Hemolytic uremic syndrome; pathogenesis, treatment, and outcome
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Purpose of review
The hemolytic uremic syndrome (HUS) is the most common cause of acute renal failure in infants and young children, and is a substantial cause of acute mortality and chronic morbidity. It is therefore relevant and appropriate that pediatricians remain familiar with the various subsets of the disease including its classification, management, and outcome.

Recent findings
This review will focus on recent information relative to epidemiology, pathogenesis, treatment, and outcome. It will include some of the newer associations between HUS and a variety of infections, including, but not limited to E. coli 0157:H7 (Shiga toxin-mediated) HUS, as well as the ever-increasing number of associations between HUS and a variety of drugs. It will review some of the newer therapies for the more common subsets, but will acknowledge that choosing evidence-based therapies is often limited by our incomplete understanding of the various pathogenic cascades, and that with the possible exception of Shiga toxin-mediated HUS(D+HUS), long-term outcome information is often limited by small numbers and limited follow-up.

Summary
This review should provide a framework for making the proper diagnosis, implementing appropriate treatment, and advising the family about anticipated outcome.

Keywords
ACE inhibitors, complement system, factor H, hemolytic uremic syndrome (HUS), shiga toxin

Introduction
As with any syndrome, the hemolytic uremic syndrome (HUS) is a constellation of features, namely the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy. Like any syndrome, HUS has many causes, but in the pediatric age group 90% will be of the post diarrheal variety (D+ HUS), due to Shiga toxin (Stx) producing E. coli (e.g., 0157:H7). It is best to refer to the renal involvement in D+ HUS as acute nephropathy, since not all patients with this syndrome develop acute renal failure with azotemia; a few express only hematuria and proteinuria. Moreover, with D+ HUS some patients experience an incomplete form of the syndrome with one or more of the features missing. It is important for the pediatrician to remain cognizant of the ever-increasing number of cases caused by other (i.e., non E. coli) infectious agents, and drugs. Moreover, we are just beginning to identify and dissect the pathogenic cascades of the numerous subsets that comprise the 10% of cases labeled as atypical (e.g., D-) HUS.

To provide the context for the recent articles (October 2003–October 2004) included in this review, we have included a substantial amount of older material that is not cited in the reference section, but is available upon request.

Of the hundreds of manuscripts dealing with some aspect of HUS during this time interval, we have chosen about 50 that we felt most relevant and useful to the pediatrician. Our selection of those of special or outstanding interest was of course subjective, and we apologize to the numerous authors who wrote excellent articles that were not included due to either their very specialized nature and/or the length constraints of this review.

Epidemiology and pathogenesis
Although 90% of childhood hemolytic uremic syndrome (HUS) follows a colitis prodrome caused by Shiga toxin (Stx) producing E. coli (e.g., E. coli 0157), there is increasing awareness that other organisms, drugs, and conditions (e.g., bone marrow transplant, SLE, glomerulonephritis, malignant hypertension, systemic sclerosis, cancer, etc.), can also initiate the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute nephropathy that defines HUS. A definite causal relation has not been proven in many of the reports. Even so, the list of drugs, infectious agents, and conditions associated with atypical (non-diarrheal) HUS continues to grow.
The antiplatelet drug ticlopididine for example, a rare but known cause of HUS, has largely been replaced by clopidogrel, initially thought to be free of this side effect. It too has been reported to cause HUS [1]. Though rare in children and adolescents, advanced pancreatic cancer is usually managed with gemcitabine, also recently reported to cause HUS [2,3]. Of greater relevance to pediatricians is a recent report of a child who developed HUS during induction therapy with L-asparaginase and vincristine for ALL [4]. A comprehensive yet concise review of drug-induced HUS/TTP is available [5**].

The occurrence of HUS as a complication of bone marrow transplant is well known, but recent evidence suggests that the relation may be augmented by concurrent H. pylori infection [6]. A report of HUS occurring in a 12-month-old infant with infectious mononucleosis [7] is the third such reported association, though the pathogenesis remains obscure. There are two recent reports of Q fever (C. burnetti, infection) [8,9], one in Greece and the other in Canada, associated with HUS. The syndrome has also been reported to follow Staphylococcus-induced perianal abscess [10], as well as group A beta hemolytic streptococcal infections [11], CMV infection following liver transplant [12], relapsing viral hepatitis A [13], Hanta virus [14], and envenomization due to scorpion bites [15] are additional novel associations and probable causes of the syndrome.

More common and better-understood causes of non-E. coli (Shiga toxin) mediated HUS are those caused by S. pneumonia. In these cases the neuroaminidase producing S. pneumonia exposes the cryptic T-antigen present on erythrocytes, platelets, and glomeruli. This exposed cryptic antigen then reacts with anti-T-antibodies that are normally present in the plasma, that in turn damage red blood cells, platelets, glomerular endothelial cells and results in glomerular thrombotic microangiopathy (TMA). When an individual presents with pneumococcal pneumonia or meningitis, the T-antigen should be tested for and if present only washed red blood cells/or platelets should be administered and plasma products avoided [16].

Factor H deficiency is another fairly common atypical subset that is characterized by complement dysregulation. It is arguably the most difficult D-subset to manage and most cases progress to end stage kidney disease despite aggressive therapy [17]. Although serum complement is vital to innate immunity, newly generated complement activation products are extremely toxic and are consequently highly restricted in terms of time and space [18]. This protection is partly mediated by factor H, the regulator of the alternative complement pathway. Defects in this vital regulatory factor activate the complement system, resulting in complement deposition on glomerular endothelial cells with subsequent endothelial cells damage and secondary TMA (HUS). Quantitative deficiencies can be suspected by a low serum C3, and documented by a measurement of factor H. Determining qualitative (functional) abnormalities are more difficult and are available in only a few research laboratories. This defect in factor H can be inherited as either a heterozygous or homozygous disorder, and is the result of a number of mutations including nucleotide substitutions, insertions, or deletions, and is thus polymorphous relative to molecular abnormalities. This helps to explain the variability in clinical expression [19].

Recently, reduced expression of the membrane cofactor (MCF; CD46), also a widely expressed transmembrane complement regulator, has been recognized as a cause of familial HUS [20,21]. It inhibits complement activation by its regulation of C3b deposition on target cells [20].

Customary maintenance therapy for these disorders has been plasma manipulation (plasma infusion or exchange), and potential definitive therapy for factor H deficiency has been a liver transplant (the site of factor H production) [22] or a combined kidney-liver transplant [22], though the outcomes to date have largely been poor. Helpful reviews of factor H in both health and disease [23**], and the role of CD46 [24**] are both recommended reading.

Although largely a disease of adults, thrombotic thrombocytopenic purpura (TTP), a disorder with many overlapping clinical features with classic D+ HUS, is known to occur due to either a congenital absence (Upshaw-Schulman-Syndrome) of von Willebrand factor (vWF) cleaving protease enzyme (ADAMTS 13) activity, or to an acquired IgG antibody directed against this enzyme. Recently, an additional cause has been discovered, namely novel mutations that either reduce vWF synthesis or result in abnormal mRNA that reduces vWF activity during severe episodes to less than 3% of normal.

We are rapidly learning more of the epidemiology and pathogenesis of classic post-diarrheal HUS (D+HUS). We know that the syndrome is caused by Shiga toxin (Stx) producing enterohemorrhagic E. coli (EHEC). These organisms produce subunit cytotoxins composed of a single A subunit surrounded by five B subunits. They are highly lethal and belong to a new family of AB [5] toxins [25]. The pathogenic cascade starts with the ingestion of EHEC. Although cattle and other domestic (e.g., sheep) and wild (e.g., deer, seagulls) fauna as well as humans and food, beverage, and water contaminated with E. coli 0157:H7 are the major vectors, and serotypes, respectively, there are dozens of non-0157: H7 Shiga toxin (Stx) producing strains that can cause HUS as illustrated in an outbreak among attendees of a cheerleading camp [26]
where the most likely vectors were salad and ice, and the pathogen was \textit{E. coli} 011.

A general overview of the cascade of events starts with the ingestion of EHEC that causes a colitis that is usually bloody. The inflamed colon facilitates transmural absorption of Shiga toxins and lipopolysaccharide (LPS) into the circulation. The Stxs are then engaged by glycoprotein (Gb3) receptors on target cells in the gut, kidney, and occasionally other vital organs. It has been shown, however, that Stx binding to glomerular cells is heterogeneous due to variation in Gb3 expression within glomeruli [27]. Subsequent cellular internalization leads to inhibition of protein production, resulting in damage and/or death of the cells and detachment from their basement membranes. This is followed by secondary activation of platelets and the coagulation cascade that in concert results in the TMA that characterizes HUS.

\textit{E. coli} 0157:H7 may be the most prevalent EHEC to cause D+ HUS because it possesses certain virulence factors [28\textsuperscript{**}]. Some of the virulence factors that account for the pathogenicity of \textit{E. coli} 0157:H7 are certain virulence genes (\textit{e.g.}, stx2, \textit{eae} intimin, Z1640) [29–32]. Of the intimin genes, \textit{eae} has been studied and characterized the most, but at least 10 others have been identified [33]. The intimin gene \textit{eae} is located within the so-called pathogenicity island of the enterocyte effacement lesion, and is responsible for the tight adherence of the bacteria to the enterocyte. This tight attachment is thought to facilitate the transmural passage of the toxins into the general circulation.

It is interesting that activated platelets bind to Shiga toxin, further amplifying the pro-thrombotic state [34]. There is reason to believe that lipopolysaccharides (LPS) and apoptosis also play a role. Recently it has been shown in cell culture of human glomerular endothelial cells that there is a reduction of thrombomodulin (TM) protein production, resulting in damage and apoptosis from their basement membranes. There still may be time to interrupt the pathogenic cascade and ameliorate full expression of the syndrome by inhibiting the p38 MAP kinase pathway, and thus block the genes required for production of prothrombotic and pro-inflammatory cytokines (\textit{e.g.}, TNF-\(\alpha\)) [41\textsuperscript{*}]. For now however, therapy includes attention to fluid and electrolyte balance, providing full nutritional support coupled with the judicious use of blood transfusions, treatment of hypertension, and dialysis or blood pump assisted continuous venous-venous hemofiltration-dialysis (CVVHD). The latter, also known as continuous renal replacement therapy (CRRT), requires an intensive care environment, and is best used with a citrate (heparin free), anticoagulation system. CRRT is very useful for hemodynamically unstable patients.

Another virulence factor for the 0157:H7 serotype may be the hardness of this organism. This was recently demonstrated when an outbreak at a county fair was traced to a contaminated multipurpose building. Organisms collected in sawdust 42 weeks after the outbreak were identified by molecular fingerprinting as the same strain of \textit{E. coli} collected from the patients stools [36]. Surveys have found active disease producing \textit{E. coli} in environments up to 10 months following initial contamination [36].

**Prevention and treatment**

Since there have been no major treatment “breakthroughs” during the past 30 years when dialysis for infants and pediatric intensive care units became available in the developed countries, the emphasis continues to be on prevention. This includes safer slaughterhouse, meat processing, food handling and cooking standards and irradiation of raw meat products. However, these hardy pathogens are now ubiquitous, and cases of Stx-mediated HUS continue to occur.

The most promising preventive measure for those who have \textit{E. coli} 0157:H7 colitis but have not yet shown signs of HUS is the administration of humanized monoclonal antibodies (\textit{i.e.}, passive immunity) against the Shiga toxins during the 3 to 5 day window from colitis to onset of HUS. To make this test practical in the outpatient setting (\textit{e.g.}, emergency room) it must be coupled to a rapid detection test for Shiga toxins in the stool [37,38,39*]. Another possible technique would be to administer Stx receptor (Gb3) analogues to bind the Stxs in the circulation and effectively inactivate them before they could attach to Gb3 [40].

There is reason to use plasma manipulation (\textit{e.g.}, plasma infusions, plasma exchange) in those with classical \textbf{D+ HUS} (unless one can document that they also have Factor H or vWF cleaving protease deficiency). Although about one half of patients with \textbf{D+ HUS} require a period of dialysis, mortality rate is now down to 3 to 5%. Even so, some patients develop life-threatening extra-renal complications including intestinal necrosis and brain infarction with or without cerebral edema. Cerebral edema without stroke can occur and lead to fatal brain stem herniation syndrome. Mild pancreatic involvement is common,
but on occasion can be severe with necrosis and/or pseudocysts [42], that can leave the patient with insulin dependent diabetes, and on rare occasion, exocrine dysfunction. Less frequent involvement of vital organs includes the heart. Troponin subtype cTnI is useful in detecting myocardial injury, as exemplified in a child with congestive heart failure due to D+HUS [43*]. This life-threatening complication has been successfully treated with extracorporeal membrane oxygenation (ECMO), which should be reserved for the most severe cases [44].

When dialysis is required, it is usually for about 5 to 7 days, though long-term dialysis support is needed for some who eventually recover kidney function, though are usually left with residual kidney damage. Amazingly, recovery has been reported in two children following anuria and dialysis that persisted for 8 and 16 months, respectively [45].

Long-term follow-up is appropriate since about 30 to 50% of those surviving the acute phase of D+HUS are later found to have signs of kidney damage and/or hypertension [46]. Some who experienced pancreatic damage (hyperglycemia) during the acute phase of their disease and regain normal glucose levels, years later develop insulin dependent diabetes. Those with proteinuria with or without an impaired glomerular filtration rate (GFR) are probably suffering from hyperfiltration injury that can progress to eventual end-stage renal disease (ESRD) requiring renal replacement therapy (dialysis or transplant) for survival. There is evidence that the HUS population, like others with renal damage, benefit from the use of angiotensin-converting enzyme (ACE) inhibitors as they slow the progression of hyperfiltration injury [47*,48*]. In the 5 to 10% of HUS survivors who eventually develop ESRD, renal transplant should be the goal for those who had D+HUS. The recurrence rate is for D+ HUS is low [49*]. Those with atypical (e.g., Factor H deficiency) HUS experience a much higher recurrence risk [49*] and should be transplanted with circumspersion.

**Conclusion**

Hemolytic uremic syndrome is a trilogy that is usually caused by Shiga toxin producing *E. coli*, but can be precipitated by a variety of infections, drugs, and conditions. Treatment and natural history varies with the type of HUS, but is generally favorable with D+HUS of childhood; less than 5% of cases are fatal, and most survivors escape severe sequelae. The management and outcome of the D-subsets is less favorable and is hampered by our limited understanding of the multiple pathogenic cascades that characterizes this challenging group of patients.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


This very comprehensive, yet concise review of drug-induced HUS/TTP is of interest to the physician because it not only lists and classifies numerous groups of drugs, but includes pathogenesis when known, and includes tables that provide clinically useful information.

This is an excellent review that provides the practitioner with an understanding of the importance of factor H in both health and disease, it walks the reader through the complex structure, function, molecular biology, and relationship of factor H to renal disease, with an emphasis on HUS.

This article provides the practitioner with a review of specific new strategies for the rapid detection of E. coli Stx 1 and 2, and their potential utilization in clinical practice.


This gives the physician an overview of p38 MAP activity, and how blocking it prevented TMA in a rat model of HUS. This may provide a strategy to prevent the production of prothrombotic and pro-inflammatory cytokines that are thought to augment the host response to Shiga toxins.


This case report describes the treatment of a patient with congestive heart failure due to D+ HUS and provides the physician information regarding the utility of using of Trooping subtype catnip in diagnosing heart involvement in HUS.


Evidence that angiotensin-converting enzyme (ACE) inhibitors can be used to reduce hyperfiltration injury in D+ HUS patients left with renal damage is documented in this study. It is important reading for all who care for the 30 to 50% of patients left with renal damage following D+ HUS.


These observations provide further evidence that angiotensin-converting enzyme (ACE) inhibitors may be used to preserve renal function in D+ HUS patients by substantially slowing the progression of hyperfiltration injury.


This article compares the recurrence rates among different types of HUS following renal transplantation, and thus provides the physician with critically important guidance.