Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome in 2014—Current Knowledge and Outcomes with Plasma Exchange

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Abstract

Great progress has been made in our understanding of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome since Moschowitz first described this entity in 1925. This review provides a contemporary insight into the pathophysiology, diagnosis, and classification of these disorders in both adults and children. Lessons learned from major worldwide registry data and disease epidemics, including the 2011 German outbreak, are discussed with recommendations for management of specific clinical conditions based on available evidence, including the role of plasma exchange, rituximab, and eculizumab.

Keywords

Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, atypical, diarrhea, idiopathic, secondary, ADAMTS-13, plasma exchange, plasma infusion, epidemic, rituximab, eculizumab

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Classification

The two basic forms of thrombotic microangiopathies, excluding disseminated intravascular coagulation (DIC), include thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS). Early historic reports noted the presence of hemolytic anemia and thrombocytopenia in both disorders and suggested differentiation of these two entities based on the presence of clinical symptoms. Predominant kidney failure, often seen in children with preceding diarrheal illness, led to the clinical diagnosis of HUS, while fever, neurologic changes, and kidney failure suggested TTP.[1–3]

This classification scheme has been challenged by several main observations. First, the classic triad of HUS (thrombocytopenia, hemolytic anemia, and renal failure) or pentad of TTP (thrombocytopenia, hemolytic anemia, neurologic signs, renal failure, and fever) is rarely complete at presentation and often in the case of TTP only at or near autopsy.[4] Second, a significant number of TTP patients are afflicted with severe kidney failure and a preceding diarrheal illness, and neurologic symptoms are commonly reported in both TTP and HUS.[5–8] Third, and most importantly, treatment with plasma exchange has dramatically reduced the mortality rate in TTP from nearly 90 % to approximately 20 %, thereby making urgent diagnosis and treatment of TTP a life-saving priority. Misclassification of a patient based on presenting clinical symptoms could have fatal consequences.

Current nomenclature has evolved to classify all adult patients who present with the dyad of unexplained thrombocytopenia and microangiopathic anemia with normal international normalized ratio (INR), partial thromboplastin time (PTT), and D-dimers as TTP-HUS. Within this category, both a primary form (either idiopathic/acquired or hereditary) and a secondary form (due to an identified underlying disorder) exist. Secondary TTP-HUS comprises 50 % of TTP-HUS cases in adults and has been described in eight major conditions as noted in *Table 1*. Registry data indicate that even when applying the above classification criteria, a small but significant number of patients with secondary TTP or DIC are misclassified as idiopathic TTP at initial presentation.[9]

The syndrome of HUS is more common in children but is also seen in adults. It comprises a primary/atypical form characterized by abnormal activation of the complement cascade, and a secondary/typical form seen in shiga toxin mediated diarrheal illness (*Escherichia coli 0157:H7, E. coli 0104:H4, Shigella*). The diagnosis of atypical HUS (aHUS) is usually, but not exclusively, made in childhood in patients with repeated episodes of clinical TTP-HUS and abnormalities in complement regulating genes.

Table 1: Recommended Classification Scheme of Thrombotic Microangiopathies, Main Pathophysiology, and Response to Initial Plasma Exchange[9,26,30,52,125,138,139,140]

	Classification	Associated Main Pathophysiologic Features	Response to Plasma Exchange
Primary TTP/HUS	Idiopathic/acquired	Severely decreased functional ADAMTS-13 Presence of inhibitory anti-ADAMTS-13 antibody	>80–90 %
	Hereditary/congenital (Upshaw-Schulman)	Severely decreased quantitative ADAMTS-13	>80–90 %
Secondary TTP/HUS	Autoimmune disease[a]	Variable ADAMTS-13 activity	50–70 %
	Drug-associated[b]	Endothelial injury (mediated by various insults)	80–90 %[c]
	infection[d]		50–70 %[e]
	Pregnancy/postpartum		50–70 %
	pancreatitis		50–70 %
	Malignancy		None
	Malignant hypertension		None
	Stem cell transplant		None
Primary aHUS	Familial	Preserved ADAMTS-13 activity	30–70 %[f]
	Sporadic	Mutations in CFH, CFHR1/3, CFI, C3, MCP (CD46), THBD, or CFB	
Secondary/typical HUS	dHUS	Preserved ADAMTS-13 activity Shiga-toxin-mediated endothelial injury	None[g]

[a]Including but not limited to systemic lupus erythematosus; [b]Including: ticlodipine, clopidogrel, quinine, valacyclovir, oral contraceptives, chemotherapy, cyclosporine, tacrolimus, sirolimus; [c]Except mitomycin C – no response; [d]Including but not limited to HIV, Streptococcus pneumonia*; [e]Except* Escherichia coli 0157:H7 *– no response; [f]Except abnormal membrane co-factor protein – no response; [g]Specific clinical circumstances may warrant trial of plasma exchange (see text).*
aHUS = atypical hemolytic uremic syndrome; CFB = complement factor B; CFH = complement factor H; CFHR1/3 = complement factor H receptor 1/3; CFI = complement factor I; C3 = complement C3; dHUS = diarrheal HUS; MCP = membrane-bound complement protein; THBD = thrombomodulin; TTP = thrombocytopenic purpura.

Pathophysiology

The underlying pathologic finding in both TTP and HUS is systemic occlusive microthrombi formation typically affecting the brain and kidneys, although any organ may be involved. In their seminal reports, Moschcowitz[1] and Baehr[10] described the presence of hyaline microthrombi rich with platelet aggregates, highlighting the major role of platelet involvement in the pathogenesis of this disease. Early kinetic analyses demonstrated that both disorders share a similar pattern of severe platelet consumption with little fibrinogen or plasminogen consumption, thereby differentiating them from the entity of DIC[11]. For decades, the pathophysiology remained a mystery until Moake demonstrated the pathogenic role of unusually large multimers of von Willebrand factor (vWF) mediating platelet-rich microthrombi formation in patients with TTP.[12–14]

vWF is normally synthesized by endothelial cells and megakaryocytes and exists in the circulation as a series of multimers containing anywhere between 2 to 40 subunits, varying in molecular weight from 540 to 20,000 kDa.[15] The variable multimeric structures each have distinct functional abilities, with high molecular weight vWF (HMWVWF) having the greatest ability to induce platelet aggregation.[16] Moake's speculation about impaired degradation of vWF multimers leading to pathogenic accumulation of HMWVWF was confirmed years later when two independent groups identified a vWF cleaving protease responsible for physiologic control of vWF multimer length, and later demonstrated a circulating inhibitory autoantibody to this protease in patients with TTP.[17–20] This protease was subsequently identified as ADAMTS-13, and a link between ADAMTS-13 deficiency and TTP pathogenesis has now been established.

Early enthusiasts suggested use of ADAMTS-13 levels as a diagnostic and prognostic criterion to distinguish primary TTP from its secondary forms and from HUS and thereby predict which patients would benefit from plasma exchange therapy.[18, 20–25] The potentially deleterious consequences of this approach have since been demonstrated by several important observations. First, patients with severe ADAMTS-13 deficiency do not always present with clinical TTP-HUS, thereby highlighting the role of other pathophysiologic variables in this syndrome. Second, registry data have demonstrated that up to two-thirds of patients with clinically diagnosed idiopathic TTP and the majority of patients with secondary TTP lack severe ADAMTS-13 deficiency and still respond to plasma exchange.[9,26–30]

Based on available data, several conclusions can be made about ADAMTS-13 at the present time (see *Table 2*). Severe ADAMTS-13 deficiency appears to be most strongly associated with primary TTP, in both its idiopathic (functional deficiency with inhibitory antibody present) and the congenital form (quantitative ADAMTS-13 deficiency). Enzyme activity is reduced but variable in secondary TTP and usually preserved in both diarrheal and aHUS. Severe ADAMTS-13 deficiency is associated with more severe thrombocytopenia and higher rates of relapse, and inversely associated with severity of renal disease. It has not been shown to predict severity of clinical disease, response to plasma exchange, or death. Therefore, the presence or absence of severe ADAMTS-13 deficiency should not be used to guide initial diagnosis or management.

Early reports about the pathogenesis of TTP and HUS questioned whether they were separate and distinct forms of thrombotic microangiopathies or in fact variants of the same disorder.[31] Although the histopathology is similar in both entities, microthrombi in TTP but not HUS are rich in vWF, and endothelial cell swelling predominates in HUS but not TTP.[32]

The exact mechanism underlying microthrombi formation in diarrheal HUS is not known. Endothelial injury induced by shiga-toxin possibly involving molecular mimicry of platelet CD36 receptors, stimulation of endothelial

Table 2: Proportion of Patients Across Spectrum of TTP and HUS with Severe ADAMTS-13 Deficiency (<10 % Enzyme Activity) as Reported in Worldwide Registry Data

	Oklahoma/US 1995–2008 (n=261)	UK 2002–2006 (n=178)	Korea 2005–2008 (n=66)	France+ 2000–2007 (n=361)	Japan* 1998–2008 (n=919)
Primary idiopathic TTP-HUS	46/98 (47 %)	67 %	14/39 (36 %)	160/214 (75 %)	195/284 (69 %)
Primary congenital TTP-HUS	NR	NR	NR	NR	40/41 (98 %)
Secondary TTP-HUS	12/141 (9 %)	50 %	6/27 (22 %)	?/118 (NR)	89/497 (18 %)
dHUS	NR	NR	NR	NR	0/132 (0 %)
aHUS	NR	NR	NR	NR	0/24 (0 %)
Mortality if severely deficient	13/60 (22 %)	NR	3/16 (19 %)	18/160 (11 %)	29/180 (16 %)
Relapse if severely deficient	16/47 (34 %)	26/178 (15 %)	2/13 (15 %)	28/142 (20 %)	NR
Overall mortality	78/261 (30 %)	21/178 (12 %)	15/66 (23 %)	25/214 (12 %)	NR

*+In this registry, the deficient group included 155 patients with <5 % activity and an additional 5 patients with 13–18 % activity and presence of an inhibitor. *In this registry, severe deficiency was defined as <3 % ADAMTS-13 activity; patients with documented* Escherichia coli 0157:H7 *infection and thrombotic microangiopathy were included as typical diarrheal hemolytic uremic syndrome (dHUS) cases for purposes of this table. aHUS = atypical HUS; NR = not reported; TTP = thrombocytopenic purpura.*

HMWVWF release, and antibody formation against shiga-toxin all seem to play major roles.[33–35] Recent advancements in the understanding of aHUS have elucidated the role of abnormal complement activation due to a variety of gain or loss of function mutations of complement regulating genes.[36] In 20 % of cases, this is due to a familial form of aHUS, which presents early in childhood and carries a 50 to 80 % rate of end-stage renal disease (ESRD) or death.[37] In 80 % of cases, aHUS occurs sporadically in adults or children without a family history of aHUS. Complement dysregulation has also been observed in shiga-toxin-mediated diarrheal HUS and raises important therapeutic considerations that will be discussed below.[38,39]

Diagnosis

The almost certain fatality of TTP-HUS has been dramatically mitigated by two major changes in the approach to this disease: rapid diagnosis and immediate treatment with plasma exchange in appropriate patients. All adult patients who present with the dyad of unexplained thrombocytopenia and hemolytic anemia without normal INR, PTT, and D-dimer are classified as having TTP-HUS, but must be investigated for dHUS or aHUS. Diagnostic tests should be sent off but not delay immediate therapy with plasma exchange in all patients, except those in whom stem cell transplantation, malignancy, mitomycin C exposure, or malignant hypertension can be identified as the underlying disorder. Diagnostic testing should include ADAMTS-13 activity (if available) (see *Table 2*), complement activity (C3, C4, and CH50 if available), and stool and serum tests for shiga toxin. Subsequent positive microbiologic results for shiga toxin suggest an alternate diagnosis of dHUS, while abnormalities in complement suggest aHUS but these tests of complement lack both sensitivity and specificity. In both these conditions, there may be a role for plasma exchange in adults, as will be discussed later.

Children who present with unexplained thrombocytopenia and microangiopathic anemia, often with severe renal failure, are assumed to have dHUS if there is a preceding history of bloody diarrhea, and the diagnosis is confirmed when microbiology is positive for shiga toxin. Supportive treatment with judicious volume repletion is indicated while plasma exchange is usually not. In the absence of a bloody diarrhea prodrome, the child may have either TTP or aHUS and plasma exchange is indicated. More detailed testing of complement dysregulation may be indicated in this setting if the ADAMTS13 testing is normal since detailed complement testing is both time-consuming and expensive. The role of plasma exchange in select circumstances in dHUS is discussed later.

Management

Whereas mortality was almost certain in early reports of TTP-HUS, rates have been reduced to 10–20 % in the last 2 decades, largely with the use of plasma exchange. Plasma exchange was first described in 1977 by Bukowski, after several prior reports of TTP patients responding to exchange blood transfusions.[40–43] In the same year, Byrnes described a young woman with pregnancy-associated TTP whom he treated sequentially with selective blood product replacement. He showed the plasma fraction of blood was the main blood component in achieving a response.[44] Following several reports of successful treatment with simple plasma infusion, the superiority of plasma exchange in the treatment of TTP was established in 1991 by two randomized controlled trials (RCTs).[45,46] This success of plasma exchange has been attributed to its ability to both remove an unwanted substance (inhibitory ADAMTS-13 antibody), replace a deficient substance (ADAMTS-13 enzyme), and allow for larger volume of plasma to be infused.

Further elucidation of the pathophysiology across the spectrum of TTP/HUS and observations about when plasma exchange and other therapies have been of benefit have advanced our understanding of the role of various therapies in specific clinical circumstances.

Primary TTP-HUS

Emergent plasma therapy is indicated in all patients with TTP-HUS and has transformed worldwide disease-related death into the exception rather than the rule in this condition.[41,42,44,47–51] Plasma infusion should only serve as a temporizing measure until plasma exchange therapy can be delivered. The superiority of plasma exchange in treatment of primary TTP-HUS was established in a landmark RCT that demonstrated a higher disease response rate (47 % versus 25 %; p=0.025) and a lower mortality rate (22 % versus 37 %; p=0.035) at 6 months.[45] In the same study, patients in the plasma exchange group received three times more plasma volume than those in the infusion group. A retrospective study of 110 TTP-HUS patients reported that patients with greater disease severity received on average an additional 10–15 ml/kg/day of plasma volume compared with those with fewer risk factors and that this approach trended toward higher survival rates.[52] A subsequent case report by Clark et al. described a patient with severe TTP (and a dismal prognosis due to advanced age, fever, coma, severe anemia, thrombocytopenia, and renal failure) who dramatically responded to a 48-hour continuous 78 liter plasma exchange session.[53]

Controlled studies are necessary to establish the role of large volume and twice-daily plasma exchange therapy in a subset of TTP patients.

Despite differences in currently available plasma product composition, theoretical benefits of one plasma product over another has not been substantiated in controlled studies.[54] There is no robust evidence for use of corticosteroid in conjunction with plasma exchange and its use is largely dictated by center-specific practices; however, a recent small RCT of high-dose therapy does suggest benefit.[55–57] At the present time most centers provide steroids either at outset or if patient is not responding early to plasma exchange. Centers that do use corticosteroids may routinely encounter lower allergic reaction rates to plasma. Solvent detergent treated (S/D) fresh frozen plasma (Octaplas; Octapharma) is now available in North America and is expected to further lower reaction rates.

Ten percent of TTP-HUS patients respond to initial therapy but relapse within 1 to 30 days (refractory TTP) and require further plasma exchange. In these patients, diagnostic investigations to rule out alternate diagnoses should be undertaken. This includes a renewed search for underlying secondary causes (including sepsis and occult malignancy) and complement testing to exclude aHUS. Large volume and twice daily exchanges have been used in these patients but require further study. A further 30 % of patients relapse within 1 month to 14 years and require further plasma exchange therapy. Registry data show that the number of plasma exchange treatments to achieve remission is lower in relapsed cases then in first episodes of acquired idiopathic TTP.[26,27]

The role of rituximab in treatment of refractory primary TTP is currently under investigation. While several patients with relapsed and refractory TTP have been successfully treated with rituximab, there is great variability in dosage and administration across reported observational studies.[27,58–102] Rituximab is a chimeric mouse/human monoclonal anti-CD20 that binds to the CD20 antigen on B-lymphocytes and mediates B-cell lysis by both complement and antibody-dependent cytotoxic pathways. It has been shown to normalize ADAMTS-13 activity in 7–24 weeks.[93,96] One study reported normalization in platelet counts within 2 weeks of treatment in 21 of 24 patients and sustained remission in 18 of these patients at 30 months.[103] There is limited evidence for rituximab use as a first-line treatment in incident patients, and preliminary results indicate potentially lower relapse rates.[104–106]

Splenectomy is an option for patients with TTP who are classified as frequent relapsers or refractory to plasma exchange or rituximab therapy.[107–109] Antiplatelet agents, vincristine, cyclophosphamide, cyclosporine, and intravenous immunoglobulin have all been used in uncontrolled studies, but RCTs demonstrating their efficacy remains lacking.[110–119] Platelet transfusions should be avoided due to theoretical harm of worsening disease severity, but may be necessary in cases of life-threatening thrombocytopenia or prior to expected surgery.[120]

Secondary TTP-HUS

While idiopathic TTP-HUS has been reported to have a response rate of approximately 80 % to plasma exchange, some patients with secondary thrombotic microangiopathies do not respond at all.[9] Evidence to support plasma exchange in secondary thrombotic microangiopathies comes largely from case series. There are no RCTs to assess the efficacy of plasma exchange in any one subgroup of secondary TTP-HUS. There are currently no consensus recommendations regarding indication, patient selection, method, timing, and duration of plasma exchange therapy for secondary TTP-HUS in general. However, expert opinion suggesting the initiation of therapeutic plasma exchange for all adults who fulfill the diagnostic criteria for TTP-HUS and investigation of secondary causes guided by the clinical presentation is widely accepted.[121]

Prompt initiation of plasma exchange remains the cornerstone of treatment in cases of TTP-HUS associated with autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and mixed connective tissues disease. Additional immunosuppressive drugs are often required and while recent case reports suggest a role for rituximab in refractory cases, routine use cannot be recommended at present.[68,77,122,123]

Many cases of TTP-HUS are reported during pregnancy and postpartum, and a distinction between severe preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome must be made. Pregnancy-associated TTP-HUS is associated with high maternal mortality and long-term morbidity, including preterm delivery and intrauterine fetal death. Improved survival in this setting has been attributed to aggressive treatment with plasma exchange.[124] Plasma exchange has also been shown to be effective in episodes of TTP-HUS precipitated by acute pancreatitis.[125,126]

TTP-HUS has been reported in association with several infections, including HIV, although the exact mechanism of this relationship remains unclear. In some cases the thrombotic microangiopathy has been thought secondary to opportunistic infections, and in some cases HIV has been considered an inflammatory trigger. If the diagnosis of TTP is suggested in a patient with HIV infection after the exclusion of opportunistic infections, prompt initiation of highly active antiviral therapy (HAART) and plasma exchange appear to be effective in reducing viral loads and inducing remission.[127,128]

Response to plasma exchange in drug-induced TTP-HUS is variable, as reported in the setting of chemotherapy and antiplatelet agents.[129,130] In all cases, the offending drug should be identified and withheld. Plasma exchange has not been shown to be effective for TTP-HUS associated with mitomycin C administration.

Syndromes resembling TTP-HUS may be also diagnosed in the setting of untreated disseminated malignancy or following allogeneic hematopoietic cell transplant. Given the frequency of diagnostic uncertainty, unclear benefit, and high risk for side effects, plasma exchange is not recommended in these cases.[131–135] Further, despite recent case reports documenting the effectiveness of rituximab in post-transplant thrombotic microangiopathy, insufficient evidence exists to support routine use.[136] Malignant hypertension, disseminated malignancy, and sepsis are often misdiagnosed as TTP-HUS given the shared clinical features. However, there is no proven role for plasma exchange in these cases.[135,137]

Atypical Hemolytic Uremic Syndrome

Major progress has been made during the last decade in understanding the role of complement dysregulation in the pathophysiology of aHUS.[36] Plasma therapy is considered first-line treatment in aHUS cases despite an absence of randomized controlled studies.[138–140] Plasma infusion is thought to replace defective complement components and regulators

Table 3: Summary of Major *Escherichia coli* Enterocolitis and Diarrheal HUS Outbreaks Worldwide

	Walkerton, Canada n=2,300 (1999)	Lanarkshire, Scotland n=262 (1996)	Canadian Nursing Home n=55 (1985)	Germany n=3,816 (2011)
Organism	*E. coli 0157:H7*	*E. coli 0157:H7*	*E. coli 0157:H7*	*E. coli 0104:H4*
Proportion HUS	33/2,299 (1.4 %)	28 (11 %)	12/55 (22 %)	845/3,816 (22 %)
Proportion adults	15 %	79 %	100 %	88 %
Adult patients treated with TPE	None	16/22 (73 %)	None	Nearly all*
Adult mortality with TPE	1/3 (33 %)	5/16 (31 %)	n/a	4 %
Adult mortality no TPE	5/7 (71 %)	5/6 (83 %)	11/12 (92 %)	Unknown*

**Preliminary communications. HUS = hemolytic uremic syndrome; TPE = therapeutic plasma exchange.*

Table 4: Renal Involvement in Adult TTP-HUS Patients at Presentation and at Time of Last Follow-up as Reported in Worldwide Registry Data

	Germany 1989–2006 n=62	France 2000–2007 n=214	US 1989–2008 n=261	Korea 2005–2008 n=66	UK 2002–2006 n=178
Initial creatinine (mean µmol/l, range) ADAMTS-13 deficient	NR	114 (46–182)	141	140	96 (49–526)
Initial creatinine (mean µmol/l, range) ADAMTS-13 preserved	NR	454 (128–780)	404	246	96 (49–526)
AKI – no HD at presentation	7/62[a] (11 %)	NR	115/261[d] (44 %)	NR	59/178 (33 %)
AKI – HD need at presentation	32/62 (52 %)	NR	115/261[d] (44 %)	NR	0/178 (0 %)
Last renal follow-up	At discharge	17.8 months	4.7 years	At discharge	7 days
HD need at last follow-up	14/55 (25 %)	10/189[c] (5 %)	NR	NR	0/157 (0 %)
Renal impairment at last follow-up	14/55[b] (25 %)		26/183[e] (14 %)	NR	NR
Creatinine at last follow-up (mean µmol/l, range)	220 (88–458)				83 (41–512)
Risk factors for persistent renal impairment	New onset hypertension	Preserved ADAMTS-13		Preserved ADAMTS-13	

[a]Defined in study as serum Creatine (sCreat) rise by 0.5 mg/dl in 48 hours if no known history of kidney disease or rise by 1 mg/dl in 48 hours if baseline sCreat >1.5 mg/dl; [b]Defined in study as sCreat >1.5 mg/dl at discharge; [c]Presented in study as "proportion of patients with [end-stage renal disease] ESRD;" [d]Included acute kidney injury (AKI) with sCreat rise by 0.5 mg/dl in 48 hours or sCreat >4 mg/dl plus hemodialysis (HD) start within 7 days of diagnosis; [e]Defined in study as "sCreat not normal." NR = not reported.

with functional proteins[141] while plasma exchange offers the additional advantage of removal of mutant CFH, CFI, CFB, C3, and CFH autoantibodies while restoring functional complement regulators. One exception to this may be in patients with abnormal CD46, a noncirculating membrane-bound complement protein (MCP), which do not seem to respond to plasma exchange but may exhibit higher spontaneous remission rates.[142,143]

The second touted therapy in aHUS is eculizumab, given its capacity to inhibit the final pathway of complement activation.[144] To date, use of eculizumab in several patients with aHUS has been described including aHUS in native kidneys, aHUS recurrence treated post-transplantation, and prevention of aHUS with pretransplant treatment.[144–162]

Preliminary results from two international multicenter phase II trials conducted in 2009–2010 in adults and adolescents with native kidney or post-transplant aHUS who were either resistant to plasma therapy (17 patients) or dependent on chronic plasma therapy (20 patients) have been presented.[163,164] In these patients, a switch to eculizumab induced a rapid increase in platelet counts, cessation of hemolysis, and improvement or stabilization of renal function. No patients needed to return to plasma therapy or initiate dialysis. Further controlled studies are necessary to establish the role of eculizumab in aHUS, which remains an investigational and costly therapy at present.

While a number of other therapies including other immunosuppressant medications and intravenous immunoglobulin have been tried in aHUS, data supporting their use remains sparse and widespread use cannot be recommended.[110,165]

Typical/Diarrheal Hemolytic Uremic Syndrome

Approximately 15 % of children with shiga-toxin-mediated diarrhea will develop dHUS, a majority of whom will have severe renal impairment.[166] Treatment is supportive with judicious volume repletion and/or renal replacement therapy. Anti-motility agents, narcotic opiates, and non-steroidal anti-inflammatory agents should be avoided. Corticosteroids, anti-platelet agents, and anti-thrombotic agents are not effective. Antibiotic therapy should generally not be administered as it nearly triples the risk for dHUS development, possibly through bacterial lysis and liberation of shiga toxin, but should be rapidly instituted in patients with bowel perforation.[167]

Plasma exchange is routinely not indicated in dHUS due to a lack of proven efficacy in controlled studies.[168] In a subset of patients with severe neurologic symptoms, consideration for plasma exchange should be given, as severe neurologic symptoms are associated with higher rates of both death and progression to ESRD. In the same review that established this association, it was also shown that studies that used plasma exchange reported lower mortality rates than those who did not, a noteworthy detail even in the face of possible selection bias in those studies.[169]

Presence of severe neurologic symptoms should also prompt consideration of eculizumab based on the following observations. Complement dysregulation can play a pathogenic role in patients with clinically severe

dHUS and alteration of complement activation could ameliorate the disease course.[38,39] Eculizumab has been used with success in patients with aHUS as well as other glomerular disorders driven by complement dysregulation.[144,170] Lapeyraque et al. recently reported three children with rapidly progressive dHUS with severe renal and neurologic involvement who responded dramatically to eculizumab therapy, providing a rationale for further controlled study into this therapy.[171]

Limited data regarding adult dHUS are largely derived from epidemic outbreak reports as shown in *Table 3*, and demonstrate considerably higher mortality rates than seen in children.[172,173] The role for plasma exchange in adult dHUS was suggested by a report from the Lanarkshire outbreak where 16 of 22 adult dHUS patients were treated with plasma exchange and only five died (31 % mortality) compared with five deaths in six patients who did not receive plasma exchange. This observational study has been criticized for lack of a comparable control group and treatment allocation bias and controlled studies in this area are most definitely needed.

Many questions have recently arisen since the 2011 German E.coli 0104:H4 epidemic, the largest outbreak to date with 3,816 cases of enterohemorrhagic enterocolitis, and 845 cases of dHUS. Nearly all dHUS cases occurred in adults (88 %) and predominantly in females (68 %), probably reflective of the disease transmission vector.[174] Preliminary communications indicate that many patients received plasma exchange, a number of patients with severe neurologic involvement also received eculizumab rescue therapy, and a limited number of patients received immunoadsorption therapy.[175,176] Adult mortality rate was astoundingly low at 4 %, and neurologic outcomes were surprisingly good despite severity of presenting symptoms.[174,177]

These outcomes have spurred a heated debate regarding the role of plasma exchange and eculizumab in adult patients with dHUS.[178] While RCTs are needed to settle these matters, it is unlikely that a sufficiently powered trial could be designed outside of an epidemic. We eagerly await further detailed publications stemming from the German outbreak to outline whether favorable outcomes were driven by differences in host, organism, or therapy. In the absence of randomized studies, history may have to be our greatest teacher for now.

Long-term Outcomes

Adult TTP-HUS

Up to 80–90 % of incident adult TTP-HUS respond to plasma exchange therapy, of whom 30 % relapse within 10 years. Given the widespread occlusive microthrombosis that occurs in TTP-HUS, a number of short- and long-term sequelae are likely mediated by impairment in several organs. Renal involvement has been shown to be not uncommon in TTP-HUS patients at presentation and at last follow-up (see *Table 4*).

Central nervous system (CNS) involvement is common in TTP and HUS and when severe contributes to disease-related mortality. Recent studies have also demonstrated the long-term impact of residual CNS microthrombosis in patients with seemingly complete neurologic recovery. These include abnormalities affecting attention, alertness, memory, motor function, and endurance, in addition to clinically undetected brain abnormalities diagnosed on magnetic resonance imaging (MRI) studies.[179,180] In addition, survivors followed up to 5 years after initial presentation report persistently reduced health-related physical and mental quality of life, regardless of cause of TTP-HUS, ADAMTS-13 activity, duration of plasma exchange therapy, or severity of neurologic symptoms at presentation.[181]

Critical cardiac involvement is most likely more common than it has been reported. A recent review identified a total of 111 patients reported in the literature with documented cardiac involvement, of whom 47 had a total of 67 cardiac events, 31 died, and only 24 had preceding cardiac symptoms.[182] The majority of 'asymptomatic' patients had abnormalities in cardiac blood flow suggestive of small vessel disease. Little is known about long-term cardiac outcomes in survivors of cardiac events and whether early cardiac therapy would alter these outcomes.[183,184]

Adult and Childhood Diarrheal Hemolytic Uremic Syndrome

While most incident children with dHUS survive without plasma exchange and recover renal function, pooled data from a systemic review of nearly 3,400 patients indicate a 9 % long-term mortality rate over an average of 4 years.[169] In addition, 25 % of children face persistent renal impairment as evidenced by a glomerular filtration rate (GFR) <80 ml/minute, hypertension, or proteinuria, and 3 % progress to ESRD. Severity of neurologic and renal involvement are important predictors of both death and ESRD.

In adults, longitudinal data from the Walkerton epidemic have highlighted associations between severe enterocolitis and proteinuria, reduced renal function, cardiovascular disease, and hypertension.[185,186] However, little is known about the long-term outcomes of adult dHUS patients. The recent German outbreak will provide opportunity to fill this gap in knowledge.

Future Treatments

As our understanding of TTP and HUS progresses, a number of future treatment strategies are on the horizon and under study. These include anti-CD36 antibodies and recombinant ADAMTS-13 in idiopathic TTP-HUS and recombinant human factor H in aHUS.[187,188] Furthermore, experimental strategies aimed at early reduction in intestinal shiga-toxin absorption and prevention of downstream effects of shiga-toxin mediated endothelial injury are under investigation.[189] ■

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