MP) of the liver on biliary complications post-transplantation, particularly ischaemic-type biliary lesions (ITBL).

METHODS

This systematic review was performed in accordance with the Preferred Reporting Systematic Reviews and Meta-Analysis (PRISMA) protocol. The following databases were searched: PubMed, MEDLINE and Scopus. The keyword "liver transplantation" was used in combination with the free term "machine perfusion". Clinical studies reporting results of transplantation of donor human livers following *ex situ* or *in situ* MP were analysed. Details relating to donor characteristics, recipients, technique of MP performed and post-operative biliary complications (ITBL, bile leak and anastomotic strictures) were critically analysed.

RESULTS

Fifteen articles were considered to fit the criteria for this review. *Ex situ* normothermic MP was used in 6

studies, *ex situ* hypothermic MP in 5 studies and the other 4 studies investigated *in situ* normothermic regional perfusion (NRP) and controlled oxygenated rewarming. MP techniques which have *per se* the potential to alleviate ischaemia-reperfusion injury: Such as hypothermic MP and NRP, have also reported lower rates of ITBL. Other biliary complications, such as biliary leak and anastomotic biliary strictures, are reported with similar incidences with all MP techniques. There is currently less clinical evidence available to support normothermic MP as a mitigator of biliary complications following liver transplantation. On the other hand, restoration of organ to full metabolism during normothermic MP allows assessment of hepatobiliary function before transplantation, although universally accepted criteria have yet to be validated.

CONCLUSION

MP of the liver has the potential to have a positive impact on post-transplant biliary complications, specifically ITBL, and expand extended criteria donor livers utilisation.

Key words: Liver transplantation; *Ex situ* machine perfusion of the liver; Donation after circulatory death; Non-anastomotic intra-hepatic stricture; Ischemic-type biliary lesions; Extended criteria donors

Core tip: Post-transplant biliary complications are one of the main culprits responsible for the high patient morbidity following extended criteria donor liver transplantation. In its most severe form, ischaemic-type biliary lesions, can lead to graft failure and re-transplantation. Machine perfusion (MP) of the liver is a promising approach in reconditioning high-risk organs. Clinical studies have, so far, focussed on the impact of MP on hepatocellular function recovery and assessment. In this review we present the clinical evidence of the effect of MP on post-transplant biliary complications and discuss how, in the future, this approach can reduce these complications further.

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INTRODUCTION

Post-transplant biliary complications: The current scenario

Post-transplant biliary complications often require laborious and costly interventions, placing a heavy burden on health resources and adversely affecting patient outcomes[1,2]. The incidence of these complications is increasing as a result of the growing utilisation of extended criteria donor (ECD) organs, mainly from donation after circulatory death (DCD). Biliary complications such as biliary leak and anastomotic strictures are primarily related to surgical technicalities and are usually successfully managed with endoscopic procedures[3]. The most severe form of post-transplant biliary complication is non-anastomotic intrahepatic strictures (NAS). NAS is characterised by the occurrence of diffuse intra-hepatic strictures in the biliary tree and it was initially associated with hepatic artery thrombosis[4]. The ischaemic donor biliary tree was found to develop necrosis with fibrotic strictures, dilatations and potentially biliary casts[4]. Thereafter it was demonstrated that similar lesions occurred in the presence of a patent hepatic artery without evidence of recurrence of biliary disease. This entity was subsequently classified as ischaemic-type biliary lesion (ITBL)[5].

The reported incidence of ITBL is approximately 10%-30% for controlled DCD and 1%-3% for donation after brain death (DBD) organs[6-10]. Patients generally present with elevated liver function tests suggesting cholestasis (bilirubin, alkaline phosphatase and gamma-glutamyltransferase) within a few months of transplantation and may be asymptomatic initially. Initial work-up includes exclusion of hepatic artery thrombosis and anastomotic biliary strictures. Imaging investigations consist of non-invasive magnetic resonance cholangiopancreatography (MRCP) and computed tomographic cholangiography, or direct cholangiographic methods, such as endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography. Due to the high reliability of current non-invasive imaging techniques in diagnosing biliary strictures, invasive procedures are currently reserved for scenarios where an intervention is planned, such as stricture dilatation, stenting or stone extraction[11,12]. With ITBL, imaging confirms the presence of fibrotic strictures, in most cases located around the bifurcation of the common bile duct leading to dilatation of the intra-hepatic biliary system[1,8]. Figure 1 illustrates these typical imaging features of ITBL following liver transplantation. The obstructive strictures cause cholestasis with formation of sludge and casts that predispose to cholangitis, frequently requiring surgical or endoscopic intervention. Despite these measures, approximately 50% of patients with ITBL require re-transplantation or die[13].

Although the pathogenesis of ITBL is still not fully understood a growing body of evidence suggest that it is partially associated with ischaemia-reperfusion injury (IRI)[14,15]. Noack *et al*[16] in a well-designed *in-vitro* study using rat-derived bile duct cells showed that they were more resistant to anoxia than hepatocytes, however during reoxygenation they produced higher amounts of reactive oxygen species (ROS). This was associated with increased rates of bile duct cell death when compared to hepatocytes[16]. It has been shown that mitochondrial ischaemic induced injury leads to ROS production during reperfusion which in turn causes

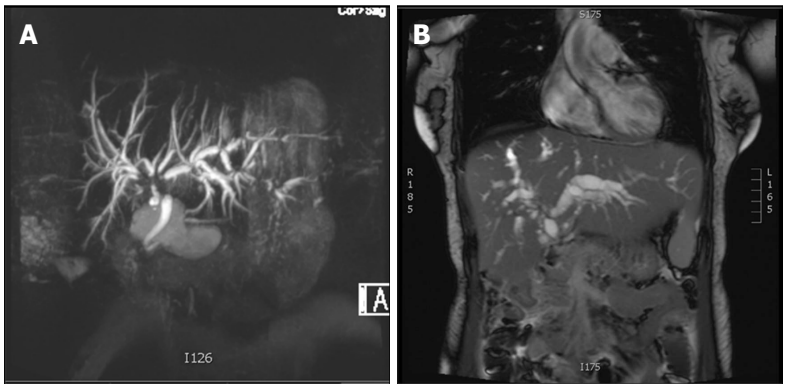

Figure 1 Magnetic resonance cholangiopancreatography images of ischemic-type biliary lesions following liver transplantation. The images show two recipients of livers from donation after circulatory death donors that developed ischemic-type biliary lesions within 60 d following transplantation. Hepatic artery thrombosis and anastomotic biliary strictures were ruled out. A: A typical lesion is seen affecting the bifurcation of the common hepatic bile duct with moderate dilatation of the intrahepatic biliary tree; B: The image shows strictures at the bifurcation of the common hepatic bile duct, diffuse intra-hepatic strictures and a severe dilatation of the intrahepatic biliary tree.

oxidative injury and activation of the inflammatory cascade[17,18]. Conversely, clinical series have reported severe injury to the biliary epithelium just after cold static storage[19,20]. Garcia-Valdecasas *et al*[15] using a porcine transplantation model suggested a direct relationship between prolonged ischaemic times and cell injury. Indeed, other clinical series have confirmed the association of longer cold ischaemic time (CIT) and higher rates of ITBL[21-24]. A similar relationship has been observed with warm ischemic time in DCD liver transplantation[15,25]. A large clinical series of donor bile duct biopsies before liver transplantation showed similar injury to the biliary epithelium after static cold storage (SCS), and that it was exacerbated after reperfusion; however, this did not correlate with the development of ITBL[26]. Nevertheless, the authors reported a strong association between ITBL and damage to the peribiliary vascular plexus and peribiliary glands. As progenitor biliary cells are known to reside in the peribiliary glands, the former finding suggests an association between ITBL and an attenuated regenerative capacity of the biliary epithelium[26,27]. Ischaemic injury is likely to play a major role in ITBL pathogenesis, although other factors have also been shown to be implicated. Immunological mediated injury to the biliary epithelium has been associated with ITBL[28]. It may be the result of direct immunological damage to the biliary epithelium *via* a rejection reaction[29]; or, indirect, secondary to the development of arteriopathy[29,30]. This cross reactivity is described in scenarios of cytomegalovirus infection[30], ABO incompatibility[31] and transplantation for primary sclerosing cholangitis[1]. Bile salt toxicity has also been investigated as a potential cause for ITBL by having a direct detergent effect on phospholipid cellular membranes of the biliary epithelium[28]. Flushing of the biliary tree during organ procurement is necessary in order to remove all bile salts that could damage cholangiocytes[5,28]. Furthermore, an imbalance in the post-transplant bile composition, with a higher bile salt/phospholipid ratio, due to inefficient ATP-dependent biliary transporters has been suggested as a predictive factor for ITBL[32]. While detail of the pathogenesis of ITBL is beyond the scope of this review, information on the implicated mechanisms can be found in a number of published reviews[9,28].

Machine perfusion of donor livers

The utilisation of DCD livers is increasing. In 2017, in the United Kingdom, they constituted 28% of the livers transplanted[33]. Furthermore, the rising prevalence of donor obesity (body mass index greater than 30 kg/m^2) and an ageing population continue to compound the risks to those livers[33]. These high-risk ECD organs are associated not only with a higher risk of graft dysfunction post-transplantation but also increased rates of ITBL[34]. Despite these disadvantages, their utilisation is required to tackle the ever-growing discrepancy between organ donor supply and demand. Machine perfusion (MP) of the liver is being developed as a means of assessment and reconditioning of ECD donors, potentially allowing for safer transplantation of these high-risk livers[34,35]. Different techniques of MP have been developed; it can be performed *in situ* during organ procurement or *ex situ* after the procedure. With regards to livers, the only technique of *in situ* MP described so far is normothermic regional perfusion (NRP)[8]. *Ex situ* MP protocols vary in terms of oxygenation (active or pre-charged oxygenation), perfusate temperature (hypothermic, subnormothermic, gradual rewarming and normothermic), timing of perfusion (preservation or end-ischemic) and via of organ perfusion (portal vein alone or dual portal vein and hepatic artery perfusion)[34,36].

Hypothermic machine perfusion (HMP) has been performed around 10 ℃ in most studies[37,38]. At this temperature liver metabolism is reduced; and, passive oxygen delivery by diffusion in an oxygen carrier-free perfusate is enough to support the organ[39]. The first published clinical series employed pre-charged oxygen delivery to the organs[37], technique that was later followed by active oxygenation of the perfusate[40].

Hypothermic oxygenated MP can be performed *via* portal vein alone (HOPE) or *via* portal vein and hepatic artery (dual hypothermic oxygenated perfusion - D-HOPE)[41-43]. Both techniques have shown the capacity of improve mitochondrial oxidative function prior to rewarming, resulting in increased adenosine triphosphate (ATP) synthesis and a reduction in ROS production, oxidative tissue injury and activation of the inflammatory cascade[42,43].

Normothermic machine perfusion (NMP) maintains the organ at physiological temperatures (37 ℃) and therefore restores full metabolic activity. This enables the possibility of functional or viability assessment prior to transplantation, a major advantage of NMP when compared to other perfusion techniques[44,45]. It also opens up a window of opportunity for *ex situ* therapeutic interventions[34]. Furthermore, previous studies have reported on the safety of extended normothermic perfusion of organs, which may facilitate transportation and logistical management of busy transplant units[46]. However, potential drawbacks of NMP are that it requires obligatorily the inclusion of an oxygen carrier in the perfusate, and NMP inevitably induces reperfusion injury to some extent.

Subnormothermic machine perfusion (SMP) has been performed at around 20 ℃ in most studies. It encompasses purely SMP and the controlled oxygenated rewarming (COR) from 10 ℃ to 20 ℃[47,48]. The increase in temperature from HMP to SMP is suggested to be enough to increase liver metabolism to an extent that it would allow assessment of organ function without inducing the detrimental changes associated with organ reperfusion at normothermic temperatures[48]. Evidence for the clinical benefits is available for COR perfusions, it was associated with lower markers of hepatocellular injury after transplantation and enhanced graft function through the avoidance of subtle changes in organ temperature[47].

For DCD livers, there are encouraging reports of *in situ* oxygenated NRP. It has been successfully applied to controlled DCD donors (withdrawal of life support in patients with irreversible clinical conditions) and uncontrolled DCD (witnessed cardiac arrest without response to resuscitative measures)[8,49,50]. NRP limits ischaemia and prevents depletion of energy stores prior to SCS and this is suggested to be essential for uncontrolled DCD donors and beneficial for controlled DCD[8].

More recently, combinations of MP techniques have been shown to merge the advantages of individual protocols, enhancing the rescue of liver function what may potentially improve graft function after transplantation[51,52]. Despite differences between techniques, MP has the potential to limit ischaemic injury to the organ, thus offering a safer preservation environment and an opportunity for organ reconditioning which could mitigate IRI.

As discussed herein, the current evidence shows that cholangiocytes are more vulnerable to IRI than hepatocytes and that the pathogenesis for biliary injury goes beyond IRI. Therefore, investigation of the impact of MP on biliary function specifically, and not only on hepatocellular function, is fundamental. The aim of this review was to investigate the current clinical evidence available regarding the effect of MP on post-transplant biliary complications, focusing on ITBL.

MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Systematic Reviews and Meta-Analysis (PRISMA) protocol[53].

The following databases were searched for the development of this review: PubMed, MEDLINE and Scopus. The keyword "liver transplantation" was used in combination with the free term "machine perfusion". The literature review was performed until June 20, 2018 and there were no limits on the date for inclusion of publications. The literature search strategy used for one database is presented in the Supplementary Table S1.

The screening and selection of articles were independently performed by two authors (Yuri L Boteon and Amanda PCS Boteon). There was no disagreement in study selection between authors. Manuscript titles that were not related to the main scope of the review were excluded. Full abstracts were then read and excluded if found not to be relevant to the review. Finally, full papers were assessed for eligibility and included in this review. The flow diagram for the literature selection process is shown in Figure 2.

Inclusion criteria were: (1) clinical studies reporting results of transplantation of donor human livers following *ex situ* or *in situ* MP; and (2) articles written in English and published. Exclusion criteria were: (1) absence of transplantation following MP; (2) exclusively animal models; (3) single case report; (4) review articles; and (5) articles not written in English.

Details relating to donor characteristics [type, age, donor risk index (DRI), warm ischaemic time (WIT), CIT], recipients [age, model for end-stage liver disease (MELD)], perfusion (type of perfusion, oxygenation, timings) and post-operative biliary complications (ITBL, leak and anastomotic strictures) were retrieved from each manuscript and critically analysed. Studies were assessed in terms of study design, methods and outcomes. No review protocol was registered before this review was started. No simplifications or assumptions were made, and any identified risk of bias is discussed throughout the review.

RESULTS

Fifteen articles were considered to fit the criteria for this review. A diagrammatic summary of the screening process is provided in Figure 2.

MP and ischemic type biliary lesions (ITBL)

Eight out of fifteen clinical studies utilised an end-

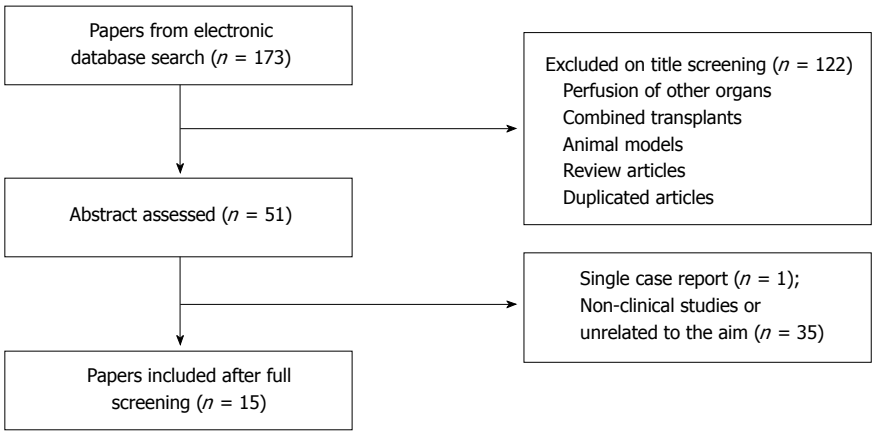

Figure 2 Study flow diagram for systematic review of the literature on the impact of machine perfusion of the liver and post-transplant biliary complications. Following literature search duplicate articles were excluded and the titles screened. The selected abstracts were then read and non-clinical studies or reports unrelated to the aim of the review were excluded.

ischemic model of MP (MP commenced after a variable period of SCS), 4 studies utilised preservation MP (MP from organ procurement up to transplantation) and 3 employed NRP. NMP was used in 6 studies, HMP in 5 studies and the other 4 studies investigated NRP and COR. HMP with active perfusate oxygenation (HOPE and D-HOPE) studies were seen to be currently focused on DCD organs and HMP with pre-charged oxygenation on DBD organs. NMP studies used both donor types, however preservation studies explored a higher proportion of DBD compared to DCD organs. The contrary was seen for end-ischemic NMP.

Donor and recipients characteristics, of the cases included in individual studies, are presented in Table 1. It also reports the rates of ITBL. Table 2 describes the incidence of bile leak and anastomotic biliary stricture within the different studies. Studies characteristics were described therein, as it was their design.

NMP and post-transplant biliary complications

The largest clinical trial involving NMP as a preservation strategy was recently published by Nasralla *et al*[46]. Following procurement, transplantable livers were randomised and allocated to the intervention group that had NMP up to the point of transplantation or a control group that had conventional SCS. From the 121 livers perfused, 87 were from DBD donors and 34 from DCD donors. Results did not shown differences in bile duct complications between groups, with one patient in each arm developing ITBL within the first year, both requiring re-transplantation. On MRCP, the rates of NAS were similar between groups for DBD (NMP 7.4% *vs* SCS 5.4%; $P = 0.678$) and DCD (NMP 11.1% *vs* SCS 26.3%; $P = 0.180$). The incidence of anastomotic strictures was also similar for DBD or DCD organs (NMP 40.7% *vs* SCS 41.8%; $P = 0.909$; and, NMP 48.1% *vs* SCS 57.9%; $P = 0.515$, respectively)[46].

Other clinical studies investigating NMP using a preservation approach[54-56] involved smaller patient numbers, the majority of which were from DBD donors, and did not specifically report the incidence of ITBL (Table 1). Ravikumar *et al*[55] published the first phase 1 clinical trial demonstrating the safety and feasibility of NMP in a preservation approach, as an alternative to SCS. In all, 20 donor livers (16 DBD and 4 DCD) were transplanted following NMP. The 30-day graft survival was similar to static cold stored livers and the median peak aspartate aminotransferase within the first 7 post-operative days was lower. In terms of biliary complications, the authors reported the occurrence of 4 cases of anastomotic biliary strictures in the NMP group[55].

The two studies of NMP after a period of SCS (end-ischaemic model) involved organs that were deemed too high risk for transplantation[57,58]. These studies predominantly used DCD livers and applied predefined viability criteria prior to transplantation. Mergental *et al*[57] did not observe any biliary complications at 7 mo of follow up post-transplantation. Watson *et al*[58] reported the occurrence of 4 cases of ITBL in 16 DCD liver transplants, of which 3 needed re-transplantation. The authors of the latter study concluded that that NMP per se does not prevent ITBL but may provide biomarkers to identify livers that are high risk, such as maximum bile pH > 7.5 and bile glucose ≤ 3 mmol/L or ≥ 10 mmol less than perfusate glucose[58].

HMP and post-transplant biliary complications

The first clinical study using HMP prior to transplantation was performed by Guarrera *et al*[37] Twenty DBD livers were perfused after a period of SCS in a non-actively oxygenated model of HMP. ITBL rate was reported as 5%, half of the incidence of the control matched cohort that was subjected to SCS. Additionally, there was one case of bile leak and 1 report of anastomotic biliary stricture[37]. The same approach was repeated later in a study of DBD livers declined by the United Network for Organ Sharing region for transplantation[59]. The authors found a significant decrease in the rate of biliary stricture in comparison with SCS (10% *vs* 33%, $P = 0.031$). One report of bile leak was noted in the HMP group and 3 in

Table 1 Comparison between donor, recipient, perfusion characteristics and the reported rates of ischemic-type biliary lesions

Ref.	Yr	Perfusion type	Timing MP	*n*	Donor age	Donor risk index	Recipient age	Recipient MELD	DBD (*n*)	DCD (*n*)	DBD ITBL (%)	DCD ITBL (%)	CIT (min)	Func. WIT (min)	Re-Tx (*n*)
Ex situ normothermic machine perfusion															
Nasralla *et al*[46]	2018	NMP	Preserv	121	56 (16-84)	1.7[3]	55	13 (6-35)	87	34	7.4	11.1	126	21	3
Selzner *et al*[54]	2016	NMP	Preserv	10	48 (17-75)	1.9	57	21 (8-40)	8	2	0	0	103	NA	0
Bral *et al*[56]	2017	NMP	Preserv	9	56 (14-71)	1.6 (0.9-2.7)	53 (28-67)	13 (9-32)	6	3	0	0	167 (95-293)	22	0
Ravikumar *et al*[55]	2016	NMP	Preserv	20	58 (21-85)	NA	NA	12 (7-27)	16	4	0	0	NA	21	0
Watson *et al*[58]	2018	NMP	End-Isc	22	57	2.3	NA	NA	6	16	0	25	386	12	3
Mergental *et al*[57]	2016	NMP	End-Isc	5	49 (29-54)	2.3	56 (47-66)	8 (8-13)	1	4	0	0	422	28	0
Ex situ hypothermic non-oxygenated machine perfusion															
Guarrera *et al*[59]	2015	HMP	End-Isc	31	57 (± 18)[1]	1.9 (± 0.5)[1]	57 (± 8.0)[1]	19 (± 5.9)[1]	31	0	9.7	NA	558	NA	0
Guarrera *et al*[37]	2010	HMP	End-Isc	20	39 (± 2.5)[1]	NA	55 (± 6.2)[1]	17 (± 7.4)[1]	20	0	5	NA	306	26	0
Ex situ hypothermic oxygenated machine perfusion															
van Rijn *et al*[43]	2017	DHOPE	End-Isc	10	53 (47-57)	1.9 (1.5-2.2)	57 (54-62)	16 (15-22)	0	10	NA	10	331	15	0
Dutkowski *et al*[38]	2015	HOPE	End-Isc	25	54 (36-63)	NA	60 (57-64)	13 (9-15)	0	25	NA	0	188 (141-264)	31 (26-36)	0
Dutkowski *et al*[40]	2014	HOPE	End-Isc	8	54 (NA)	2.2 (NA)	60 (NA)	12 (NA)	0	8	NA	0	141 (NA)	31 (22-41)	0
In situ normothermic regional perfusion															
De Carlis *et al*[60]2	2017	NRP	NRP	7	48[1]	NA	54[1]	10.6[1]	0	7	NA	0	414[1]	33	0
Oniscu *et al*[49]	2014	NRP	NRP	11	46 (16-74)	NA	68 (43-74)	NA	0	11	NA	0	389 (169-450)	26 (13-48)	0
Minambres *et al*[50]	2017	NRP	NRP	11	58 (50-67)	NA	55 (± 13)[1]	NA	0	11	NA	0	266 (± 82.7)[1]	12 (11-16)	0
Controlled oxygenated rewarming															
Hoyer *et al*[47]	2016	COR	End-Isc	6	58 (51-71)	1.9 (1.5-2.5)	52 (43-65)	18 (11-23)	6	0	0	NA	508 (369-870)	NA	0

[1]Data presented as median or median (± SD), if available. Otherwise, all data presented as median (Interquartile range); [2]Combined hypothermic oxygenated machine perfusion after normothermic regional perfusion. Six uncontrolled DCD were included in this study; [3]Eurotransplant DRI. MP: Machine perfusion; MELD: Model for end stage liver disease; DBD: Donation after brain death; DCD: Donation after circulatory death; ITBL: Ischemic-type biliary lesions; CIT: Cold ischemic time; Func; WIT: Functional warm ischemic time; Re-Tx: Re-transplantation; NA: Not applicable or not available; Preserv: Preservation; End-Isc: End ischemic; NMP: Normothermic machine perfusion; HMP: Hypothermic machine perfusion; DHOPE: Dual vessel hypothermic oxygenated machine perfusion; HOPE: Hypothermic oxygenated machine perfusion; NRP: Normothermic regional perfusion; COR: Controlled oxygenated rewarming.

SCS respectively (Table 2).

Following these initial studies, the Zurich group developed the concept of HOPE, with active oxygenation of the perfusate, and applied this MP strategy to DCD donors[38,40]. Their first clinical trial was published in 2015, reporting the results of transplantation of 25 DCD livers[38]. The authors reported no cases of ITBL at one year follow-up of patients who received perfused DCD livers, whereas control livers subjected to SCS developed a significantly higher rate of ITBL (0/25 *vs* 11/50, $P = 0.013$). The same benefit of HOPE was not seen for extra-hepatic biliary complications, as the reported rates of leaks and anastomotic strictures were similar (HOPE 5/25 *vs* Control 12/50)[38].

The Groningen group published the first clinical series using D-HOPE in 2017[43]. Ten DCD livers were transplanted following two hours of D-HOPE, one patient in the perfusion group developed ITBL compared to 7 out of 20 in the control group. The case in the D-HOPE group was described as NAS in segments II and III of the liver and was managed with endoscopic stenting. Three control livers which developed ITBL required re-transplantation. The rate of anastomotic biliary strictures was comparable between groups (D-HOPE 2 *vs* Control 3, $P = 1.000$) as was the reported rate of biliary cast formation (D-HOPE 3 *vs* Control 3, $P = 0.372$)[43].

Normothermic reginal perfusion and post-transplant biliary complications

The first series reporting the results for transplantation of livers following NRP was published in 2014 by Oniscu *et al*[49] The authors reported the results of transplantation of

Table 2 Prevalence of bile leak and anastomotic biliary strictures between clinical studies using different techniques of machine perfusion of donor livers

Ref.	Yr	Study design	Perfusion type	Timing machine perfusion	*n*	DBD (*n*)	DCD (*n*)	Bile leak (*n*)	Anastomotic stricture (*n*)
Ex situ normothermic machine perfusion									
Nasralla *et al*[46]	2018	RCT	NMP	Preservation	121	87	34	0	0
Selzner *et al*[54]	2016	PS	NMP	Preservation	10	8	2	0	0
Bral *et al*[56]	2017	PS	NMP	Preservation	9	6	3	0	0
Ravikumar *et al*[55]	2016	PS	NMP	Preservation	20	16	4	0	4 (DBD)
Watson *et al*[58]	2018	DS	NMP	End-Ischaemic	22	6	16	0	0
Mergental *et al*[57]	2016	DS	NMP	End-Ischaemic	5	1	4	0	0
Ex situ hypothermic non-oxygenated machine perfusion									
Guarrera *et al*[59]	2015	PS	HMP	End-Ischaemic	31	31	0	1	0
Guarrera *et al*[37]	2010	NCS	HMP	End-Ischaemic	20	20	0	1	1
Ex situ hypothermic oxygenated machine perfusion									
van Rijn *et al*[43]	2017	PS	DHOPE	End-Ischaemic	10	0	10	0	2
Dutkowski *et al*[38]	2015	PS	HOPE	End-Ischaemic	25	0	25	5 (in total)	
Dutkowski *et al*[40]	2014	PS	HOPE	End-Ischaemic	8	0	8	1	1
In situ normothermic regional perfusion									
De Carlis *et al*[60]1	2017	DS	NRP	NRP	7	0	7*	0	1
Oniscu *et al*[49]	2014	DS	NRP	NRP	11	0	11	1	1
Minambres *et al*[50]	2017	DS	NRP	NRP	11	0	11	NA	NA
Controlled Oxygenated Rewarming									
Hoyer *et al*[47]	2016	PS	COR	End-Ischaemic	6	6	0	NA	NA

[1]Combined hypothermic oxygenated machine perfusion after normothermic regional perfusion. Six uncontrolled DCD were included in this study. RCT: Randomised controlled trial; PS: Single-arm non-randomised pilot study; DS: Descriptive study; NCS: Non-randomised cohort studies; DBD: Donation after brain death; DCD: Donation after circulatory death; NA: Not applicable or not available; NMP: Normothermic machine perfusion; HMP: Hypothermic machine perfusion; DHOPE: Dual vessel hypothermic oxygenated machine perfusion; HOPE: Hypothermic oxygenated machine perfusion; NRP: Normothermic regional perfusion; COR: Controlled oxygenated rewarming.

11 controlled DCD livers, with a minimum follow-up of 3 mo, with no clinical or radiological evidence of ITBL. One patient developed an anastomotic stricture, treated endoscopically by cholangio-pancreatography (exact intervention performed is not described), and one patient had a bile leak[49]. Minambres *et al*[50] 2017, studying controlled DCD transplantation after NRP, reported no cases of ITBL after 1-year follow-up. De Carlis *et al*[60] 2017 performed NRP on 1 controlled DCD liver and 6 uncontrolled DCD. On arrival at the transplant centre, the livers were subjected to D-HOPE until transplantation. No cases of ITBL were observed and one patient had an anastomotic biliary stricture 45 d after transplantation, which was successfully treated with endoscopic stenting[60]. In terms of SMP, Hoyer *et al*[47] reported transplantation of 6 DBD livers following COR perfusion. No biliary complications were reported within a follow-up period of six months.

DISCUSSION

Post-transplant biliary complications are associated with high rates of morbidity and re-transplantation and are a major obstacle to the wider clinical utilisation of ECD livers. There is a growing body of evidence suggesting that MP can offer safer organ preservation when compared to SCS, and also offer an opportunity for organ assessment and/or reconditioning prior to transplantation[38,43,46,49,58]. In this review we have assessed the available literature investigating the impact of MP on post-transplant biliary complications, with special reference to ITBL. MP techniques which have per se the potential to alleviate IRI, such as HMP and NRP, have also reported lower rates of ITBL. Other biliary complications, such as biliary leak and anastomotic biliary strictures, are reported with similar incidences with all MP techniques.

Liver IRI is thought to be a major driver of biliary injury and, therefore, it is associated with complications following transplantation. More specifically, during ischemia, without oxygen as a terminal acceptor of electrons in the electron transport chain, succinate accumulates and acts as a store for electrons. Succinate oxidation during the early stage of reperfusion, blocks mitochondrial complex II of the electron transport chain resulting in a reverse flow of electrons towards mitochondrial complex I leading to accentuated leakage of electrons, and generation of ROS[61]. Various experimental findings using the HOPE technique have shown that oxygen at hypothermic temperatures is able to promote mitochondrial metabolism of succinate prior to reperfusion[36,42,62]. By re-establishing adequate mitochondrial oxidative function, HOPE is able to recover ATP stores, since during hypothermia mitochondria have lower energy requirements due to a minimum activation of the organ metabolism. Therefore, mechanistically, HOPE can in theory prevent the reverse flow of electrons during reperfusion, ROS generation and activation of the inflammatory cascade[36]. These factors may mitigate IRI, which would be beneficial not only

for hepatocellular function but also for the prevention of further biliary injury.

Extensive research focussing on the effect of oxygenated HMP on post-transplant biliary complications has been performed by the Groningen group. In a recent publication exploring the effects of D-HOPE on bile duct biopsies from a previous published series of cases, they showed less injury to deep and periluminal peribiliary glands after reperfusion during transplantation in the perfused group in comparison with SCS control livers[43,63]. Peribiliary glands have been described as stores for biliary progenitor cells, therefore injury to them would potentially decrease the regenerative capacity of the biliary system[64,65]. The authors acknowledge that definitive evidence to support this would require a clinical randomized trial that has since been initiated at their centre[63].

There is currently less clinical evidence available to support NMP as a mitigator of biliary complications following liver transplantation[58]. Preservation NMP shortens the ischaemic injury and offers a more physiological environment for the organ before transplantation. Nevertheless, as previously discussed, the injury to biliary cells would not be restricted to an ischaemic mechanism but may also be worsened during reperfusion. This observation could imply that NMP is of limited benefit in terms of biliary complications, since biliary injury may worsen during organ reperfusion on the machine and is not prevented or mitigated beforehand. NMP restores the full metabolism of the organ, resulting inevitably in the production and circulation of ROS and potential activation of the inflammatory response leading to tissue injury[66]. On the other hand, restoration of organ to full metabolism allows assessment of hepatobiliary function before transplantation, although universally accepted criteria have yet to be validated[35]. Watson *et al*[58] suggested bile pH and glucose content as markers of bile duct injury and associated those with the development of ITBL, however the authors recognise that NMP was not able to prevent biliary damage.

Promisingly, *in situ* NRP has shown excellent biliary outcomes after transplantation of DCD livers[49,50,60]. NRP may potentially prevent ischaemic injury and deterioration of ATP stores during organ procurement. Additionally, NRP allows assessment of the liver metabolism even before SCS[8]. Despite these points, there is no mechanistic evidence available to demonstrate any alleviation in IRI after reperfusion. It is also difficult to rule out the possibility that this beneficial effect was as a result of a potential selection bias when recruiting organs for transplantation during the procedure.

The present body of work has several limitations. First and foremost, donor livers and recipient characteristics as well as MP technique protocols exhibit a high degree of variability between studies. So far, there has been no standardisation in terms of methodology and reporting of results. Furthermore, some studies neglect to report important data variables, such as DRI, recipient age, recipient MELD and CIT. All these features are presented in Table 1 to allow an unbiased assessment of the retrieved information by the readers. Additionally, few clinical studies from each MP technique are available and most of them are originated from small pilot studies, which limit definitive interpretation of the data. MRCP was performed in some of the studies at different post-operative periods, but the significance of findings without clinical correlation is not clear. In addition, they have focussed mainly on evaluation of hepatocellular function rather than biliary function and injury. Despite the subject of this review being a relevant topic with important clinical implications, the direct effects of MP on biliary tree integrity are still relatively under-researched. More clinical randomized trials will be reported in the field in the next few years.

Higher rates of ITBL following transplantation of ECD livers, mainly DCD, place a major restraint on the wider use of these marginal livers. Each technique of MP offers different advantages and they all have the potential to tackle this problem. A feasibility study has shown that a combination of HOPE and NMP increased the rescue of metabolic parameters of high-risk ECD organs[52]. This approach may derive benefits from the individual methods, thus optimising gains also in terms of biliary function. Pharmacological interventions during NMP may potentially alleviate IRI, positively affecting biliary cells[67], and may have a direct effect on post-transplant biliary complications. Supplementation of the perfusate with substances that may induce proliferation and maturation of progenitor cells from peribiliary glands may be a feasible option to be considered[9]. We hypothesize that therapies promoting increase in secretion of phospholipids and cholesterol in the bile would equilibrate the phospholipids/bile salts balance mitigating further injury to the biliary tree. Although promising, these are options that still need to be explored in future studies. A diagrammatic summary of the current and future impact of MP on ITBL is presented in Figure 3.

The high incidence of post-transplant biliary complications, specifically ITBL, is a major constraint to wider utilisation of ECD livers. MP is currently considered a promising tool to increase ECD utilisation. However, the focus of most of the studies up to date has been the effect of MP on hepatocellular function. In this review we explored the clinical evidence currently available for the impact of MP on post-transplant biliary complications. From those studies that have looked at the effects of MP on biliary integrity, oxygenated HMP and NRP studies have been shown to exhibit better postoperative biliary outcomes in comparison with NMP and non-oxygenated HMP. However, larger clinical studies and randomised clinical trials powered for the occurrence of biliary complications as a primary endpoint are needed to confirm this data.

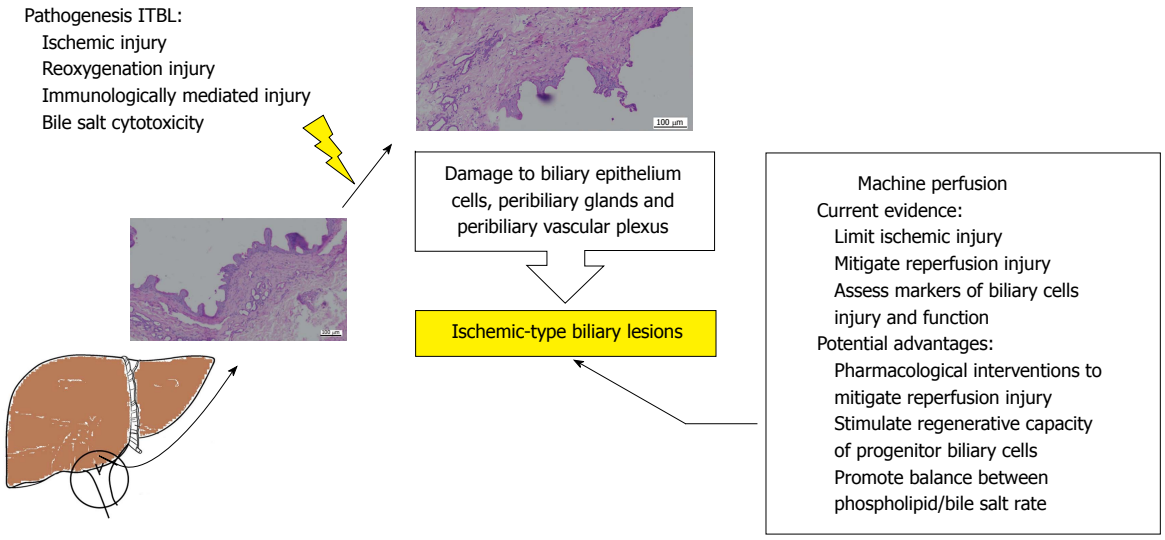

Figure 3 Diagrammatic summary of the current evidence for the impact of machine perfusion of the liver on post-transplant ischemic-type biliary lesions and future perspectives. The current evidence suggests that ischaemic-type biliary lesions (ITBL) have a multifactorial pathogenesis. These diverse factors lead to injury to the biliary epithelium, peribiliary glands and peribiliary vascular plexus. Currently, there is evidence for the potential benefits of machine perfusion on post-transplant ITBL. The figure summarises those and possible future interventions that could enhance increase these benefits further.

ARTICLE HIGHLIGHTS

Research background

The ever-growing discrepancy between donor organ availability and patients on the transplant waiting list has led to increased acceptance of extended criteria donors (ECD). However, ECD liver transplantation, mainly donation after circulatory death, is associated with poor patient and graft outcome. A major factor is the increased risk of biliary complications, in particular ischaemic type biliary lesions (ITBL). Machine perfusion (MP) of the liveris a promising tool to recondition ECD organs prior to transplantation. Therefore investigation of the impact of MP on post-transplant biliary complications is a highly relevant topic.

Research motivation

Understanding the current evidence available for the effect of MP on post-transplant biliary complications, in particular ITBL, may guide further studies in this field.

Research objectives

Revise the current clinical evidence available regarding the effect of MP on post-transplant biliary complications, focusing on ITBL.

Research methods

A systematic review was carried out with literature searches in PubMed, MEDLINE and Scopus databases. The keyword "liver transplantation" was used in combination with the free term "machine perfusion". Only clinical studies reporting results of transplantation of donor human livers following ex situ or in situ MP were included.

Research results

MP techniques which have demonstrated the potential to mitigate ischaemia reperfusion injury, such as *ex situ* oxygenated hypothermic MP and *in situ* normothermic regional perfusion, have also reported lower rates of ITBL. Other biliary complications, such as biliary leak and anastomotic biliary strictures, are reported with similar incidences with all MP techniques. Clinical studies have focused on evaluation of hepatocellular function rather than biliary function and injury so far. The direct effects of MP on biliary tree integrity are still relatively under-researched and further studies are needed.

Research conclusions

Post-transplant biliary complications are a major obstacle to the wider utilisation of ECD livers. MP has the potential to have a positive impact on this issue, specifically ITBL, and expand ECD livers utilisation. Mechanistically, mitigation of ischaemia-reperfusion injury appears to be the key mechanism involved.

Research perspectives

Supplementation of the perfusion fluid during *ex situ* MP with drugs can stimulate protective/regenerative mechanisms of the biliary tree. Pharmacological strategies may potentially modulate progenitor cells proliferation and equilibrate the phospholipid/bile salts balance in the bile.

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CASE REPORT

Treatment of transplant renal artery pseudoaneurysm using expandable hydrogel coils: A case report and review of literature

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Author contributions: Marie Y and Shrestha B managed the patient and prepared the manuscript; Kumar A, Hinchliffe S and Curran S were involved in managing the patient and contributed to manuscript preparation; Brown P and Turner D performed radiological investigations, managed the patient and contributed to manuscript preparation.

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Abstract

Transplant renal artery (TRA) pseudoaneurysm can result in bleeding, infection, graft dysfunction and graft loss. We report the management of a renal transplant recipient who presented five months after renal transplantation with deterioration of renal function, who was found to have TRA pseudoaneurysm and TRA stenosis. Both were treated radiologically by using expandable hydrogel coils (EHC) in combination with stenting. Improvement in clinical, biochemical and radiological parameters were observed after the intervention. To our knowledge, this is the first report in the transplant literature on the use of EHC for the treatment of a TRA pseudoaneurysm.

Key words: Pseudoaneurysm; Transplant renal artery; Expandable hydrogel coils; Outcomes

Core tip: Transplant renal artery (TRA) pseudoaneurysm is an uncommon complication after renal transplantation, which can cause transplant dysfunction, bleeding, infection

and graft loss. Expandable hydrogel coils should be considered in the treatment of TRA pseudoaneurysm as they have been effective in our patient.

Marie Y, Kumar A, Hinchliffe S, Curran S, Brown P, Turner D, Shrestha B. Treatment of transplant renal artery pseudoaneurysm using expandable hydrogel coils: A case report and review of literature. *World J Transplant* 2018; 8(6): 232-236 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i6/232.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i6.232

INTRODUCTION

Transplant renal artery (TRA) pseudoaneurysm can result in bleeding, infection, graft dysfunction, graft loss, lower limb ischaemia, limb loss and mortality[1]. The treatment of TRA pseudoaneurysm remains challenging. The expandable hydrogel coil (EHC) embolization system is a relatively new type of device that has been described to successfully treat intracranial and peripheral pseudoaneurysms. These are helical platinum coils coated with exapandable hydrogel polymer. The hydrogel coating undergoes full expansion within 20 min attending a size between 4-5 times the size of the coils on coming in contact with blood. The stasis of the blood causes organization of thrombus, which fills the aneurysm causing complete its occlusion[1]. To our knowledge, there is no published data in the transplant literature on the application of EHC in the treatment of TRA pseudoaneurysm. We describe the successful management of a case of TRA pseudoaneurysm using EHC and review the pertinent literature.

CASE REPORT

A 38-year-old male patient received a renal transplant (RT) of a kidney from a donation after circulatory death donor. The right donor kidney had a single real artery on an aortic patch and the short renal vein which was elongated by using a segment of inferior vena cava. The kidney was implanted in the right iliac fossa by anastomosing the renal artery to the external iliac artery in an end-to-side fashion using continuous 5/0 prolene sutures (Ethicon Inc., United Kingdom) and renal vein to the external iliac vein in the similar fashion. An extravesical ureteroneocystostomy was performed as describe by Lich-Gregoir. The vascular anastomosis time was 45 min while the total cold ischaemic time was 15 h and 38 min. The patient received basiliximab (Sandoz, United Kingdom) and methyl prednisolone as induction therapy and tacrolimus, mycophenolate mofetil and prednisolone as maintenance immunosuppression.

The transplant had delayed graft function and required haemodialysis during the first week until renal function started to improve. The initial ultrasound scan of the transplant kidney showed a well perfused graft with no evidence of hydronephrosis or any collection and the resistive indices (RI) were within normal limits. The renal function was stable with a serum creatinine of 136 μmol/L and an estimated glomerular filtration rate (eGFR) of 51 mL/min per 1.73 m^2 at 3 mo post-transplantation.

At five months post-transplantation, on routine outpatient review, deterioration in kidney renal function with a rise in serum creatinine to 633 μmol/L (eGFR 13 mL/min per 1.73 m^2) was observed. A duplex ultrasound scan showed a well-perfused kidney with no evidence of hydronephrosis. An ultrasound-guided biopsy of the kidney, which was treated with three pulses of intravenous methyl prednisolone, showed features of acute cellular rejection. However, there was no improvement in renal function. A repeat duplex ultrasound scan showed damped flow signals on the intra-renal blood vessels with reduced RI ranging between 0.4 and 0.45. There were associated high velocities at the transplant artery origin which were suspicious of TRA stenosis. A computerized tomography (CT) scan was done which showed a 20 mm × 25 mm pseudoaneurysm arising from the aortic patch and the TRA origin lying adjacent to the pseudoaneurysm was tightly narrowed (Figures 1 and 2). After discussion in the departmental multidisciplinary team meeting and with patient's informed consent, he underwent radiological intervention as described below.

Under ultrasound guidance, the right common femoral artery was punctured, and a 5Fr sheath was inserted. 7500 unit of heparin was administered intravenously. The dimensions of the TRA were confirmed and were found to be like those of CT scan findings. The TRA was catheterized using a size 4Fr Berenstein® catheter and Terumo® wire (Terumo Medical Corporation, United States), subsequently exchanged for a 0.014 Thruway wire (Boston Scientific Inc., Ireland) and was left in situ as a "safety wire". The left common femoral artery was punctured and a 6Fr destination sheath was placed over the aortic bifurcation. Through the ipsilateral 6Fr sheath, a 10 mm percutaneous transluminal angioplasty (PTA) balloon was placed opposite the aneurysm neck. From the 6Fr sheath, a 4Fr Cobra (Cook Medical, United States) and 2/7 Progreat® microcatheter (Terumo Medical Corporation, United States) were used to gain access to the aneurysm sac. Within the right external iliac artery, the PTA balloon was inflated to reduce the risk of coil prolapse and migration and the aneurysm was embolized using two Azur® 20 mm Framing coils (Terumo Medical Corporation, United States), and packed with Azur® Hydrogel Coils. The pseudoaneurysm was filled with coils and hydrogel leading to its complete occlusion. Subsequently, the stenosed transplant RA was stented using a 6 mm × 20 mm Hippocampus stent (Medtronic, United Kingdom), which restored the patency of the stenosed renal artery and normal blood flow (Figure 3).

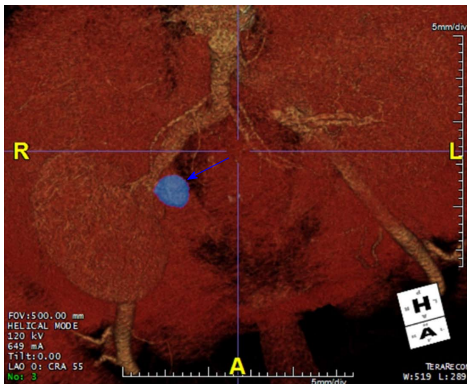

Figure 1 Computerized tomography angiogram showing a 20 mm x 25 mm pseudoaneurysm arising from the aortic patch (blue arrow).

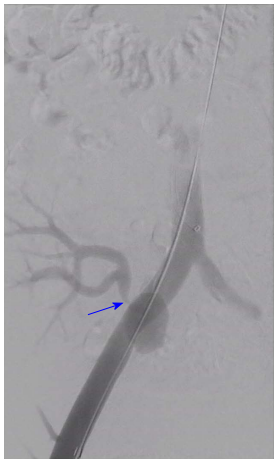

Figure 2 Angiogram showing transplant renal artery stenosis (blue arrow) due to compression caused by the pseudoaneurysm. Guide wire is present within the right common and external iliac artery.

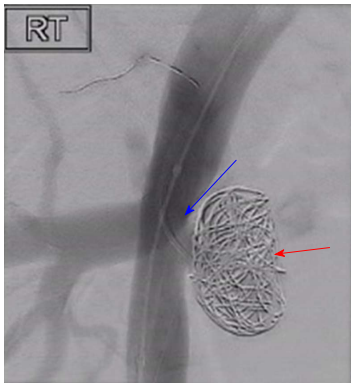

Figure 3 Successful coiling of the pseudoaneurysm (red arrow) and stenting of the transplant renal artery stenosis (blue arrow).

Following embolization of the pseudoaneurysm and stenting of the TRA, improvement in renal function occurred leading to a fall in the serum creatinine level to 159 μmol/L (eGFR 47 mL/min per 1.73 m^2). A follow-up CT angiogram one month after the intervention showed a patent TRA with successful coiling of the pseudoaneurysm and satisfactory position of the stent with no evidence of TRA stenosis. The patient continues to be followed up in the routine RT clinic and has a serum creatinine of 150 μmol/L (eGFR 49 mL/min per 1.73 m^2).

DISCUSSION

Renal Transplantation remains the treatment of choice in end stage renal disease patients. Vascular complications after RT include TRA stenosis, TRA thrombosis, transplant renal vein thrombosis, arteriovenous fistula and TRA pseudoaneurysm[2]. TRA pseudoaneurysm is an uncommon complication and can be classified anatomically as intrarenal or extrarenal based on the involvement of either TRA or iliac artery, respectively. Aetiologically, TRA pseudoaneurysms can be of infective or non- infective origin. Infective pseudoaneurysms are more common and can be of fungal (mycotic) and non-fungal (non-mycotic) origin. Amongst the infective pseudoaneurysms, Candida albicans and Aspergillus species have been reported to be the predominant microorganisms, while Pseudomonas species were the leading cause of non-mycotic infective pseudoaneurysms[2-8]. Non-infective TRA pseudoaneurysms can result from injury to the arterial wall, faulty suture techniques[9-11] or following a biopsy[12,13].

TRA pseudoaneurysms can be asymptomatic[14] or can present with RT dysfunction, fever, pain (mainly at the site of the transplant) or a combination of these presentations. Graft loss is a recognized complication of TRA pseudoaneurysms and sometimes bleeding from the ruptured pseudoaneurysm can lead to hemorrhagic shock or death of the patient[8,15]. Lumbar plexopathy has been reported in a previous literature because of pressure effect of the pseudoaneurysm[16], while malignant hypertension is a rare presentation[17].

The choice of the modality of treatment of TRA pseudoaneurysms depends on several factors including the aetiology, haemodynamic stability of the patient, presentation, anatomy, graft function and the radiological features of the pseudoaneurysm[18-22]. Aneurysms larger than 25 mm, progressive enlargement, deterioration of renal function or presentation with symptoms are the main indications for repair[18]. Treatment modalities include minimally invasive techniques using mainly exclusion stents to the external iliac artery, but this may sacrifice the graft[14]. Ultrasound-guided percutaneous thrombin injection in combination with a covered stent has been reported as a successful way of treating TRA pseudoaneurysm with preservation of renal function[18,19].

Traditional aneurysm coiling in general can be associated with complications such as migration, non-target embolisation, inadequate filling, compaction and the technical difficulty in placing the coils leading to added risk to organs, patients and increase in cost[23].

Expandable hydrogel technology coils have been described to treat intracranial and peripheral pseudo-aneurysms successfully for number of years. The main

advantage of using EHC is related to their superior mechanical occlusion properties resulting in fewer coils deployed and a lower recurrence rate. They are also compatible with imaging modalities[24-26].

In our case, successful radiological and clinical outcomes were achieved with return of serum creatinine to baseline within 48 h of intervention without any complication related to the RT or lower limb. We have employed EHC system to treat TRA pseudoaneurysm, achieved excellent volumetric filling and targeted embolisation and subsequently deployed a stent leading to restoration of transplant renal function to its normality. It offers a new non- invasive technique to treat TRA pseudoaneurysms with preservation of renal grafts; therefore, it should be considered as a first line treatment modality in this clinical situation.

ARTICLE HIGHLIGHTS

Case characteristics

A 38-year-old male, who had received a deceased donor renal transplant presented with deterioration of renal function five months post-transplantation.

Clinical diagnosis

On examination, there were clinical features pointing to definitive diagnosis.

Differential diagnosis

Differential diagnosis included obstructive uropathy, acute rejection, infections, drug nephrotoxicity and transplant renal artery stenosis.

Laboratory diagnosis

The serum creatinine was significantly elevated.

Imaging diagnosis

The Duplex ultrasound scan showed reduced resistive index with high velocity flow in the renal artery suggestive of transplant renal artery stenosis. A computerized tomography angiogram showed a 20 mm × 25 mm pseudoaneurysm at the anastomosis site and stenosis of the transplant renal artery adjacent to the pseudoaneurysm.

Treatment

Endovascular embolisation of the pseudoaneurysm using expandable hydrogel coils (EHC) followed by deployment of stent lead to resolution of the pseudoaneurysm and transplant renal artery stenosis and restoration of renal function to normality.

Related reports

Follow-up of the patient was satisfactory with no adverse events related to the procedure.

Experiences and lessons

This is the first reported case of treatment of a transplant renal artery pseudoaneurysm with wide neck with the use of EHC leading to successful outcomes.

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