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HUS AND TTP

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SYNOPSIS

This review will describe the epidemiology, pathophysiology, presentation, clinical causes, treatment, and long-term prognosis of pediatric patients who present with thrombotic microangiopathy (TMA). The focus will be on hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), the most common phenotypes of TMA.

Keywords

thrombotic microangiopathy (TMA); hemolytic uremic syndrome (HUS); thrombotic thrombocytopenic purpura (TTP); Shiga toxin (Stx); alternative pathway of complement (APC)

I. INTRODUCTION

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two rare clinical entities. They share a common underlying pathological process termed thrombotic microangiopathy (TMA), characterized by endothelial cell injury, intravascular platelet-fibrin thrombi, and vascular damage. The two illnesses can occur as sporadic cases, in epidemic outbreaks, or in a genetic/familial pattern. Although HUS and TTP are orphan diseases, they remain among the most common causes of acute kidney injury (AKI) in non-hospitalized infants and children. While most children exhibit recovery of renal function after an episode of TMA, some patients are left with permanent residual sequelae or progress to end stage kidney disease (ESKD).

The pivotal involvement of endothelial cells in both HUS and TTP was clear from the start based on histopathological examination of biopsy and autopsy material. However, the underlying basis of these disorders remained obscure for several decades after the original description of HUS by Gasser in the 1955 and TTP by Moschcowitz in 1925 (1). The landmark article by Karmali linking diarrhea-associated HUS to antecedent gastrointestinal infection by strains of *E. coli* that elaborate a toxin to cultured Vero cells was the first step that advanced the understanding of the cause of TMA (2). Subsequent studies indicated that the Vero toxin was, in fact, closely related to Shiga toxin (Stx). This was followed by studies that established a role of ADAMTS13 in the processing of von Willebrand factor (VWF) multimers. Moake demonstrated that TTP was caused by abnormally high levels of

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ultralarge VWF multimers due to congenital or acquired reductions in ADAMTS13 activity (3,4). In 1998, Goodship confirmed a linkage of atypical HUS (aHUS) to the region on chromosome 1 that contained the genes for a number of complement regulatory proteins (5). This was followed by the sequential demonstration that mutations in Factor H, Factor I, membrane cofactor protein (MCP, CD46), Factor B, C3, and thrombomodulin can cause familial cases of aHUS and contribute to all forms of TMA (6,7). These advances in molecular genetics began to unravel the cause of hereditary forms of HUS and TTP and led to the development of targeted therapies for both of these causes of TMA.

Thus, there has been substantial progress in the understanding of the pathogenesis and treatment of TMA. This chapter will focus on both HUS and TTP, with an emphasis on HUS because it is more common than TTP in children. A number of excellent reviews of diarrhea-associated HUS, aHUS, and TTP have been published in the last few years. As a consequence, this chapter will detail work done during the last decade, from 2000 to the present and highlight key advances in diagnostic and therapeutic aspects of this fascinating group of disorders.

II. CLASSIFICATION

HUS and TTP are characterized by the triad of microangiopathic anemia with red blood cell fragmentation, thrombocytopenia and AKI. TTP has the same three features plus the presence of fever and neurological symptoms, creating a pentad. HUS and TTP share a histopathological phenotype called thrombotic microangiopathy (TMA). This pattern of injury is characterized by primary damage to the vascular endothelial cell. The endothelium initially becomes detached from the underlying basement membrane and the subendothelial space is filled with amorphous material and fibrin. Within the vascular lumen, there are platelet-fibrin thrombi that can completely occlude the vessel. Fibrin predominates in HUS and platelets are more prominent in patients with TTP (8). There are four clinical categories of TMA:

1. Typical, diarrhea-associated HUS
2. Atypical, non-familial HUS
3. Atypical familial HUS
4. TTP

In the past, episodes of HUS that developed after a prodromal gastrointestinal illness were called diarrhea-associated or D+HUS. However, in view of the close linkage between infections with Stx-producing strains of *E. coli* (STEC) in the vast majority of cases of HUS, the term STEC-HUS has become the preferred nomenclature for this category of TMA (9). Clinical studies verify that episodes of STEC-HUS can be associated with significant neurological manifestations and TTP can be triggered by gastrointestinal illnesses, suggesting overlap between these two illnesses. However, the distinction between the entities is now on much more solid footing because the contribution of Stx, defective regulation of the alternative complement pathway, and disordered release of VWF in STEC-HUS, aHUS, and TTP, respectively, has been well established by basic science and clinical investigations.

III. PATHOPHYSIOLOGY

STEC HUS

There are two main variants of Stx produced by STEC. Stx2 is more likely to be associated with HUS (10). The diarrhea and colitis that occur during the prodromal illness probably

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reflect direct damage to gastrointestinal cells and ischemia from the disseminated microangiopathy. When a person becomes infected with an STEC strain, bacteremia does not result. Instead, Stx is elaborated by the microorganism, crosses the gastrointestinal epithelium via a transcellular pathway, and enters the bloodstream (11). Stx binds to polymorphonuclear leukocytes which may enable the toxin to be delivered and unloaded in the peripheral vasculature. Neutrophil-associated Stx is detectable in 60% of patients with STEC HUS and the amount of cell-bound toxin correlates with the extent of kidney injury (12). After entering the circulation, Stx rapidly binds to the glycosphingolipid, globotriaosylceramide (Gb_3), which is found on glomerular endothelial cells, mesangial cells, podocytes, and tubular epithelial cells. It also binds to Gb_3 on the endothelium in other organs, especially the brain (10). Once Stx binds, it is internalized via a retrograde pathway to the Golgi apparatus where it inhibits protein synthesis and causes damage to endothelial cells (13). The intracellular trafficking of Stx is blocked by manganese and administration of this cation protects against Stx-induced disease in experimental animals (14). The vascular damage leads to the release of thrombin, and increased fibrin concentrations. In addition to the increased fibrin, increased levels of plasminogen activator inhibitor-1 (PAI-1) block fibrinolysis and potentiate the thrombotic cycle (10,15). Increased shear stress within occluded vessels leads to perturbations in the processing of VWF multimers with uncoiling of the molecule and fragmentation. Both of these alterations activate platelets and promote thrombus formation. Although HUS only develops in 15% of people infected, microangiopathy and microvascular thrombi occur whether or not a diagnosis of HUS is made (10,16).

In addition to its direct effects on the endothelium, Stx induces an inflammatory response that is triggered by much lower levels of Stx than the amount needed to inhibit protein synthesis. This process includes a ribotoxic stress response, upregulation of adhesion molecules for leukocytes, and promotion of a prothrombotic state in blood vessels (15). Stx also directly leads to the release of multiple cytokines such as interleukin-8 (IL-8) and fractalkine and chemokines which contribute to cell damage (15). Recent findings indicate that Stx increases endothelial cell expression of the chemokine receptor CXCR4 and its ligand stromal cell-derived factor 1 (SDF-1). Specific blockade of this ligand-receptor system ameliorated STEC-HUS in mice (17). Plasma levels of SDF-1 are nearly fourfold higher in children with STEC enteritis who progress to HUS than in children who do not (17). Finally, there is activation of the alternative pathway of complement in children with STEC HUS, evidenced by high circulating levels of activated factor B (Bb) and the soluble membrane attack complex (SC5b-9), both of which normalize within 4-7 days after the onset of the illness (7,18).

aHUS

The injury to endothelial cells in aHUS is direct and is due to medications, infections or systemic illnesses. In patients with non-familial aHUS, the provoking disturbance is generally severe in nature, leading to overt TMA. In contrast, in children with familial aHUS, even slight endothelial damage during a mild viral upper respiratory illness can trigger TMA because of defective regulation of the alternative complement pathway. The alternative complement cascade is constitutively active because binding of C3 to factor B generates a catalytically active complex that leads to continued formation of C3bBb, the pivotal alternative pathway C3 convertase. A number of circulating (Factors B, H and I) and membrane bound (MCP, thrombomodulin) molecules interact to prevent continuous activation of the pathway and endothelial injury (19). Both inactivating (Factor H and I) and activating mutations (Factor B) have been linked to increased activity of the complement cascade and the development of aHUS (7).

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TTP

VWF is synthesized by endothelial cells and megakaryocytes and stored as ultra-large VWF multimers in Weibel-Palade bodies in the endothelium and as α-granules in platelets. Ultralarge VWF is proteolytically degraded by ADAMTS13 (a disintegrin-like and metalloprotease domain with thrombospondin type-1 motif, number 13) after it is secreted by endothelial cells, preventing accumulation in the blood stream. In addition, in vitro experiments in the absence of ADAMTS13 have demonstrated that a proportion of these ultralarge VWF multimers remain anchored to the activated endothelium. These multimers unravel, bind platelets, and wave in the direction of the flow. Inadequate ADAMTS13 activity on the cell surface and in the circulation promotes platelet aggregation and the formation of intravascular platelet-fibrin thrombi that are associated with episodes of TTP (20). In patients with TTP, there can be congenital deficiency (Upshaw-Shulman syndrome) inherited as an autosomal trait with disease onset in the neonatal period. Alternatively, there can be an acquired or idiopathic reduction in the synthesis of ADAMTS13 as a consequence of autoantibodies that disrupt protease activity. Antibody synthesis can be secondary to autoimmune diseases, systemic inflammation, or medications such as clopidogrel (8,21). ADAMTS13 proteolytic function declines to undetectable levels during episodes of overt TTP and normalization with resolution of the acute event (22).

IV. EPIDEMIOLOGY

Because the onset of all forms of TMA is usually abrupt and severe, and occurs in previously healthy children, most cases rapidly come to medical attention with prompt diagnosis. There have been case reports of unusual presentations in which one target organ was disproportionately affected, obscuring the systemic nature of the illness and delaying recognition of the underlying TMA. However, STEC infection is included in infectious disease surveillance programs sponsored by the Centers for Disease Control. Moreover, in most states in the US, STEC HUS is a reportable disease which yields accurate epidemiological information about this form of TMA

The incidence of STEC-HUS ranges from 6:100,000 in children under the age of 5 years to 1-2:100,000 in the overall population including adults over 18 years of age (10,15,23). The incidence of STEC-HUS has been steady despite increased public awareness and efforts by governments and the food industry to reduce the risk of food and waterborne transmission of STEC. Girls are affected more often than boys for no apparent reason. It occurs globally and in all racial/ethnic groups, except for African Americans among whom the disease is distinctly less common than in whites. Again, there is no explanation for this observation. STEC-HUS is primarily seen in children except in epidemics when it may occur in patients with a wider age spectrum. For example, from May 2011 until July 2011, several European countries, particularly Northern Germany, experienced one of the largest STEC-HUS outbreaks ever reported. The *E. coli* strain O104:H4 caused a unique multinational epidemic with 3,816 patients who suffered from enterohemorrhagic *E. coli* (EHEC) infection, 845 HUS cases, and 54 deaths (24,25). The illness predominately affected adults who experienced severe renal and neurological complications.

The incidence of both non-familial aHUS and familial aHUS is lower than STEC HUS, and taken together, they occur at a rate that is at most 10% of that for STEC-related forms of HUS (23). These two subcategories of TMA have been documented in virtually every country without an increased susceptibility by gender or racial group. TTP is as rare as aHUS, with an annual incidence in the range of 1-2 cases per million population. Like STEC HUS, it is more common in girls (3:2) and in whites more than in blacks (3:1). However, in contrast to STEC HUS, the incidence of TTP peaks during the third and fourth decades of life and is uncommon in pediatric patients (8,21).

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V. CLINICAL CAUSES

STEC HUS

E. coli O157:H7 remains the most common strain that causes STEC-HUS with a minority of cases due to other serotypes such as O111 and O26 (10). The causative strains vary with time and region. Non-O157 strains of *E. Coli* are an increasingly common cause of STEC HUS. In a report about the microbiology of STEC HUS during the period 2000-2006, these strains accounted for half of all STEC infections and the same percentage of isolates produced Stx2 as O157 strains (26). This underscores the importance of tests to detect Stx directly and that do not rely on stool culture to make the microbiological diagnosis.

Non-familial aHUS

The most common infectious trigger is *S. pneumonia*, linked to neuraminidase production by the microorganism (23,27,28). The incidence has been fairly steady, despite widespread use of pneumococcal vaccines with reduced overt disease rates in children. In fact, when serological studies are performed in a timely manner, it can be demonstrated that pneumococcal-related HUS is caused by bacterial strains that are not included in the 7- or 23-valent vaccines such as serotype 19A. Affected children with pneumococcal HUS tend to be young with a mean age of 1-2 years. In general, the disease is more severe compared to STEC-related disease. Up to 80% of affected patients require dialysis, compared to 40% in STEC HUS and there is a higher frequency of serious extra-renal complications; however, despite the initial intensity of the episode, most children recover from the acute illness and have normal kidney function at long-term follow-up (23).

Other infections, medications, and miscellaneous medical conditions can cause aHUS. HIV, *Mycoplasma pneumoniae*, Histoplasmosis, and Coxsackie virus are among the well-recognized infectious causes of sporadic aHUS. The most commonly prescribed drug class associated with TMA is calcineurin inhibitors (e.g., cyclosporine and tacrolimus). Chemotherapeutic agents such as mitomycin C, cytosine arabinoside, cisplatinum, and gemcitabine have also been implicated in this complication. Antiplatelet drugs, such as ticlopidine and clopidogrel can cause aHUS. Anti-angiogenesis treatment of malignancies can also provoke TMA. This complication has been reported after treatment with biological agents that block the activity of vascular endothelial growth factor (bevacizumab) or the tyrosine kinase vascular endothelial growth factor (VEGF) receptor (29). The range of malignancies that can cause TMA and aHUS includes solid organ tumors and the various forms of leukemia. SLE and the anti-phospholipid syndrome can lead to aHUS, especially in women. When TMA occurs in the context of pregnancy, it is described by the acronym HELLP (hemolysis, elevated liver enzymes, and low platelet count). In its milder form, it is characterized by hypertension and proteinuria, i.e., pre-eclampsia. The full-blown syndrome is associated with increased maternal and infant mortality and high circulating levels of the soluble VEGF receptor (sFlt1) or endoglin that inhibit the activity of VEGF (30).

The most common causes of non-familial HUS in pediatric patients are summarized in Table 1.

Familial aHUS

A genetic mutation in one or more of the complement regulatory proteins can be documented in 44-61% of patients with hereditary aHUS – a single mutation is present in most patients with combined mutations in less than 10% of cases (31,32). The genetic defects in patients with aHUS generally demonstrate incomplete penetrance, indicating that additional factors are needed for the disease to be manifest. Multiple mutations are three-fold more common in patients with a defect in the MCP or factor I genes compared to

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patients with a mutation factor H factor B or C3. The presence of combined mutations or single mutations along with risk haplotypes is most significant for patients with MCP mutations because that subgroup had an increased risk of progression to ESKD and less favorable outcomes after kidney transplant (31). The gene that has been most recently linked to aHUS is diacylglycerol kinase ε (DGKE), an enzyme present in endothelial cells. Using exome sequencing, recessive mutations were detected in 9 unrelated kindreds with aHUS. The altered DGKE protein activated protein kinase C and caused a prothrombotic state (33).

TTP

This form of TMA shares the same etiologic factors as HUS. For example, SLE is a trigger for TTP in both pediatric and adult patients, and recent reports suggest that up to 18% of individuals with this rheumatological disorder will develop TMA (34). Because of the higher prevalence of TTP in adults versus children, the underlying causes reflect disorders seen in older patients such as pregnancy, anti-phospholipid syndrome, anti-platelet and anti-arrhythmic drugs, cryoglobulinemia, and solid organ malignancies. Patients with cancer- and/or chemotherapy-induced TTP generally have a poor prognosis despite treatment.

VI. DIAGNOSIS

HUS is defined as the triad of hemolytic anemia with erythrocyte fragmentation, thrombocytopenia, and AKI occurring after a prodromal infection by a Stx-producing strain of bacteria. Some recent reports have made a diagnosis of “incomplete” HUS if only 2 out 3 criteria are present (35). This less stringent definition may introduce variability into the incidence of the disease in different locales. The criterion for anemia is age and gender dependent and the confirmation of the microangiopathic character is based on microscopic review of the peripheral smear and detection of schistocytes. The combination of hemolysis and tissue ischemia results in high serum LDH levels in all patients with HUS or TTP. The direct anti-globulin test (Coombs test) is negative. The platelet count that is diagnostic is below $150 \times 10^9/mm^3$. In contrast to patients with disseminated intravascular coagulation, the PT/INR, PTT and fibrinogen levels are normal in patients with HUS and TTP. However, there can be activation of the fibrinolytic pathway with increased circulating levels of fibrin degradation products. Complement levels are usually normal except for select patients with aHUS, in whom hypocomplementemia may be a clue to an underlying disturbance in complement metabolism.

The definition of renal dysfunction varies in different reports and ranges from abnormalities in the urinalysis to an elevation in the serum creatinine concentration above the 95th percentile for age and gender. Variations in the stringency of the definition of kidney disease may account for some of the variation in the severity of HUS (25).

Patients with STEC HUS have an antecedent episode of hemorrhagic enterocolitis, within 2-12 days before the onset of TMA. The diarrhea becomes bloody in 80-90% of cases as the colitis worsens. Among children with STEC enteritis, 5-15% will develop HUS, while the rest will have complete resolution of symptoms. Methods to prove STEC infection include stool culture, assays for free Stx in the stool, PCR assay to detect Stx genes in the stool, and serological tests to confirm a rise in antibody titer to the STEC strain. Less than 50% of patients with STEC HUS shed the bacteria in their stool at the time of diagnosis. Assays for free Stx or the toxin gene are more sensitive but are not routinely performed in all microbiology laboratories. In current practice, most clinical laboratories utilize only culture-based methods to detect STEC infection; however, the use of Stx assay kits rose nearly two-fold, from 6% in 2003 to 11% in 2007 (36). Demonstration of a rise in antibody titer confirms the bacterial infection but the information is usually unavailable at the time of the acute episode and cannot be used in making the diagnosis in real time.

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Non-familial forms of HUS occur sporadically and are diagnosed based on the complete history and physical examination with laboratory testing to confirm the suspected cause.

Patients with familial aHUS generally have disease that occurs throughout the year, that develops after an upper respiratory infection, and that follows a recurrent pattern with rapidly deteriorating kidney disease. Patients with aHUS secondary to a genetic mutation in a complement regulatory protein are just as likely to present during childhood and adulthood (32). The current recommendation is to measure the levels of complement components and to perform genetic testing for all known complement regulatory protein in patients who present with aHUS (6,28). The complete genetic profile helps delineate the short-term response and outcome after kidney transplantation if needed.

Patients with TTP have the same three features seen in children with HUS but also have fever and neurological findings. The diagnosis is made by assaying ADAMTS13 activity. This test requires care to standardize the assay procedure to ensure the accuracy and validity of the results. Recent reports have suggested that documentation of ADAMTS13 deficiency may not be sufficient to diagnosis of TTP. Instead it may be critical to assay enzymatic activity and to quantitate levels that are below 10% (37). This residual ADAMTS13 may be a major determinant of the clinical manifestations of TTP and account for disease heterogeneity.

VII. CLINICAL FEATURES

All of the forms of TMA are characterized by diffuse endothelial injury and can have adverse effects on every body organ. The kidney and brain are the primary targets in HUS and TTP (38), but other organs can be impacted as well and the percentage and severity will vary depending on the subcategory of TMA. Severe complications include seizures, cortical blindness, hemiparesis, adult respiratory distress syndrome (ARDS), myocardial dysfunction, pancreatitis, and liver failure (39). The frequency of major target organ involvement in the four categories of TMA is summarized in Table 2.

Mortality is generally higher in adults compared to children with STEC HUS. The situation is reversed in those with familial aHUS, in which children have a nearly nine-fold higher mortality rate compared to adults (32).

VIII. TREATMENT

STEC-HUS

Optimal care of children with STEC enteritis involves removal from their home environment to prevent spread of the disease to other household contacts. In addition, provision of adequate amounts of sodium-containing intravenous fluids may prevent activation of the coagulation cascade within the glomerular microcirculation and prevent the progression of the disease to full-blown HUS (40,41)

There is no proven therapy for STEC-HUS and, therefore, treatment centers on supportive management of renal failure, anemia, hypertension, and fluid-electrolyte imbalances. Renal replacement therapy is advised if there is anuria for at least 24 hours or oliguria (<0.5 ml/kg/hr) for at least 72 hours (42). This guideline is probably relevant to all forms of TMA. Clinical trials have failed to demonstrate a significant benefit, namely, reduced need for dialysis support or occurrence of serious extra-renal complications, for any of the following therapeutic options: antibiotics, anti-platelet drugs, intravenous immunoglobulin G, corticosteroids, anticoagulants, fibrinolytic agents, plasma infusion, plasmapheresis, and oral administration of a Stx binding agent.

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The agent that has received the most attention recently as a potential treatment for STEC HUS is eculizumab, a monoclonal antibody to C5a. During the peak of the large German outbreak in 2011, a Letter to the Editor of the New England Journal of Medicine was published describing three children, all three years of age, with severe STEC-HUS who were treated with eculizumab (43). The patients already required dialysis and two of them had been unresponsive to plasmapheresis. The neurological status as well as the platelet count and LDH improved dramatically after the first dose of eculizumab. Dialysis was discontinued within 16 days and all three children were discharged without neurological findings (43). Based on this limited experience, German nephrologists approached the manufacturer of eculizumab (Alexion Pharmaceuticals, Inc.) and received authorization to provide the antibody for “off-label” compassionate use during the outbreak of STEC-HUS to patients with the most severe clinical symptoms. At the Paul Ehrlich Institute, a multi-center, single arm, open-label 28 week clinical study was conducted to test the safety and efficacy of eculizumab on clinical markers of TMA and the serious complications in STEC-HUS. The protocol involved intravenous administration of the monoclonal antibody, 900 mg weekly for four weeks, then 1200 mg biweekly for a total of seven doses, based on prior experience in treating atypical HUS. Treatment could be extended for an additional eight weeks. A total of 328 patients with STEC-HUS received eculizumab during the outbreak. The study included 198 patients from 25 centers (38,44). The report of Loos el al (45) focuses on the clinical disease in 90 children who were treated at centers that participated in the German HUS Registry. 71% of the patients (64/90) required at least temporary renal replacement therapy and 23/90 (26%) had neurological symptoms. Most of the patients (77/90, 74%) received supportive care only, 17 received PE, and 13 were given eculizumab (together with plasma exchange therapy in 7 cases). The vast majority of the patients recovered and only one child died. After a median follow-up of four months, all but four patients had returned to normal kidney function and only five had residual neurological deficits that were slowly improving in all cases. Based on their findings, the authors conclude that the clinical profile of O104:H4 STEC is comparable to the disease caused by the O157 serotype and that there is no need for novel treatments such as plasmapheresis, besides intensive supportive care (46). However, regardless of the findings of the effect of eculizumab during the outbreak, it will be important to evaluate this agent in a randomized clinical trial. Extended follow-up of all patients of all ages is needed to document the incidence of long-term renal and neurological sequelae comparable to what has been done after the outbreak in Walkerton, Ontario (47).

Atypical HUS

Following FDA approval of eculizumab in September 2011, the monoclonal antibody has become the standard of care for all patients with aHUS (48). Plasma infusion or plasmapheresis may be implemented temporarily until the drug is received (53). However, prompt initiation of eculizumab therapy is associated with more rapid control of the disease and better outcomes. Eculizumab is currently prescribed regardless of the underlying genetic defect. The drug is usually given weekly until there is normalization of the platelet count and microangiopathic anemia. The frequency can then be reduced to every 2-4 week based upon the clinical response. Discontinuation of eculizumab has been associated with recurrence of disease (unpublished observations). Therefore, Alexion recommends maintaining antibody therapy indefinitely. However, in view of the high cost of the drug and the logistical issues involved in long-term intravenous administration of the agent, further clinical investigation is needed to determine the minimum dosage and frequency of eculizumab infusion that results in stable kidney function and prevention of relapses. . There are no data about efficacy in relationship to specific genetic causes or rescue therapy in patients who do poorly on eculizumab therapy.

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TTP

Unlike HUS, in patients with TTP, prompt implementation of plasmapheresis yields an overall response rate of 60-90%. Controlled trials have confirmed the superiority of plasma exchange therapy compare to plasma infusion. The usual protocol involves daily one plasma volume exchanges; however, the regimen can be intensified with an increased exchange volume or frequency of treatment in patients with a suboptimal response. Because children have a greater likelihood of responding to supportive care, plasmapheresis is often reserved for patients with poor prognostic indicators. Corticosteroids can induce a remission in up to 30% of patients. Other immunosuppressive agents such as vincristine, azathioprine, cyclosphosphamide, intravenous IgG can be implemented as primary therapy. The most recent biological agent that has been tried in patients with TTP is rituximab, the monoclonal antibody to CD20 on the surface of B-cells (49). Splenectomy and prostacyclin infusions have been tried as last ditch approaches to prevent repeated relapses of TTP in patients who are refractory to the standard of care. An overall approach to treatment of the various forms of TMA is summarized in Table 3.

IX. PROGNOSIS

STEC HUS

The prognosis of STEC HUS is generally good and most children recover fully from the acute episode without subsequent relapses (50). The mortality rate in children with STEC HUS is less than 5% (39). The vast majority of patients have normal renal function five years after their illness. The short-term risk factors for decreased renal function and poor outcomes (including death) are the severity of the initial disease (e.g. oligo-anuria fever, leukocytosis, colitis) and the need for dialysis (51,52). A more accurate assessment of kidney outcomes is possible one year after resolution of the episode. Those children with persistent proteinuria, i.e., urine protein:creatinine ratio >1, or hypertension are at greater risk of progression to CKD (53). In a recent meta-analysis of the long-term outcome of children with STEC HUS, up to 25% of children have evidence of CKD including hypertension, proteinuria, or reduced GFR (54). Children with STEC HUS who require kidney transplantation are not at risk for recurrent disease in the allograft.

aHUS

The outcome in children with non-familial atypical HUS is determined by the underlying disease. In addition, because the patients do not usually experience recurrences, the prognosis will reflect the degree of renal damage and the severity of any extra-renal complications that developed during the diagnostic episode of TMA. In most cases, there is recovery of renal function without permanent loss of renal function. Nonetheless, in general, the prognosis in these cases as a group is worse than in children with STEC HUS.

The overall prognosis for children with familial aHUS is much worse than in children with STEC HUS. Nearly 25% of patients die of CKD stage 5 or other serious complications of the disease. In addition, up to 70-80% progress to ESKD and require permanent dialysis. A higher percentage of adults compared to children with aHUS progress to ESKD after their first episode of disease (32). There is a substantial risk of recurrent disease after transplantation that is highest for factor H and I and lowest with MCP mutations (32). .

TTP

Although most patients with TTP respond to initial therapy, nearly 40% will have relapses that occur at a mean interval of 20 months from the initial episode. The long-term mortality rate with current therapy is well below 10%. Patients with malignancy-related TTP have a

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worse prognosis (74% 1-year survival), especially in those who have actively treated cancer (22% 1-year survival).

X. CONCLUSION

TMA is a rare but important manifestation of disease in pediatric patients. Although the clinical syndromes – STEC HUS, aHUS, and TTP – overlap, there are significant differences in the pathogenesis of these illnesses. The basis of treatment in most cases is reversal of the abnormality triggering the episode of TMA coupled with intensive supportive care. In some cases, improved understanding in disease has resulted in marked improvements in care, e.g. eculizumab in familial aHUS and plasmapheresis in TTP. However, the mortality and morbidity resulting from the TMA syndromes continues to be substantial. It is anticipated that future research in HS and TTP will result in more sensitive diagnostic methods to detect disease earlier in the course of the illness and the design of therapeutic agents that target the causative step in each subtype of TMA.

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KEY POINTS

- Thrombotic microangiopathy is a histopathological lesion that is present in all patients with HUS or TTP
- HUS is usually caused by antecedent infection with Shiga toxin producing strains of bacteria. Most patients recover with intensive medical care and less than 25% develop chronic kidney injury
- Familial forms of atypical HUS are linked to genetic mutations in proteins that regulate the activity of the alternative pathway of complement. Eculizumab, a monoclonal antibody to C5a is the standard of care for these patients.
- TTP is rare in children and responds well to treatment with plasmapheresis.

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TABLE 1

CAUSES OF NON-FAMILIAL ATYPICAL HUS IN CHILDREN

Category	Examples
Medications	Ticlopidine, tacrolimus, bevacizumab
Infections	S. pneumoniae, HIV
Systemic disease	SLE
Malignancy	Acute lymphoblastic leukemia (ALL) Bone marrow transplantation
Pregnancy	HEELP (Hemolytic anemia, Elevated Liver enzymes, Low Platelets) syndrome

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TABLE 2

MAJOR TARGET ORGAN INVOLVEMENT IN TMA

	STEC HUS	Non-familial aHUS	Familial HUS	TTP
Kidney involvement	100%	100%	100%	80-90%
Need for acute dialysis	40%	50%	50%	10%
Brain	40%	20%	40%	85%
Cardiovascular	30%	10-20%	30-40%	20%
Pancreas	25%	10%	20%	10%
Liver	10%	10%	10%	10%
Mortality	2-3%	5-30%	25%	10%

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TABLE 3

OVERALL APROACH TO TREATMENT OF CHILDREN WITH TMA

	STEC HUS	Non-familial aHUS	Familial aHUS	TTP
Supportive care	+	+	+	+
Treat triggering illness	−	+	−	−
Eculizumab	?	−	+	−
Plasmapheresis	+	?	Temporarily until start of eculizumab treatment	+