

# Liver-Kidney Transplantation to Cure Atypical Hemolytic Uremic Syndrome

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## ABSTRACT

Atypical hemolytic uremic syndrome is often associated with mutations in genes encoding complement regulatory proteins and secondary disorders of complement regulation. Progression to kidney failure and recurrence with graft loss after kidney transplantation are frequent. The most common mutation is in the gene encoding complement factor H. Combined liver-kidney transplantation may correct this complement abnormality and prevent recurrence when the defect involves genes encoding circulating proteins that are synthesized in the liver, such as factor H or I. Good outcomes have been reported when surgery is associated with intensified plasma therapy. A consensus conference to establish treatment guidelines for atypical hemolytic uremic syndrome was held in Bergamo in December 2007. The recommendations in this article are the result of combined clinical experience, shared research expertise, and a review of the literature and registry information. This statement defines groups in which isolated kidney transplantation is extremely unlikely to be successful and a combined liver-kidney transplant is recommended and also defines those for whom kidney transplant remains a viable option. Although combined liver-kidney or isolated liver transplantation is the preferred therapeutic option in many cases, the gravity of risk associated with the procedure has not been eliminated completely, and assessment of risk and benefit requires careful and individual attention.

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Hemolytic uremic syndrome (HUS) is a rare disease of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Typical HUS follows a diarrheal illness caused by a verocytotoxin-producing bacterium, commonly *Escherichia coli* O157:H7, and resolves in most cases without sequelae.<sup>1</sup> Atypical HUS (aHUS) is much less common and has a considerably worse prognosis in terms of both mortality and development of ESRD.<sup>2</sup>

Mutations in genes encoding complement regulatory proteins and secondary disorders of complement regulation seem to play a central role in the pathogenesis of most cases of aHUS. Triggering of an unregulated complement cascade is thought to damage endothelium, producing microangiopathic hemolytic anemia and thrombosis. Gene mutations

are identified in at least 50% of cases. The most frequently reported mutations are in the gene encoding complement factor H (*CFH*) and account for 50 to 60% of cases associated with documented genetic abnormalities. Less frequent are mutations in the genes encoding membrane co-factor protein (*MCP*) and complement factor I (*CFI*) and are observed in approximately 20% and 10 to 15% of the overall disease-associated mutations, respectively.<sup>3–6</sup>

More recently, gain-of-function mutations in the genes encoding the complement-activating protein complement factor B (*CFB*) as well as complement C3 (*C3*) have been reported in a few cases with aHUS.<sup>7,8</sup> Antibodies against factor H have also been observed in patients with aHUS, particularly children, and in

most cases in association with homozygous deletion of the genes encoding complement factor H–related proteins 1 and 3 (*CFHR1* and *CFHR3*).<sup>9</sup> Indeed, there is a growing list of the mutations, polymorphisms, and other complement abnormalities that alone or in combination may lead to aHUS.<sup>8–13</sup>

## KIDNEY TRANSPLANTATION AND RISK FOR DISEASE RECURRENCE

Compared with patients with typical HUS, those with aHUS also have worse outcomes after kidney transplantation, largely because of the high rates of disease recurrence.<sup>14,15</sup> The disease recurs in nearly 80% of transplant recipients with *CFH* mutations, and recurrences are usually associated with graft loss.<sup>2,16,17</sup> Although the data are more limited because of a lower frequency of cases, similar rates of recurrence and graft loss after transplantation are reported in aHUS associated with a *CFI* mutation. Indeed, nine of 10 renal transplants in six patients with a *CFI* mutation were complicated by early recurrence and graft loss. The exceptional patient without early recurrence had a functioning graft for 11 yr. This patient then also lost the graft to recurrent disease and received a second transplant with no recurrence at 2 yr after transplantation.<sup>3,5,6</sup> Data regarding cases of

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aHUS related to *CFB*<sup>8</sup> or *C3* mutations<sup>7</sup> are emerging and suggest these patients are also at risk for recurrence; however, outcome data are insufficient to be used as the basis for clinical recommendations.<sup>13</sup>

Mutations in *CFH*, *CFI*, *CFB*, and *C3* all lead to abnormalities in circulating complement components that are mainly produced by the liver. These abnormalities will persist after a kidney transplantation, and this may explain the very high rate of recurrences in these patients. In contrast, MCP is a transmembrane protein expressed by nearly all cell types, highly so in the kidney, where it functions locally to limit complement activity. This may explain why among individuals with aHUS secondary to MCP mutation, recurrence is unusual after transplantation of kidneys that, presumably, express normal MCP.<sup>18</sup>

The risk for aHUS recurrence after isolated kidney transplantation is more difficult to quantify in those rare cases with combined mutations in two or even three different complement genes. We are aware of five such cases, in which outcomes after transplantation were, not surprising, varied. Two patients with combined heterozygous mutations, one involving *MCP/CFH* and the other involving *MCP/CFI*, had uneventful transplants without recurrences (International Registry of HUS and TTP, unpublished data). Seitz *et al.*<sup>19</sup> reported two other patients with combined *MCP/CFH* mutations (patients 3 and 7) and one patient with three mutations involving *MCP*, *CFH*, and *CFI* (patient 8) who had aHUS recurrence; all received intensive plasma exchange, which allowed graft recovery in patients 3 and 8 but did not prevent graft loss in patient 7. One reported patient with *CFH/CFI* mutation had no recurrence through 5 yr after transplantation.<sup>20</sup>

## EMERGENCE OF LIVER TRANSPLANTATION TO PREVENT RECURRENCE

Liver transplantation corrects the complement abnormality and prevents disease recurrence in patients with defects in genes encoding circulating complement proteins

that are synthesized in the liver. With this rationale, a patient with recurrent aHUS and CFH deficiency received an auxiliary partial orthotopic liver to restore CHF bioavailability. Factor H plasma levels progressively increased and were persistently close to normal range from the eight post-transplantation day. During the subsequent 7 mo, the child developed posttransplantation lymphoproliferative disease, renal failure with pancytopenia, and red cell aplasia, a clinical scenario in which aHUS recurrence could not be excluded. Eventually, the patient succumbed to pneumonia and bacterial sepsis 11 mo after transplantation.<sup>21,22</sup>

In other patients with aHUS and ESRD, combined liver-kidney transplantation was explored as a way both to restore renal function and to prevent recurrence of aHUS related to a *CFH* mutation. The first report was about a child who had recurrent disease and was at imminent risk for death because he had no further vascular access for extracorporeal dialysis and the efficiency of peritoneal dialysis was rapidly declining. The child received an orthotopic split liver transplant followed by a kidney transplant from the same deceased donor. Kidney function promptly recovered, but, after an initial improvement, liver function progressively deteriorated and the child developed severe hepatic encephalopathy. A liver biopsy showed changes consistent with humoral hyperacute rejection. A second liver transplant was undertaken a few days later and was followed by prompt recovery of liver function, but the neurologic abnormalities only partially improved. On subsequent follow-up, the child had no sign of hemolysis or disease recurrence but died 3 yr later as a result of the neurologic sequelae.<sup>23</sup> Regardless of the unfortunate outcome, this was the first evidence that aHUS associated with a complement abnormality could be cured by combined liver-kidney transplantation. The clinical course of the second reported case was also complicated by irreversible liver failure with a fatal outcome just after transplantation. At autopsy, the liver showed widespread microvascular thrombosis with diffuse deposition of IgG, IgM, and

complement membrane attack complex in liver sinusoids consistent with complement activation.<sup>24</sup> It was conjectured that the surgical stress with liver ischemia and reperfusion might have induced intense local complement activation that could not be regulated, as occurs normally, as a result of the deficiency in functional CFH. A reassessment of the histology material suggested that similar mechanisms might have been involved in the liver graft failure that complicated the course of the previously reported case.<sup>23</sup> Thus, combined liver-kidney transplantation seems to be an effective approach to prevent disease recurrence but is associated with an unexpected and unacceptable risk for premature and irreversible liver failure secondary to uncontrolled complement activation.

After these initial reports, a modified approach to combined liver-kidney transplantation that demonstrated no acute hepatic events and good long-term outcome was developed for a young child who had ESRD and whose other clinical options had been nearly exhausted. The pivotal modification was to exchange large quantities of plasma before transplantation with further plasma supplementation during the procedure. This both increased the bioavailability of functional factor H during the critical period needed for the liver graft to recover synthetic functions and, at the same time, removed the endogenous mutant CFH preventing possible antagonism of normal CFH supplied with plasma.<sup>25</sup> The modified, combined liver-kidney transplant procedure also included empiric use of low molecular weight heparin and low-dosage aspirin to counteract the potential increased thrombogenicity associated with allograft endothelial activation and the additional clotting factors in the infused plasma. A second transplant in another child with a *CFH* mutation at the same center was also successful; in that case, a split liver graft was used.<sup>26</sup> The technique was successfully adopted, with few modifications, by a second center that also reported success with two children<sup>27</sup> and an adult patient (H. Jalanko, University Hospital for Children and Adolescents,

Helsinki, Finland, December 15, 2007) all with *CFH* mutations.

After the success of the initial combined transplants undertaken with this modified protocol, a Consensus Conference on Kidney and Liver Transplantation in Atypical Hemolytic Uremic Syndrome was held in December 2007 to discuss this emerging procedure. The aim was to develop recommendations that would enable more widespread use of liver transplantation. Since the conference, a third center has used the technique to perform an isolated liver transplant in a child who had a *CFH* mutation and whose renal function had been maintained with long-term plasma therapy (D. Milford, The Children's Hospital, Birmingham, England, February 16, 2008) as well as a fourth center that undertook a combined liver-kidney transplant in a dialysis-dependent child with a *CFH* mutation (L. Milner, Floating Hospital for Children at Tufts University Medical Center, Boston, MA, May 9, 2008). These transplants have been uncomplicated to date. Most recently, a combined transplant for a child with imminent ESRD resulted in death. This was undertaken without additional modification at the center that developed the revised technique. Severe hemodynamic instability developed upon portal vein clamping. Additional plasma exchange treatments were provided, and although some postoperative improvement in liver function was noted, hepatic artery thrombosis occurred, followed by fatal hepatic encephalopathy. Histopathologic examination of hepatic graft excluded both thrombotic microangiopathy and hyperacute rejection; there was no deposition of C3 or Igs, although rare C1q and fibrinogen staining of central veins was present. Renal graft biopsy

demonstrated acute tubular necrosis without aHUS. Although the experience since the conference has included this one fatal outcome, there remains consensus that this procedure, with proper consideration of individual risks and benefits, offers the best opportunity for long-term transplant success.

## CONSENSUS RECOMMENDATIONS

What follows is the approach adopted by the consensus conference.

### Recommendation 1: Initial Diagnosis and Management of aHUS

On the basis of a recent classification strategy<sup>1</sup> and in agreement with recommendations made by the European Pediatric Study Group for HUS,<sup>28</sup> Table 1 presents criteria to identify patients whose initial presentation with HUS is atypical. As shown in Table 1, we recommend investigation and empiric treatment for all patients who present with certain atypical features, *regardless* of whether they have typical signs such as a prodromal diarrheal illness or evidence of sepsis/pneumonia caused by *Streptococcus pneumoniae*. We also recommend investigation and empiric treatment if none of those atypical features is present but typical features are absent. We are of the opinion that this pragmatic approach will not only identify patients who are most likely to have an underlying complement disorder but also increase the chance of a response to treatment.

#### Empiric Treatment.

For patients who satisfy these criteria, plasma exchange should be commenced

as soon as a diagnosis of aHUS is established and continued as in the recommendations in Table 2. We emphasize prompt empiric plasma exchange because clinical deterioration and irreversible renal or extrarenal manifestations may occur very rapidly.

#### Genetic Studies.

In conjunction with empiric management, accurate diagnosis of the disorder is critical and can be optimized by directed laboratory analyses, some that are widely available and some that are available only in specialized laboratories (Table 3). Genetic screening for *CFH*, *CFI*, *MCP*, *CFB*, and *C3* mutations is indicated for the patient. Screening of available relatives may provide information about the pathogenicity of any mutations identified and highlight important coincident risk haplotypes in related genes; however, the benefits and risks of such screening should be carefully discussed before this is undertaken. Screening of all exons is recommended rather than "hot spot" analysis. Analysis of the copy number of the *CFHR1* and *CFHR3* genes should be considered, particularly when anti-*CFH* antibodies are detected. Accurate genetic diagnosis is essential if patients are to be considered for combined liver and kidney transplantation, liver transplantation, or isolated kidney transplantation. Finally, a rapid pace of discovery means the list of related genes is likely to expand in the future, and, as has occurred with previous<sup>13,29</sup> screening recommendations, future updates will be required.

#### Referral to aHUS Registry.

Enrollment of patients into national or international registries for the study of aHUS is encouraged for affected families. It is this voluntary participation and international collaboration that has produced the current knowledge base about this condition and thus enabled the development of these consensus recommendations. It is hoped that registry participation will lead to further improvement in the understanding and treatment of this rare illness.

**Table 1.** Criteria for empiric plasma therapy treatment of aHUS

Presence of any of the Following	or	Absence of the Following
Patient age <6 mo		Prodromal diarrhea
Slow or insidious onset of HUS		Invasive <i>Streptococcus pneumoniae</i> infection
Multiple HUS episodes or relapses		
Associated family history of HUS		
Previous unexplained anemia		
HUS after any type of organ transplantation		

**Table 2.** Recommended treatment of a patient presenting with aHUS on the basis of forthcoming recommendations from European Society of Pediatric Nephrology regarding management of cases of aHUS<sup>a</sup>

Before plasma exchange
measure C3 and C4 plasma levels in local laboratories
send/save EDTA plasma samples for factor H, factor I, MCP, anti-factor H antibodies, C3d
send/save plasma samples for measurement of ADAMTS13 activity (if TTP is not ruled out)
Commence plasma exchange within 24 h of diagnosis
one plasma volume is exchanged per session
five daily exchanges are followed by five sessions per week for 2 wk, then three sessions per week for 2 wk, with further treatment determined on a case-by-case basis.
Encourage enrollment in national or international registries

<sup>a</sup>See text for definition. TTP, thrombotic thrombocytopenic purpura.

**Table 3.** List of genetic and biochemical tests and laboratories conducting the tests

Target	Test	Method	Laboratory <sup>a</sup>
CFH and CFH related			
<i>CFH</i> gene	Coding sequence analysis	Direct sequencing	1, 2, 3, 4, 5, 6, 7, 8
	CFH-CFHR1 hybrid gene	MLPA	2, 3, 4, 5, 6
	CFHR1-CFHR3 deletion/duplication	MLPA/PCR	2, 3, 4, 5, 6
CFH protein	CFH serum levels	ELISA/RID	1, 2, 3, 4, 5, 8
	Anti-CFH antibodies	ELISA	2, 3, 4, 5, 8
	CFH activity	Hemolytic assay	3, 4, 5, 6, 8
CFHR1 protein	CFHR1-CFHR3 in serum	Western Blot	1, 2, 3, 4, 5
	CFHR1 serum levels	ELISA	5
MCP			
<i>MCP</i> gene	Coding sequence analysis	Direct sequencing/MLPA	1, 2, 3, 4, 5, 6, 7, 8
MCP protein	MCP expression on leukocytes	FACS	1, 2, 3, 4, 5, 8
CFI			
<i>CFI</i> gene	Coding sequence analysis	Direct sequencing	1, 2, 3, 4, 6, 7, 8
CFI protein	CFI serum levels	ELISA	1, 2, 3, 4, 5, 8
CFB			
<i>CFB</i> gene	Coding sequence analysis	Direct sequencing	1, 2, 3, 4, 5, 6, 7, 8
CFB protein	CFB/Bb serum levels	ELISA/RID/nephelometry	1, 3, 4, 5, 8
C3			
C3 gene	Coding sequence analysis	Direct sequencing	1, 2, 3, 4, 5, 6, 7, 8
C3 protein	C3/C3a/C3d in serum, plasma	ELISA, nephelometry	1, 2, 3, 4, 5, 6, 8

<sup>a</sup>1, Mario Negri Institute, Clinical Research Center for Rare Diseases, Dr. Marina Noris (Italy); 2, University of Newcastle-upon-Tyne, Institute of Human Genetics, Dr. Tim Goodship (United Kingdom); 3, Hôpital Européen Georges Pompidou, Immunology Department, Dr. Véronique Frémeaux-Bacchi (France); 4, Centro de Investigaciones Biológicas and University Hospital La Paz, Drs. Santiago Rodríguez de Córdoba and Pilar Sanchez-Corral (Spain); 5, Leibniz Institute for Natural Product Research and Infection Biology, Department of Infection Biology, Dr. Peter Zipfel (Germany); 6, University of Iowa, Molecular Otolaryngology Research Laboratories, Dr. Richard Smith (USA); 7, Center for Nephrology and Metabolic Disorders, Laboratory for Molecular Diagnostics, Dr. Mato Nagel (Germany); 8, Department of Pediatrics, BMC C14, Lund University, Dr. Diana Karpman (Sweden). MLPA, multiplex ligation-dependent probe amplification; RID, radial immunodiffusion.

### Bilateral Nephrectomy.

Bilateral nephrectomy should be considered when there is severe refractory malignant hypertension and/or ongoing evidence of disease activity (persistent hemolysis and thrombocytopenia) in dialysis-dependent patients despite treatment with plasma exchange.

### Recommendation 2: Combined Liver-Kidney Transplantation or Isolated Liver Transplantation

Patients who have ESRD and a *CFH* or *CFI* mutation should be considered for combined liver-kidney transplantation

because of the high risk for graft loss to disease recurrence. Isolated liver transplantation should be considered for patients who have a *CFH* or *CFI* mutation and have recovered native renal function after one or more episodes of aHUS (Table 4). Registry data show that age of onset, clinical features, and complement levels do not affect the risk for disease recurrence in patients with a *CFH* mutation.

Published reports<sup>2,10,30–34</sup> and unpublished data from the International Registry of HUS and TTP indicate that mutations affecting the first 15 short

consensus repeats of *CFH* are associated with a lower risk for recurrence and/or acute graft loss (four [44%] of nine grafts failed) than mutations affecting the last short consensus repeats 19 through 20 (25 [76%] of 33 grafts failed). Because the various international and national registries continue to acquire mutation-specific and potentially clinically important information, it is recommended that for each individual, especially individuals for whom transplantation is considered, an inquiry of such a registry be made to acquire an accurate view of current knowledge. Nonetheless, because

**Table 4.** Eligibility for combined liver and kidney transplant or liver transplant alone

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<i>CFH</i> or <i>CFI</i> mutation with the exceptions listed in Table 7
Less than 10% normal <i>CFH</i> levels in plasma
Patients who have identified mutations of genes encoding and
have aHUS recurrence after isolated kidney transplantation or
have a family member who had the same mutation and had aHUS recurrence after isolated kidney transplantation
HUS recurrence after isolated kidney transplantation in patients with identified mutations of genes that may have both hepatic and
nonhepatic sites of expression and protein synthesis (see Table 7)

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the vast majority of individuals with *CFH* or *CFI* mutations are at very high risk for recurrence and graft loss,<sup>10</sup> combined liver-kidney transplantation or liver transplantation should be considered for individuals with *CFH* or *CFI* mutations when the risk for recurrence associated with their specific mutation cannot be inferred on the basis of registry inquiry.

Special consideration should be given to patients who have a *CFH* or *CFI* mutation and have aHUS but have preserved renal function through intermittent plasma therapy. We note that such patients have maintained a reasonable quality of life with individualized plasma therapy over an extended period of time. Although no other treatments are available, biologicals blocking complement activity, such as eculizumab, and purified factor H (yet to be developed) are major agents of interest. Although there is no knowing whether the future will find those agents either safe or effective, it is possible that intermittent plasma therapy over several years may provide time for such new treatments to reach the clinical arena. Unfortunately, the literature suggests at best variable response to plasma therapy,<sup>35–37</sup> and the combined clinical experience of the authors suggests that there is a high risk for progression to ESRD over several years for those using this treatment strategy; therefore, it is reasonable to consider isolated liver

transplantation as an option for such patients to preserve native kidney function.

For patients who have had one or more episodes of aHUS but do not have ESRD, the degree of chronic kidney disease that is present should be established before the decision to recommend a liver transplantation alone *versus* combined liver-kidney transplantation is made. Although the literature does not paint a clear picture of the long-term risk to renal function after isolated liver transplantation,<sup>38,39</sup> having experienced one or more episodes of aHUS must be considered a risk factor for chronic renal insufficiency after liver transplantation; therefore, in cases in which there is evidence of chronic kidney disease, we recommend that a renal biopsy be undertaken before isolated liver transplantation. Significant histologic abnormalities, in conjunction with the prospect of future nephrotoxicity as a result of post-transplantation use of calcineurin inhibitors, may reasonably indicate a high risk for short-term kidney failure and should be an indication for a combined transplant.

Because our understanding of aHUS is incomplete, we present in Table 5 situations in which it is not possible currently to make a recommendation for or against combined liver-kidney transplantation, liver transplantation, or isolated kidney transplantation. The num-

ber of patients who have combined mutations in two or three different complement genes and have had kidney transplantation is too few and the outcomes too varied to make a definitive recommendation for a first transplantation; however, combined transplantation is recommended for such patients if they have already experienced aHUS recurrence after isolated kidney transplantation. Patients with *CFHR1-CFHR3* deletion with or without anti-*CFH* antibodies have unknown rates of success after isolated kidney transplantation.

Whether combined liver-kidney transplantation should be recommended for patients with *C3* or *CFB* mutations is unclear. Although *C3* is predominantly synthesized in the liver,<sup>40</sup> there is concern there may still be sufficient extrahepatic production of mutant protein for a patient to remain at risk for recurrent renal disease after a combined transplant. This is because the majority of individuals with aHUS-associated *C3* mutations have gain-of-function mutations<sup>7</sup> and even residual mutant protein could prove pathogenic.

Whether the liver is the exclusive site of factor B production is also unclear, but the clinical phenotype of patients with aHUS related to a *CFB* mutation suggests the operative risk of a combined liver-kidney transplant may be greater. Cerebrovascular disease, vasoactive phenom-

**Table 5.** Criteria for which currently available information is insufficient to indicate a specific recommendation for or against liver transplantation or combined liver and kidney transplantation *versus* isolated kidney transplantation

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<i>C3</i> mutation <sup>a</sup>
<i>CFB</i> mutation <sup>a</sup>
Combined mutations among <i>MCP</i> , <i>CFI</i> , and <i>CFH</i> <sup>b</sup>
<i>CFHR1-CFHR3</i> deletion without anti-FH autoantibody <sup>b</sup>
Low-risk <i>CFH</i> or <i>CFI</i> mutation as defined by mutations already reported to the registry as not being associated with recurrence after isolated renal transplantation <sup>b</sup>

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<sup>a</sup>Current knowledge is insufficient to presume liver transplantation would correct complement regulation.

<sup>b</sup>Evidence is sufficient to support liver or combined liver-kidney transplantation for such individuals if they or a family member with the same mutation experienced aHUS recurrence after isolated kidney transplantation.

ena, and other potential vascular abnormalities have been reported in unrelated individuals with *CFB* mutations<sup>8</sup> (C. Loirat, Rovert Debré Hospital, Paris, France, December 15, 2007). These features may require further investigation to determine the risk of combined transplantation. Moreover, plasma infusion and plasma exchange with fresh-frozen plasma (FFP) in patients with a gain-of-function *CFB* mutation induce increased complement activation, presumably because additional complement substrate is provided in the continued presence of active mutant *CFB*. At this stage, there is no solution to this issue; however, a potential approach is to provide plasmapheresis with albumin replacement to deplete the mutant *CFB*, followed by plasma exchange with FFP. Additional plasma exchanges with FFP would be required to maintain the effect. The effectiveness and duration of this approach are unknown and will likely vary from patient to patient.

### Recommendation 3: Surgical and Perioperative Management

In contrast to the poor results of isolated kidney transplantation, the outcome of isolated liver or combined liver-kidney transplantation performed using the guidelines in Table 6 have been successful in seven of eight cases. These preliminary outcome results are consistent with the 3-mo (85% pediatric, 92% adult) and 1-yr (85% children, 85% adult) patient survival rates after combined liver-kidney transplantation for other indications.<sup>41</sup> Thus, despite the limited experience, it is possible to recommend, with appropriate consideration of individual risk and benefit, that this approach be used for all patients receiving a combined liver-kidney transplant or a liver transplant alone according to the criteria listed in Table 4.

#### *Intensified Plasma Therapy.*

We emphasize strongly the importance of preoperative plasma exchange and intraoperative plasma infusion. These to-

gether allow the depletion of mutant complement regulators and replenish wild-type regulators, thereby facilitating control of the complement activation associated with the surgical procedure.<sup>42,43</sup> It is likely that individual variability in the amount of plasma required to control complement activation and clinical circumstances may dictate that more be used than recommended in this statement. The amount of required plasma may also depend on how long it takes for the transplanted liver to establish its synthetic function and the rate of synthesis of complement regulatory proteins. Patients with surgical complications leading to prolonged warm ischemia and delayed liver graft function will probably require more plasma over an extended period.

#### *Anticoagulation.*

Anticoagulation was used in each of the successful procedures to date. Because of this and because it was recently established that the coagulation pathways

**Table 6.** Guidelines to surgery and perioperative treatment of patients receiving a combined liver and kidney transplant or a liver transplant alone<sup>a</sup>

Dialysis <sup>b</sup>	better before plasma exchange in all cases mandatory before plasma exchange in cases with evidence of complement activation (e.g., angioedema) during dialysis
Plasma exchange <sup>b</sup>	a minimum of 1.5 Vol of FFP is exchanged within 4 to 6 h of surgery exchange must be repeated if surgery is delayed
Plasma infusion	10 to 20 ml/kg body wt FFP is infused intraoperatively after native hepatic explant additional plasma may be given as clinical need dictates
Surgery	split or whole liver transplantation is indicated adequate liver mass must be provided (minimum 2% liver to recipient mass ratio) auxiliary liver transplantation is not recommended living-related donation is not recommended
Monitoring	posttransplantation liver function should be judged by coagulation profile in cases of inadequate liver function, plasma exchange in conjunction with standard care is indicated <sup>c</sup>
Posttransplantation anticoagulation <sup>d</sup>	low molecular weight heparin at prophylactic dosages (e.g., enoxaparin 0.5 mg/kg twice daily) aspirin (2 mg/kg per d up to 80 mg/d) to be continued for 3 mo
Immunosuppression	per standard practice of each center mTOR inhibitors are not encouraged

mTOR, mammalian target of rapamycin.

<sup>b</sup>Dialysis and plasma exchange should be completed within 5 h.

<sup>c</sup>Liver dysfunction in this setting may be atypical and related to vascular damage, not hepatocellular dysfunction alone.

<sup>d</sup>May be held in the setting of clinical contraindications.

**Table 7.** Eligibility for isolated kidney transplantation

No evidence of <i>CFH</i> , <i>CFI</i> , <i>CFB</i> , or <i>C3</i> gene mutations
<i>MCP</i> mutation
Mutations associated with successful isolated kidney transplantation in affected family members <sup>a</sup>
Anti-factor H autoantibodies

<sup>a</sup>Conversely, combined liver and kidney transplantation is recommended (see Table 5) for patients who have certain gene mutations and (1) have aHUS recurrence after isolated kidney transplantation or (2) have a family member who had the same mutation and had aHUS recurrence after isolated kidney transplantation.

themselves activate complement, we recommend continued use of anticoagulation using a standard prophylactic regimen as detailed in Table 6.<sup>25–27,44</sup>

#### *Surgical Procedure.*

Although both split and whole liver grafts have been used with success, we recommend a minimum graft mass of 2% of the recipient's mass. We do not recommend auxiliary grafts for the following reasons. First, hepatic graft rejection might not be clinically apparent yet abruptly result in recurrent aHUS. Second, without removing the source of mutant proteins from the native liver, one cannot be certain that the continued presence of mutant complement proteins will not interfere with the function of wild-type protein.<sup>45,46</sup>

#### *Immunosuppression.*

The consensus statement makes no specific recommendations about immunosuppression protocols. In particular, aHUS is not considered *per se* a specific contraindication to treatment with calcineurin inhibitors; however, initial immunosuppression with mammalian target of rapamycin inhibitors is not encouraged in the absence of

clear clinical advantages because of the possible association with impaired wound healing and delayed graft function.<sup>47</sup>

#### **Recommendation 4: Use of Isolated Kidney Transplantation**

At present, there is no scientific rationale for liver transplantation for patients with no mutations identified in any of the aforementioned complement genes (Table 7). A small minority of patients with *CFH* or *CFI* mutations may reasonably be offered isolated kidney transplantation. These exceptional patients include those who have affected family members (with the same mutation) who have had a successful isolated kidney transplant or patients who carry an isolated mutation known from data recorded in the international registries to be at “lower risk” for posttransplantation recurrence. A preliminary report from the French cohort described a successful kidney transplant without recurrent aHUS in a young child with anti-*CFH* autoantibodies,<sup>48</sup> and there seems to be little reason to suggest that liver transplantation *per se* would benefit such patients. Rather, an antibody-depleting strategy such as the one reported is recommended.

#### *Plasma Therapy.*

On the basis of expert opinion, prophylactic plasma therapy is recommended preoperatively, postoperatively, and under certain clinical conditions outlined in Table 8 for patients for whom isolated kidney transplantation is undertaken. This recommendation reflects the report of a child who had ESRD secondary to familial aHUS and a *CFH* mutation and underwent successful kidney transplantation followed by long-term prophylactic plasma exchange.<sup>35</sup> Two recurrences of aHUS occurred in association with cytomegalovirus infections, but remission was achieved in each instance with increased frequency of plasma exchange.<sup>33</sup> If aHUS does recur after isolated kidney transplantation, then we recommend that liver or liver-kidney transplantation be performed. In addition, genetic analysis should be repeated for patients who have an unsuccessful isolated kidney transplantation as a result of aHUS recurrence. Patients and clinicians are encouraged to update national and international registries after transplantation to guide management of future cases.

#### *Living-Related Donors.*

We strongly recommend that organ donation from related individuals be avoided even if the presence of known mutations in the donor is excluded. This is because the full host of complement-related genes and mutations associated with disease has not been elucidated. As suggested by genetic analysis of families, most aHUS-associated mutations have an incomplete penetrance, and healthy related carriers are frequently

**Table 8.** Guidelines to perioperative treatment and follow-up of patients receiving an isolated kidney transplant

Dialysis
better before plasma exchange in all cases
mandatory before plasma exchange in cases with signs of complement activation (e.g., angioedema) during dialysis
Plasma exchange
a minimum of 1.5 Vol of FFP is exchanged within 4 to 6 h of surgery
exchange must be repeated if surgery is delayed and within 24 h after transplantation
therapy is continued following the same schedule as for patients initially presenting with aHUS (see Table 1).
in the setting of postoperative complications (e.g., surgical revision, delayed graft function, rejection) or for definitive recurrence of HUS,
plasma exchange is instituted and following the same schedule as for patients initially presenting with aHUS (see Table 2)
anti-factor H antibodies, if present, must be depleted to very low levels; additional immunosuppression may be indicated (see text and reference <sup>48</sup> )
Monitoring
close monitoring for early detection of recurrent HUS, particularly in the setting of acute illness or surgery, is recommended

identified.<sup>3</sup> There is a remote likelihood that such mutations may be present even in unrelated donors; therefore, for patients who have the characteristics listed in Table 7 and undergo isolated kidney transplantation, when possible, we recommend genetic screening of donors through the registry to exclude healthy carriers of known mutations and for the purpose of future categorization of additional risk haplotypes among complement-related genes.

## CONCLUSIONS

The recommendations of our consensus conference are the result of combined clinical experience, shared research expertise, and a review of the literature and registry information. The statement defines groups for whom isolated kidney transplantation is extremely unlikely to be successful as a result of disease recurrence and for whom a combined liver transplant is recommended and also defines those for whom kidney transplantation remains a viable option. The gravity of risk associated with liver or combined transplantation as a clinical procedure has not been eliminated completely, and that assessment of risk and benefit requires careful and individual attention. Nonetheless, in contrast to early experience, the success of the protocol and approach outlined in this statement shows that combined liver-kidney transplantation or isolated liver transplantation is the preferred therapeutic option in many cases.

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## DISCLOSURES

None.

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