Extended clinical history of 3 patients with identified anti-factor I autoantibody:

Patient 1

Presented aged 26 with postpartum aHUS. At 41 weeks gestation she was noted to have proteinuria and Caesarian section was performed delivering a healthy female infant. Laboratory investigations post delivery demonstrated a creatinine of 2.6 mg/dL, a platelet count of 46,000/mm^3 and a hemoglobin of 5.8 g/dl with microangiopathic hemolytic anemia on blood film. Despite daily plasma exchange for 7 days with fresh frozen plasma as replacement she remained anuric. A renal biopsy revealed changes consistent with thrombotic microangiopathy with severe irreversible vascular changes and plasma exchange was stopped.

After 1 year of hemodialysis, she received a cadaveric renal transplant. The HLA mismatch at the A, B and Dr loci was 1:2:0. Both the donor and recipient were CMV IgG positive. Initial immunosuppression consisted of anti-thymocyte globulin, cyclosporine, azathioprine and prednisolone. The cold ischemic time was 30 hours and because of delayed graft function a transplant renal biopsy was undertaken at 6 days post transplant. This demonstrated mild acute cellular rejection with features of vascular rejection with some evidence of acute tubular necrosis. She was treated with 3 doses of methylprednisolone and the immunosuppression switched to tacrolimus, MMF and prednisolone. Despite a transient improvement in renal function by day 28 post transplant the plasma creatinine was increasing. A renal transplant biopsy demonstrated recurrent aHUS. The tacrolimus was stopped and plasma exchange started. However, there was no improvement in renal function and a transplant nephrectomy was undertaken.

Following a further 18 months on dialysis she received a 0:0:0 cadaveric renal transplant from a CMV negative donor. She received 4 units of fresh frozen plasma pre-operatively and immunosuppresion consisted of Sirolimus, prednisolone and MMF. On the second post-operative day there was evidence of hemolysis with an increase in LDH and red cell fragments on blood film. This resolved within 24 hours without plasma therapy. Renal function was stable with a creatinine of ~1 mg/dl. After several months sirolimus was replaced with tacrolimus because of wound necrosis. 2 years post transplant she developed nephrotic range proteinuria and worsening graft function. She underwent a transplant biopsy which showed

transplant glomerulopathy. At 4 years post engraftment she underwent a repeat renal biopsy for worsening renal function which again showed transplant glomerulopathy with moderate chronic damage. The renal function continued to worsen and she recommenced on hemodialysis.

Patient 2

Presented at 5 years of age with aHUS. Laboratory studies revealed a creatinine of 3.5mg/dl, hemoglobin of 7.1g/dl and a platelet count of 24,000/mm^3. The peripheral blood film showed evidence of marked microangiopathic hemolytic anemia. Her C3 was transiently low at 61mg/dl but returned to normal within a few days where it has remained since. Her C4 was normal and has been so throughout her clinical course. She did not have diarrhea. There was no family history of aHUS. She was initially treated conservatively. However, her renal function continued to deteriorate and a renal biopsy was undertaken 15 days after presentation. This showed intimal oedema and proliferation of arterioles and interlobular arteries with luminal narrowing and thrombosis. Ischemic and shrunken glomeruli were also noted. Daily plasma exchange was undertaken for 3 weeks but proved ineffective and end stage renal failure ensued. Peritoneal dialysis was instituted. She remained well for a number of years but gradually became markedly hypertensive. This proved impossible to control medically and at 9 years of age bilateral nephrectomies were performed. After a year of hemodialysis, peritoneal dialysis was recommenced. Subsequently, at 10 years of age, she received a deceased donor renal transplant. HLA A, B, and Dr loci mismatches were 1,1,0. Both donor and recipient were CMV naïve. The cold ischemic time was 13 hours. Initial immunosuppression was with azathioprine, tacrolimus and prednisolone alone. There was good graft function with no significant proteinuria. At 6 months post-graft an episode of biopsy proven mild rejection was noted but there was no histological evidence of disease recurrence. In view of the rejection episode, azathioprine was replaced with mycophenolate mofetil. Since that time she has had stable graft function without proteinuria. Currently, aged 15 years and 4½ years post-transplant her creatinine is 0.8mg/dl.

Patient 3

Presented at 13 months of age with bloody diarrhea. She had previously been healthy with no family history of aHUS. She was Amish. Early management was supportive consisting of oral rehydration. After two days with no clinical improvement she was admitted to hospital for intravenous hydration. Admission laboratory studies showed hemoglobin 11g/dL, platelets 503,000/mm^3 and creatinine 0.2 mg/dL. Her stool culture was positive for *Clostridium difficile* and Rotavirus but negative for *E.Coli* O157:H7. She was started on oral Vancomycin and Metronidazole. After two days of hospitalization, her urine output steadily decreased and she became anuric with a weight gain of ~1kg over 24 hours. Further laboratory tests at that time showed an increased creatinine of 2.1 mg/dL, decreased platelets of 106,000/mm^3 and a decreased hemoglobin of 1.9 g/dL. Due to her worsening renal function, anemia and thrombocytopenia in the setting of bloody diarrhea, initially a diagnosis of typical HUS was made. However, complement analysis revealed that both C3 and C4 were low (56mg/dL and 8mg/dL respectively), which raised suspicion for aHUS. On transfer to a tertiary referral centre she was started on peritoneal dialysis. Fresh frozen plasma infusions 15mL/Kg were given every other day for 6 treatments. After a three-week period of anuria during which she needed peritoneal dialysis she recovered sufficient renal function for the dialysis to be stopped. At the time of hospital discharge, approximately four weeks after admission, her creatinine was 1.9 mg/dl and her complement levels were normal. At this point, more than 3 years after the acute presentation, she has a creatinine of 0.7mg/dL. She has hypertension which is under good control with Captopril.