American Journal of Transplantation 2010; 10: 1517–1523
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03156.x

Minireview

Thrombotic Microangiopathy After Kidney Transplantation

M. Noris[a,*] and G. Remuzzi[a,b]

[a] *Clinical Research Center for Rare Diseases 'Aldo e Cele Daccò', Mario Negri Institute for Pharmacological Research, Ranica, Bergamo, Italy*
[b] *Division of Nephrology and Dialysis, Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo, Italy*
**Corresponding author: Marina Noris, marina.noris@marionegri.it*

Thrombotic microangiopathy (TMA) is a severe complication of kidney transplantation that often causes graft failure. TMA may occur *de novo*, often triggered by immunosuppressive drugs and acute antibody-mediated rejection, or recur in patients with previous history of hemolytic uremic syndrome (HUS). Recurrent TMA is very rare in patients who had developed end-stage renal failure following HUS caused by Shiga-toxin producing *E. scherichia coli*, whereas disease recurrence is common in patients with atypical HUS (aHUS). The underlying genetic defect greatly impacts the risk of posttransplant recurrence in aHUS. Indeed recurrence is almost the rule in patients with mutations in genes encoding factor H or factor I, whereas patients with a mutation in membrane-cofactor-protein gene have a good transplant outcome. Prophylactic and therapeutic options for posttransplant TMA, including plasma therapy, combined kidney and liver transplantation and targeted complement inhibitors are discussed in this review.

Key words: Complement activation, hemolytic uremic syndrome, kidney transplantation, thrombotic microangiopathy

Received 23 March 2010, revised 05 May 2010 and accepted for publication 06 May 2010

Thrombotic microangiopathy (TMA) defines a histopathological lesion of vessel wall thickening (mainly arterioles or capillaries), intraluminal platelet thrombosis and obstruction of the vessel lumina. Consumption of platelets and erythrocytes occurs in the microvasculature of kidney, brain and other organs, which causes laboratory features of thrombocytopenia and microangiopathic hemolytic anemia. Depending on whether brain or renal lesions prevail, two clinical entities have been described: the thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome (HUS) (1).

The Hemolytic Uremic Syndrome

HUS is rare, with a worldwide incidence of about 2 cases/year/10 0000 people. In about 90% of childhood cases HUS is caused by strains of *E. coli* (STEC) that produce Shiga-like toxins (Stx) and cause a hemorrhagic colitis. Stx-HUS usually recovers completely upon supportive therapies although long-term renal sequelae have been reported (1).

There are rare atypical forms, which are unrelated to STEC and account for less than 10% of cases (aHUS). These forms can occur sporadically or within families. The clinical outcome of aHUS is unfavorable (1). About 50% of cases progress to end-stage renal disease (ESRD) and up to 25% may die during the acute phase.

Complement Abnormalities in Atypical HUS

Complement activation is involved in the immediate defense against microbes and occurs by three pathways: the classical, the lectin and the alternative pathways, all converging at the cleavage of C3. The activation of the classical and lectin pathways occurs after binding of complement components to immune-complexes or microorganisms, respectively, whereas the alternative pathway is continuously activated in plasma and generates C3b, which binds indiscriminately to pathogens and host cells (Figure 1). On pathogens, C3b forms the C3 convertase that provides exponential cleavage of C3, and the C5 convertase that leads to the lytic membrane-attack complex. On host cells, complement activation is controlled by membrane-anchored and fluid-phase regulators, favoring the inactivation of C3b and dissociating the C3 and C5 convertases (Figure 1).

In the last 12 years, a clear link has been established between aHUS and abnormal activation of the alternative complement pathway.

Overall 40–50% of patients carry loss-of-function mutations in genes coding for the complement regulators, factor H (CFH), membrane-cofactor protein (MCP) and factor I (CFI) (Table 1). In 6–10% of cases, mainly children, autoantibodies against CFH were found that cause functional CFH deficiency. Most patients with anti-CFH antibodies have a homozygous deletion of genes for factor H-related proteins

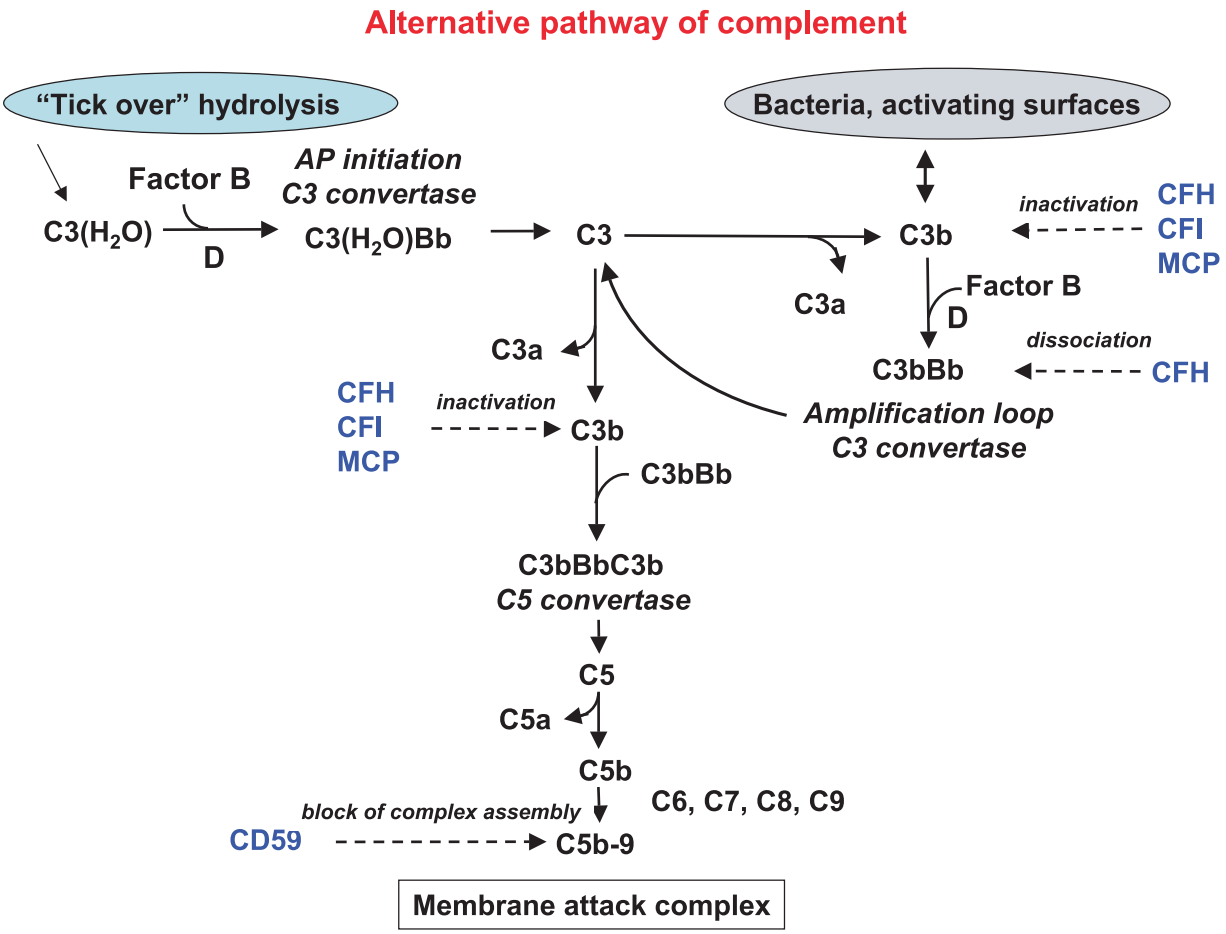

Figure 1: The alternative pathway of complement. The alternative pathway is continuously activated in plasma by low-grade hydrolysis of C3. The latter binds factor B. Factor D cleaves factor B to form the alternative pathway initiation C3 convertase that cleaves C3 to C3b. The activation is then amplified by the covalent binding of C3b to hydroxyl groups on cell-surface carbohydrates and proteins of target cells, such as bacterial cells. This C3b binds factor B, to form the amplification loop C3 convertase C3bBb that cleaves many molecules of C3 to form the anaphylatoxin C3a and C3b resulting in a positive feedback amplification loop. C3b also forms the C5 convertase enzyme $C3b_2Bb$ that cleaves C5 to C5a and C5b. The latter then initiates the formation of the membrane-attack complex. A number of membrane-anchored and fluid-phase regulators inactivate complement products formed at various levels in the cascade and protect host tissues. CFB, complement factor B; CFI, complement factor I (degrades C3b and C4b); CFH, complement factor H (acts as a cofactor for factor I for C3b cleavage and favors the decay of the C3 convertase); MCP, membrane cofactor protein (binds C3b and has cofactor activity); CD59, protectin (prevents the terminal polymerization of the membrane attack complex).

Table 1: Posttransplant recurrence in aHUS patients with identified complement abnormalities, published data

Complement abnormality	Frequency (%)	Number of transplanted patients	Recurrences (% of patients)	Number of grafts	Recurrences (% of grafts)	Graft failure for recurrence (% of all recurrences)
CFH mutations and CFH/CFHR1 hybrid gene	20–30	42	76 (32/42)	51	71 (36/51)	86 (31/36)
CFH autoantibodies	6	5	20 (1/5)	9	22 (2/9)	2/2
CFI mutations	4–10	12	92 (11/12)	17	88 (15/17)	85 (11/13)[1]
MCP mutations	10–15	10	20 (2/10)	12	17 (2/12)	1/2
C3 mutations	5–10	7	57 (4/7)	14	50 (7/14)	80 (4/5)[1]
CFB mutations	1–2	3	3/3	3	3/3	2/3
THBD mutations	5	1	1/1	1	1/1	1/1

[1]The outcome was not reported for two recurrence episodes.

1 (CFHR1) and 3 (CFHR3). A heterozygous hybrid gene, deriving from an uneven crossover between *CFH* and *CFHR1*, has been found in 3.5% of aHUS patients. About 5% of aHUS patients carry heterozygous mutations in *THBD*, the gene encoding thrombomodulin, a membrane-bound anticoagulant glycoprotein that facilitates complement inactivation (2).

Gain-of-function mutations in genes for the C3 convertase components C3 or factor B have also been reported in association with aHUS (1).

Finally, about 5% of patients have combined mutations, usually in *CFH* with either *MCP* or *CFI* (1). Patients with anti-CFH autoantibodies and mutations in complement genes have also been described.

Mutations in complement regulatory proteins impair the capability of endothelial cells to protect themselves from complement attack and predispose to aHUS. Gain-of-function mutations in *C3* and *CFB* lead to a hyperactive C3-convertase that is resistant to inactivation.

TMA in Kidney Transplant Patients

Posttransplant TMA (3) may ensue for the first time in patients who never suffered the disease (*de novo* posttransplant TMA), or may affect patients whose primary cause of ESRD was HUS (recurrent posttransplant TMA).

Pathology

Typical histologic changes include glomerular and arteriolar thrombosis, intracapillary accumulation of erythrocytes and red cell fragments, endothelial cell swelling and detachment from the basement membrane, glomerular ischemia and, in the healing phase, onion-skin hypertrophy of the arteriolar walls. Inciting events are difficult to distinguish on the basis of biopsy findings. Signs of cyclosporine nephrotoxicity—such as proximal tubular vacuolization and obliterative arteriopathy—can accompany the typical TMA changes. TMA lesion may also be associated with acute antibody-mediated rejection, in this case intraluminal thrombi, C4d staining of peritubular capillaries and circulating donor-specific antibodies are typical. Differential diagnosis between these two entities is difficult because both share the features of impaired renal function, and do not respond to antirejection therapy and affect kidney vessels. However, predominant endarteritis and general involvement of the entire vascular tree of the graft are peculiar findings of acute antibody-mediated rejection.

De novo *posttransplant TMA*

In renal transplant patients treated with cyclosporine, the incidence of *de novo* TMA is 4–15% with 43% graft survival (1). TMA usually sets in the first weeks posttransplant when patients are treated with high doses of the immunosuppressant. *De novo* TMA has been documented in approximately 1% of patients receiving FK506. The disease triggering effects of cyclosporine and FK506 have been related to vasoconstriction, endothelial toxicity and prothrombotic and antifibrinolytic actions. In the past, the mTOR inhibitor rapamycin, unlike calcineurin inhibitors (CNI), was not considered a risk factor for posttransplant TMA. However, cases of *de novo* TMA in patients receiving rapamycin have been reported later on (3).

The use of donors after cardiac death has been associated with posttransplant TMA. Endothelial lesions in the graft, caused by prolonged warm ischemia might increase antigenic presentation giving rise to acute rejection and TMA. Infections, *de novo* carcinoma or acute antibody-mediated rejection may also precipitate posttransplant TMA. Scleroderma and antiphospholipid antibody syndrome have been associated with increased risk of posttransplant TMA.

In about 30% of cases (4) TMA localizes only to the graft with no signs of hemolysis and thrombocytopenia. In these cases only a renal biopsy can allow a diagnosis. The possibility of TMA should be raised if a relatively young patient develops severe hypertension with progressive decline in the graft function.

Among 24 patients with *de novo* posttransplant TMA, 7 (29%) carried mutations in either *CFH* or *CFI* or combined *CFH*/*CFI*, indicating that genetic complement abnormalities may represent important risk factors (5).

Recurrent posttransplant TMA

In past reports the incidence of posttransplant recurrences among HUS patients ranged from 4% to 60%. The reasons for such variability became apparent when the graft outcome was evaluated separately depending on the cause of the original disease. In a review including 118 children who received 137 kidney transplants after HUS with diarrhea prodrome (D^+HUS), which conceivably mostly include Stx-HUS cases, only one patient had recurrence after transplantation. Among 62 children with Stx-HUS, no recurrence occurred and graft survival at 10 years was better than that in children who received a transplant for other causes (6). STEC-released toxins are the causative agents of Stx-HUS; therefore, a reexposure to STEC would be required to trigger a recurrence. However, patients with Stx-HUS develop neutralizing anti-Stx antibodies that persist for long time, thus protecting from recurrences (6).

On the other hand, among 78 patients with aHUS (STEC infection excluded), 60% of cases manifested recurrence posttransplant, 90% of whom developed graft failure (7). One-year graft survival was 32% for deceased donor transplants and 50% for living donor transplants. The percentage of graft failure from recurrence was higher in adults than in children (7). In a French cohort including 24 renal transplants in 15 children (8), recurrence was reported in

53% of patients and 33% of grafts. However, only 31% of graft failures were due to HUS recurrence (8).

The time between renal transplantation and recurrences of aHUS (7,8) varies from few days to 2 years, however 60% occur during the first month. In patients with aHUS and complement gene abnormalities or anti-CFH autoantibodies kidney endothelial cells are vulnerable early after transplantation as ischemia triggers complement activation. The risk of recurrence may be increased by posttransplant viral or bacterial infections that activate complement. Further injury and inflammation are caused by alloimmune response to the graft and indeed recurrence often occurs in concomitance with rejection episodes.

Impact of complement abnormalities on aHUS recurrence and outcome

The outcome of transplantation in aHUS is influenced by the underlying complement abnormality (1,8–10). Kidney transplantation in patients with *CFH* mutations is associated with high-recurrence rate and 1-year graft survival is poorer than in patients without *CFH* mutations (7). Of 42 published transplanted patients with *CFH* genetic abnormalities 32 had recurrence; 86% of recurrences induced graft loss (Table 1). The recurrence rate is 92% in patients with *CFI* mutations (graft loss in 85% of recurrences). Data are emerging that patients with *C3* and *CFB* mutations are at risk as well (Table 1). Mutations in the above-mentioned genes cause abnormalities in circulating complement proteins mainly produced by the liver. These abnormalities persist after kidney transplantation predisposing to recurrence. The transplant outcome appears better in patients with anti-CFH autoantibodies. Of five patients, only one had disease recurrence and lost the graft (Table 1).

MCP is a membrane-associated regulator that limits complement activity at cell surface. Recurrence of aHUS in transplanted patients carrying *MCP* mutations is rare because endothelial cells within kidney allograft express normal MCP. Only 2 out of 10 patients (12 grafts) with *MCP* mutations had posttransplant recurrence. In one, colonization of the graft endothelia by the recipient's MCP-deficient endothelial cells was proposed as the explanation of recurrence.

Patients with *THBD* mutations are expected to be at low risk for recurrence as thrombomodulin is a transmembrane protein, like MCP. However, in one patient, aHUS recurred 3 days after renal transplantation, with graft loss; another patient developed aHUS, probably *de novo* (2). Thrombomodulin also exists in a soluble active plasma form. It is possible that endothelial thrombomodulin is downregulated by ischemia/reperfusion in the graft, thus resulting in greater dependence on the recipient plasma form for renal protection from complement and thrombosis. In patients with *THBD* mutations, the mutant soluble thrombomodulin may be inadequate to provide sufficient protection, so that HUS recurs in the graft.

Finally, the recurrence risk is difficult to quantify in those rare cases with combined mutations. A patient (11) with heterozygous mutations in *CFI* and *MCP* received a deceased donor kidney transplant, which was uneventful, suggesting that the normal MCP in the graft was sufficient to prevent HUS recurrence. Of note, the patient received plasma infusion during the first days posttransplant, to supply additional CFI to counterbalance the systemic *CFI* genetic defect. Another patient with combined *MCP*/*CFI* mutations and one with *CFH*/*CFI* mutations had no recurrence in the graft. At variance, in two patients with combined *MCP*/*CFH* mutations, in one with *CFH*/*CFI* mutations and in one with three mutations (*MCP*/*CFH*/*CFI*) HUS recurred in the graft (10,12).

Prevention of Posttransplant TMA

Nephrectomy of native kidneys does not appear to be beneficial to prevent posttransplant recurrence. Bilateral nephrectomy should be considered when there is severe refractory malignant hypertension and/or ongoing evidence of disease activity despite treatment with plasma-exchange (13).

Avoidance of CNI does not appear to reduce incidence of recurrences. Artz et al. (13) showed that early use of cyclosporine increases the risk, but others denied it (14). HUS recurrence has been reported in patients with *CFH, MCP* or *CFI* mutations receiving CNI-free immunosuppression (12).

Plasma therapy

Recently, prophylactic intensive plasma treatment has been given before and after transplantation, in aHUS patients with mutations affecting plasma complement proteins, to provide enough normal proteins while removing the mutant molecules as to prevent complement hyperactivation in the graft.

Successful kidney allograft without recurrences was reported in a patient with aHUS and a *CFH* mutation receiving multiple plasma infusions peri- and postoperatively (15). On the other hand, HUS recurred in two sisters with a *CFH* mutation despite plasma prophylaxis and one of the two lost the graft (16).

Plasma-exchange and immunosuppression with corticosteroids and/or Rituximab have been successfully employed in patients with anti-CFH autoantibodies to lower the antibody titer and prevent recurrence (17,18).

Liver–kidney transplantation

Simultaneous kidney and liver transplant was performed in children with aHUS and *CFH* mutations (19). The first

two cases were complicated by premature liver failure with widespread microvascular thrombosis and complement deposition. It was reasoned that the surgical stress with ischemia/reperfusion induced complement activation in liver that could not be regulated because of functional CFH deficiency. A modified approach was applied to subsequent cases (19), including extensive plasma-exchange before transplant to provide sufficient normal CFH until the liver graft recovered synthetic functions. The modified procedure also included heparin and low-dosage aspirin to counteract the potential increased thrombogenicity associated with allograft endothelial activation and the additional clotting factors present in infused plasma. This procedure was successful in six patients with *CFH* mutations and one with combined *CFH*/*CFI* mutations; however, another child with a *CFH* mutation (19) developed severe hepatic thrombosis and fatal encephalopathy.

The above cases offered the proof-of-concept that liver transplantation can correct the complement abnormality and prevent recurrence in patients with *CFH* mutations and possibly in other genes encoding complement proteins of liver origin.

Eculizumab

Eculizumab, a high-affinity humanized anti-C5 monoclonal antibody that prevents generation of the membrane-attack complex was reported as promising to cure aHUS in the native kidneys (1,20) and may represent a strategy for prophylaxis of recurrences in patients with complement gene abnormalities.

A 17-year-old girl with aHUS and a *CFH* mutation (21) on chronic plasma treatment after her third renal graft, developed severe allergic reaction to plasma. Eculizumab was introduced in place of plasma-exchange. The patient maintained a stable graft function at 6-month follow-up.

Treatment of Posttransplant TMA

There are no treatment guidelines for *de novo* or recurrent posttransplant TMA. Reduction or withdrawal of CNI or switching to sirolimus have been attempted to limit drug-related nephrotoxic insult. However, 60–100% graft loss has been reported with these procedures alone (22).

Others combined cyclosporine withdrawal with plasma-exchange. Among 29 patients with *de novo* post-transplant TMA, 80% recovered graft function after cyclosporine stop and plasma therapy (23). Of eight patients, who received plasma-exchange during aHUS recurrences, six (four with complement gene mutations) maintained a functioning graft. Of note three of them were switched from CNI to sirolimus (12). However, CNI withdrawal leaves the patient at risk of acute rejection. A strategy could be to substantially reduce CNI during recurrence and restore the dose after clinical recovery (23).

Recently, plasma-exchange combined with belatacept, a second generation CTLA4-Ig, which blocks the interaction between CD80/86 and CD28, in a patient with recurrent TMA allowed CNI discontinuation and reversed TMA while preventing acute rejection. In another report, belatacept has been safely used as maintenance immunosuppression with prednisone and azathioprine in a patient, who previously developed three episodes of posttransplant TMA, while on cyclosporin, tacrolimus and sirolimus, respectively (22).

TMA associated with antibody-mediated rejection is often refractory to treatment and most patients eventually loose the graft. Depletion of plasma cells with the proteasome inhibitor bortezomib and complement inhibition with Eculizumab, have been proposed as new therapeutic strategies.

Eculizumab was used to treat aHUS recurrence in patients with complement gene abnormalities. In a 30-year-old woman with a *CFH* mutation, who developed recurrent HUS in the second graft despite intensive plasma-exchange, treatment with Eculizumab blocked hemolysis and improved transplant function (24). A women with a *C3* mutation on chronic plasma-exchange to control HUS recurrence in her second graft, was shifted to Eculizumab, which allowed to stop plasma therapy, stabilized graft function and blocked hemolysis (25). However, after 10 weeks' treatment a delay of the subsequent Eculizumab dose was temporarily associated with a return of hemolysis and deterioration of graft function, suggesting the need for chronic treatment.

Conclusions and Recommendations

Identification of the defect underlying aHUS is instrumental to make informed decisions regarding listing for transplantation based on risk of recurrence. Recommendations can reasonably be as follows (Figure 2):

- Screening for mutations in *CFH, MCP, CFI, C3, CFB* and *THBD*, search of *CFHR* deletions and of anti-CFH autoantibodies should be done in all patients with aHUS before transplantation. Screening should not be stopped after finding a mutation or antibodies as combined mutations or mutations plus anti-CFH antibodies have been reported.
- Living-related donation should be avoided for aHUS patients whatever their genetic background due to high recurrence risk. When live-related donation is the only possible option, complete genotyping of the donor should be performed to identify hitherto unsuspected mutation carriers. The donor himself may

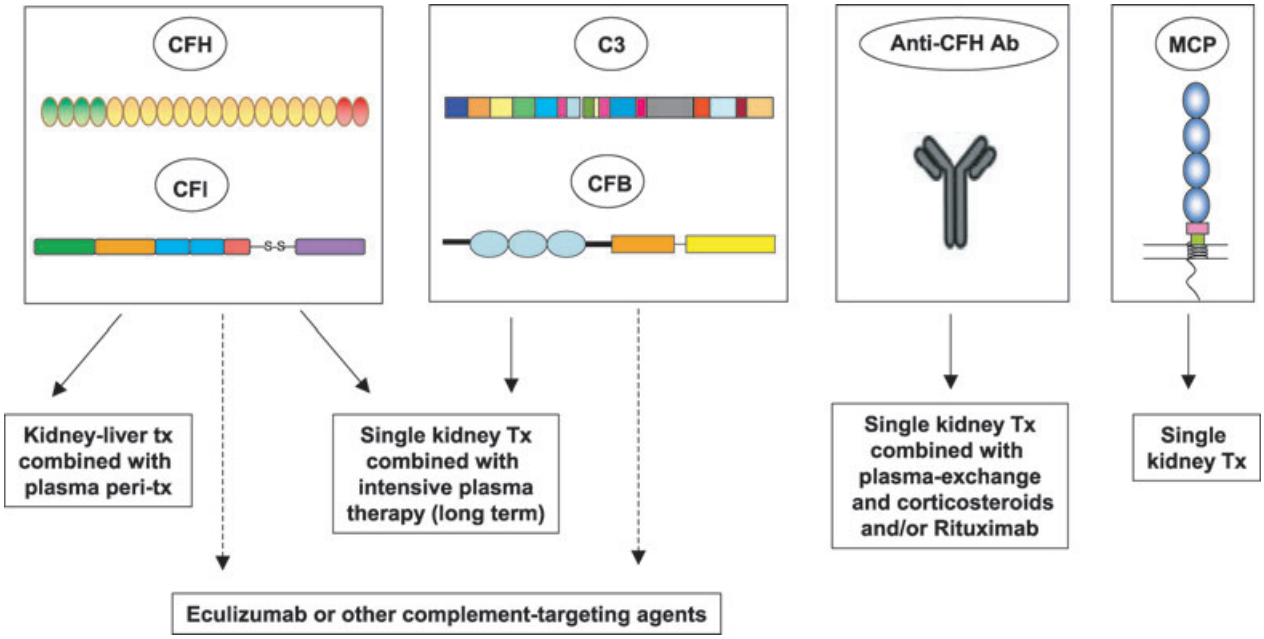

Figure 2: Schematic representation of transplant options in aHUS patients. Tx: transplantation.

develop HUS after kidney donation (1,8). The hemodynamic changes induced by unilateral nephrectomy and the surgical stress could trigger HUS in genetically predisposed donors.

- Patients with *MCP* mutations can reasonably undergo single kidney transplantation providing that mutations in other genes are excluded.
- For patients with anti-CFH antibodies single kidney transplantation is a safe option when combined with therapeutic approaches (plasma-exchange, high doses corticosteroids) to substantially lower the antibody titer. CFH autoantibodies should be monitored post-transplant and Rituximab should be administered to patients with persistently elevated levels.
- For patients with *CFH* or *CFI* mutations, the risk of recurrence on the kidney graft is very high. There are three options.

(1) Combined kidney and liver transplantation with preoperative plasma-exchange and intraoperative plasma infusion and posttransplant anticoagulation. The severity of risks associated with the procedure requires careful assessment of individual risk/benefit.
(2) Single kidney transplantation combined with intensive plasma-exchange starting just before operation, daily during at least 1 week, progressively tapered to once a week, maintained life-long and reintensified during infectious episodes. However, recurrence may occur despite plasma prophylaxis and patients may become unresponsive or develop intolerance to plasma.
(3) Single kidney transplantation combined with Eculizumab will hopefully be soon a therapeutic and prophylactic option.

- Options (2) and (3) could be reasonably applied also to patients with *C3* and *CFB* mutations, whereas there is concern about the applicability of the combined kidney and liver transplant to these patients (19). For patients with *C3* mutations, there may be sufficient extrahepatic production of mutant protein to remain at risk for recurrent disease after a combined transplant. The clinical phenotypes of patients with *CFB* mutations, who often have cerebrovascular disease, suggest a high operative risk of a combined liver–kidney transplant.
- Patients with *THBD* mutations appear to be at risk of recurrences, however available data are too limited at present for therapeutic recommendations.

Acknowledgments

A report published in the May 6 issue of the *New England Journal of Medicine* describes the prophylactic use of Eculizumab to prevent aHUS recurrence after kidney transplant in a boy with a CFH mutation (Zimmerhackl LB, Hofer J, Cortina G, Mark W, Wurzner R, Jungraithmayr TC. Prophylactic Eculizumab after renal transplantation in atypical hemolytic-uremic syndrome. N Engl J Med 2010; 362: 1746–1748).

Funding sources: This paper has been supported by grants from Fondazione ART per La Ricerca Sui Trapianti, Fondazione Aiuti per la Ricerca sulle Malattie Rare and from the Telethon Foundation.

References

1. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med 2009; 361: 1676–1687.
2. Delvaeye M, Noris M, DeVriese A et al. Mutations in thrombomodulin in hemolytic-uremic syndrome. N Engl J Med 2009; 361: 345–357.
3. Reynolds JC, Agodoa LY, Yuan CM, Abbott KC. Thrombotic microangiopathy after renal transplantation in the United States. Am J Kidney Dis 2003; 42: 1058–1068.
4. Schwimmer J, Nadasdy TA, Spitalnik PF, Kaplan KL, Zand MS. De novo thrombotic microangiopathy in renal transplant recipients: A comparison of hemolytic uremic syndrome with localized renal thrombotic microangiopathy. Am J Kidney Dis 2003; 41: 471–479.
5. Le Quintrec M, Lionet A, Kamar N et al. Complement mutation-associated de novo thrombotic microangiopathy following kidney transplantation. Am J Transplant 2008; 8: 1694–1701.
6. Ferraris JR, Ramirez JA, Ruiz S et al. Shiga toxin-associated hemolytic uremic syndrome: Absence of recurrence after renal transplantation. Pediatr Nephrol 2002; 17: 809–814.
7. Bresin E, Daina E, Noris M et al. Outcome of renal transplantation in patients with non-Shiga Toxin-associated haemolytic uremic syndrome: Prognostic significance of genetic background. Clin J Am Soc Nephrol 2006; 1: 88–99.
8. Loirat C, Fremeaux-Bacchi V. Hemolytic uremic syndrome recurrence after renal transplantation. Pediatr Transplant 2008; 12: 619–629.
9. Caprioli J, Noris M, Brioschi S et al. Genetics of HUS: The impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood 2006; 108: 1267–1279.
10. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA et al. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 2007; 18: 2392–2400.
11. Cruzado JM, de Cordoba SR, Melilli E et al. Successful renal transplantation in a patient with atypical hemolytic uremic syndrome carrying mutations in both factor I and MCP. Am J Transplant 2009; 9: 1477–1483.
12. Seitz B, Albano L, Vocila F et al. Recurrence of hemolytic uremic syndrome after renal transplantation. Transplant Proc 2007; 39: 2583–2585.
13. Artz MA, Steenbergen EJ, Hoitsma AJ, Monnens LA, Wetzels JF. Renal transplantation in patients with hemolytic uremic syndrome: High rate of recurrence and increased incidence of acute rejections. Transplantation 2003; 76: 821–826.
14. Quan A, Sullivan EK, Alexander SR. Recurrence of hemolytic uremic syndrome after renal transplantation in children: A report of the North American Pediatric Renal Transplant Cooperative Study. Transplantation 2001; 72: 742–745.
15. Hirt-Minkowski P, Schaub S, Mayr M et al. Haemolytic uraemic syndrome caused by factor H mutation: Is single kidney transplantation under intensive plasmatherapy an option? Nephrol Dial Transplant 2009; 24: 3548–3551.
16. Davin JC, Strain L, Goodship TH. Plasma therapy in atypical haemolytic uremic syndrome: Lessons from a family with a factor H mutation. Pediatr Nephrol 2008; 23: 1517–1521.
17. Kwon T, Dragon-Durey MA, Macher MA et al. Successful pre-transplant management of a patient with anti-factor H autoantibodies-associated haemolytic uraemic syndrome. Nephrol Dial Transplant 2008; 23: 2088–2090.
18. Le Quintrec M, Zuber J, Noel LH et al. Anti-Factor H autoantibodies in a fifth renal transplant recipient with atypical hemolytic and uremic syndrome. Am J Transplant 2009; 9: 1223–1229.
19. Saland JM, Ruggenenti P, Remuzzi G. Liver-kidney transplantation to cure atypical hemolytic uremic syndrome. J Am Soc Nephrol 2009; 20: 940–949.
20. Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. N Engl J Med 2009; 360: 544–546.
21. Davin JC, Gracchi V, Bouts A, Groothoff J, Strain L, Goodship T. Maintenance of kidney function following treatment with Eculizumab and discontinuation of plasma exchange after a third kidney transplant for atypical hemolytic uremic syndrome associated with a CFH mutation. Am J Kidney Dis 2010; 55: 708–711.
22. Ashman N, Chapagain A, Dobbie H, Raftery MJ, Sheaff MT, Yaqoob MM. Belatacept as maintenance immunosuppression for postrenal transplant de novo drug-induced thrombotic microangiopathy. Am J Transplant 2009; 9: 424–427.
23. Karthikeyan V, Parasuraman R, Shah V, Vera E, Venkat KK. Outcome of plasma exchange therapy in thrombotic microangiopathy after renal transplantation. Am J Transplant 2003; 3: 1289–1294.
24. Nurnberger J, Witzke O, Saez AO et al. Eculizumab for atypical hemolytic-uremic syndrome. N Engl J Med 2009; 360: 542–544.
25. Chatelet V, Fremeaux-Bacchi V, Lobbedez T, Ficheux M, de Ligny BH. Safety and long-term efficacy of eculizumab in a renal transplant patient with recurrent atypical hemolytic-uremic syndrome. Am J Transplant 2009; 9: 2644–2645.