

Hemolytic-Uremic Syndrome

Background

Hemolytic-uremic syndrome (HUS) is a clinical syndrome characterized by progressive renal failure that is associated with microangiopathic (nonimmune, Coombs-negative) hemolytic anemia and thrombocytopenia.

Hemolytic-uremic syndrome (HUS) is the most common cause of acute renal failure in children and is increasingly recognized in adults.[1, 2] Thrombotic thrombocytopenic purpura (TTP), childhood HUS, and adult HUS differ in their clinical presentations, but these conditions have many common features. Gasser et al first described hemolytic-uremic syndrome (HUS) in 1955. In 1988, Wardle described hemolytic-uremic syndrome (HUS) and TTP as different entities, but in 1987, Remuzzi suggested that these 2 conditions are various expressions of the same entity. With the discovery of von Willebrand factor (vWF)-cleaving metalloprotease ADAMTS-13, hemolytic-uremic syndrome (HUS) and TTP are clearly different diseases despite their clinical similarities.[3, 4, 5, 6]

For excellent patient education resources, see eMedicineHealth's patient education articles Anemia, Blood in the Urine, and Acute Kidney Failure.

Pathophysiology

Damage to endothelial cells is the primary event in the pathogenesis of hemolytic-uremic syndrome (HUS). The cardinal lesion is composed of arteriolar and capillary microthrombi (thrombotic microangiopathy [TMA]) and red blood cell (RBC) fragmentation.

Classification

Hemolytic-uremic syndrome (HUS) is classified into 2 main categories, depending on whether it is associated with Shiga-like toxin.

Shiga-like toxin (Stx)-associated HUS (Stx-HUS) is the classic or typical, primary or epidemic form of hemolytic-uremic syndrome (HUS). Stx-HUS is largely a disease of children younger than 2-3 years and often results in

diarrhea (denoted D+HUS). One fourth of patients present without diarrhea (denoted D-HUS). Acute renal failure occurs in 55-70% of patients, but they have a favorable prognosis, and as many as 70-85% of patients recover renal function.

Non-Stx-associated HUS (non-Stx-HUS) can be sporadic or familial. As the name implies, infection by Stx-producing bacteria is not the cause, and disease may occur year-round without a gastrointestinal prodrome (D-HUS). Overall, patients with non-Stx-HUS have a poor outcome, and as many as 50% may progress to end-stage renal disease (ESRD) or irreversible brain damage. Up to 25% of patients die during the acute phase. The familial form is associated with genetic abnormalities of the complement regulatory proteins.

Recent concepts in the pathogenesis of HUS [7, 8]

Stx-associated HUS

In North America and Western Europe, 70% of cases Stx-associated HUS are secondary to *Escherichia coli* serotype O157:H7. Other *E coli* serotypes are O111:H8, O103:H2, O121, O145, O26, and O113. In Asia and Africa, it is often associated with Stx-producing *Shigella dysenteriae* serotype 1. Regarding Stx associated with *E coli*, Stx-1 is almost identical to Stx associated with *S dysenteriae* type 1, differing by a single amino acid. Stx-1 is 50% homologous with Stx-2. Stx-2 is associated with severe disease.

After ingestion, Stx-*E coli* closely adheres to the epithelial cells of the gut mucosa by means of a 97-kd outer-membrane protein (intimin). The route by which Stx is transported from the intestine to the kidney is debated. Some studies have highlighted the role of polymorphonuclear neutrophils (PMNs) in the transfer of Stx in the blood, because Stx rapidly and completely binds to PMNs when incubated with human blood. However, the receptor expressed on glomerular endothelial cells has 100-fold higher affinity than of PMN receptors; in this way, they thereby transfer the Stx-ligand to glomerular endothelial cells.

The binding of Stx to target cells depends on B subunits and occurs by means of the terminal digalactose moiety of the glycolipid cell-surface receptor globotriaosylceramide Gb3. Both Stx-1 and Stx-2 bind to different

epitopes on the receptor with different affinities. Stx-1 binds to and detaches easily from Gb3, whereas Stx-2 binds and dissociates slowly, causing more severe disease than that due to Stx-1.

Data from some studies have suggested that Stx favors leukocyte-dependent inflammation by altering endothelial cell-adhesion properties and metabolism, ultimately resulting in microvascular thrombosis. Findings from earlier studies suggested that fibrinolysis is augmented in Stx-HUS, but results of more recent studies revealed higher-than-normal levels of plasminogen-activator inhibitor type 1 (PAI-1), indicating that fibrinolysis is substantially inhibited.

Non-Stx-associated HUS

Non-Stx-HUS, or atypical hemolytic-uremic syndrome (HUS), is less common than Stx-HUS and accounts for 5-10% of all cases. It may occur at all ages, but non-Stx-HUS is most frequent in adults and occurs without prodromal diarrhea (D-HUS). Patients have an unfavorable prognosis. Stx-HUS can occur in sporadic cases or in families.

Sporadic non-Stx-associated HUS

In sporadic non-Stx-HUS, various triggers have been identified: nonenteric infections, viruses, drugs, malignancies, transplantation, pregnancy, and other underlying medical conditions (rare) (eg, antiphospholipid syndrome [APL], systemic lupus erythematosus [SLE]), among others).

Streptococcus pneumoniae infection accounts for 40% of all causes of non-Stx-HUS and 4.7% of all causes of hemolytic-uremic syndrome (HUS) in children in the United States. Bacterial neuraminidase removes sialic acids and thus lyses cell-surface glycoproteins and exposes Thomsen-Friedenreich antigen to preformed circulating immunoglobulin (Ig) M antibodies. These bind to the neoantigen on platelets and endothelial cells and cause polyagglutination and damage to endothelial cells. On clinical examination, the disease is usually severe and causes respiratory distress, neurologic involvement, and coma, with a mortality rate of up to 50%.

Familial non-Stx-associated HUS

Familial non-Stx-HUS accounts for < 3% of all cases of hemolytic-uremic syndrome (HUS). Both autosomal dominant and autosomal recessive forms

of inheritance are observed. Some data suggest genetic abnormalities in the complement regulatory proteins. Autosomal recessive hemolytic-uremic syndrome (HUS) often occurs early in childhood. The prognosis is poor, recurrences are frequent, and the mortality rate is 60-70%. Autosomal dominant HUS often occurs in adults, who have a poor prognosis. The risk of death or ESRD is 50-90%.

Factor H[9, 10, 11, 12]

Factor H (HF1) consists of 20 homologous units called short consensus repeats (CSRs) and plays an important role in the regulation of the alternative pathway of complement. HF1 also serves as a cofactor for the C3b-cleaving enzyme factor I in the degradation of newly formed C3b molecules. It controls the decay, formation, and stability of C3b convertase (C3bBb), and it protects glomerular endothelial cells and the basement membrane against complement attack by binding to the polyanionic proteoglycans on the surface of endothelial cells and in the subendothelial matrix.

Fifty HF1 mutations have been described in 80 patients who had familial (36 patients) and sporadic (44 patients) forms of non-Stx-HUS. The mutation frequency is 40% in the familial form and 13-17% in the sporadic form. One patient with Stx-HUS who did not recover renal function was noted to have a mutation in exon 23 of the factor H gene.[11]

Patients with HF1 mutations have partial HF1 deficiency that causes a predisposition to the disease rather than the disease itself. Mutant HF1 has normal cofactor activity in the fluid phase, but its binding to proteoglycans is reduced, because the mutation affects the polyanion interaction at the C-terminus of HF1. Suboptimal HF1 activity is often enough to protect the patient from complement activation in physiologic conditions. However, activation of complement pathways results in higher-than-normal concentration of C3b, and its deposition on vascular endothelial cells cannot be prevented because of the inability of mutant HF1 to bind to polyanion proteoglycans.

Two thirds of patients with non-Stx-HUS have no HF1 mutation, although as many as 50% have overactivity of the alternative complement pathway. This observation suggests that uncommon polymorphic variants of the gene for HF1 may be responsible for the disease in patients without an HF1 mutation.

Abnormalities in genes encoding for complement modulatory proteins (MCP gene) have been shown to predispose people to non-Stx-HUS.

Epidemiology

Frequency

United States

Stx-HUS occurs with a frequency of 0.5-2.1 cases per 100,000 population per year, with a peak incidence in children younger than 5 years, in whom the incidence is 6.1 cases per 100,000 population per year.

Non-Stx-HUS accounts for 5-10% of all cases of hemolytic-uremic syndrome (HUS), and the incidence in children is about one-tenth of that of Stx-HUS. This rate corresponds to about 2 cases per 100,000 population per year.

International

In children younger than 15 years, typical hemolytic-uremic syndrome (HUS) occurs at a rate of 0.91 cases per 100,000 population in Great Britain, 1.25 cases per 100,000 population in Scotland, and 1.44 cases per 100,000 population in Canada.

Seasonal variation occurs, with hemolytic-uremic syndrome (HUS) peaking in the summer and fall.

Mortality/Morbidity

For Stx-HUS, acute renal failure occurs in 55-70% of patients; up to 70-85% recover renal function.

For non - Stx-HUS, patients have poor outcomes, with up to 50% progressing to ESRD or irreversible brain damage. As many as 25% die during the acute phase.

Race

Hemolytic-uremic syndrome (HUS) occurs infrequently in blacks.

Sex

Both sexes are affected equally with hemolytic-uremic syndrome (HUS).

Age

Hemolytic-uremic syndrome (HUS) occurs mainly in young children; however, adolescents and adults are not exempt. In young children, spontaneous recovery is common. In adults, the probability of recovery is low when hemolytic-uremic syndrome (HUS) is associated with severe hypertension.

History

History findings may include the following:

Prodromal gastroenteritis (83%) - Prodrome of fever (56%), bloody diarrhea (50%) for 2-7 days before the onset of renal failure

Irritability, lethargy

Seizures (20%)

Acute renal failure (97%)

Anuria (55%)

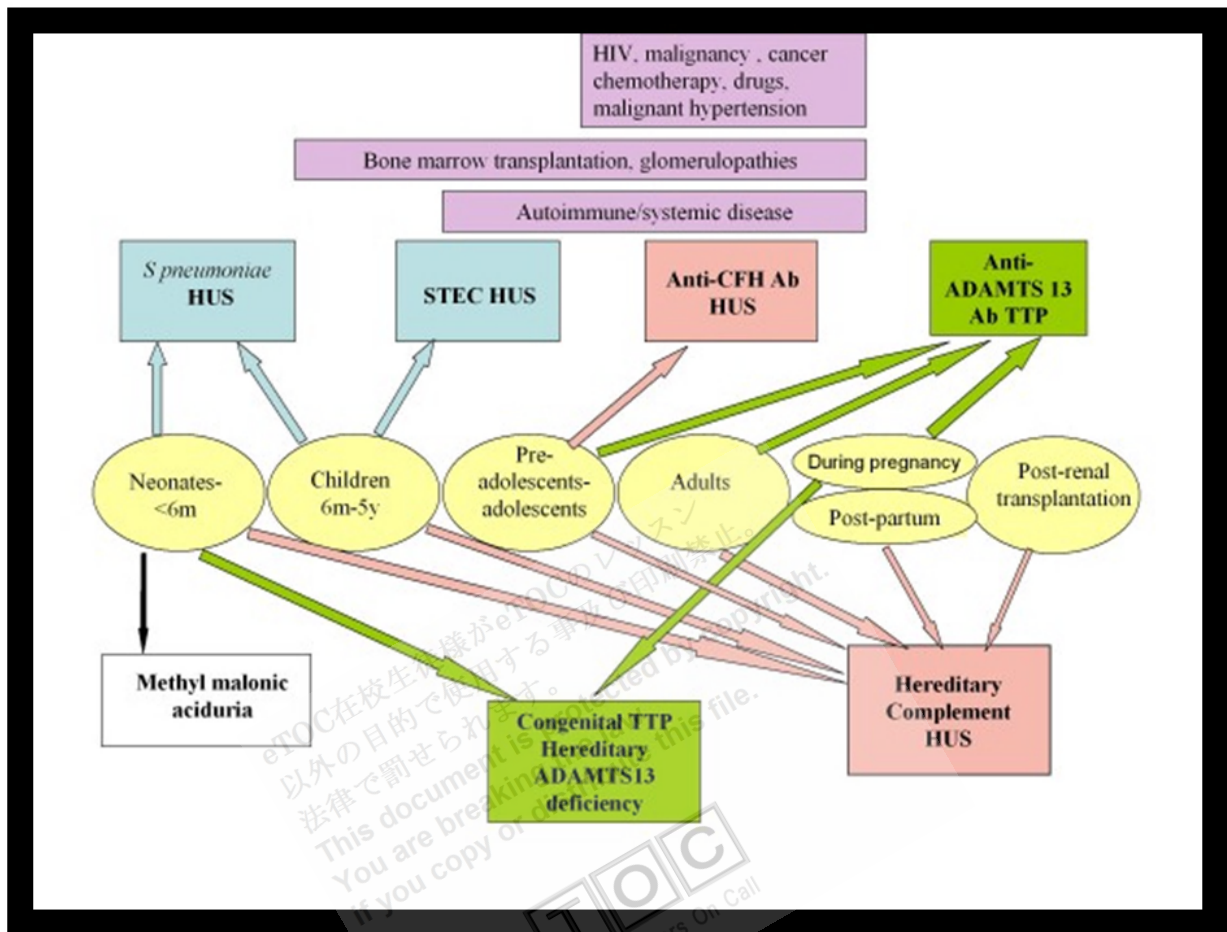
Physical

Physical findings may include the following:

Hypertension (47%)

Edema, fluid overload (69%)

Pallor, often severe



<http://www.ojrd.com/content/6/1/60/figure/F8>

Causes

Hemolytic-uremic syndrome (HUS) predominantly occurs in infants and children after prodromal diarrhea. In summer epidemics, the disease may be related to infectious causes.

Bacterial infections may include the following:

S dysenteriae

E coli

Salmonella typhi

Campylobacter jejuni

Yersinia pseudotuberculosis

Neisseria meningitidis

S pneumoniae

Legionella pneumophila

Mycoplasma species

Rickettsial infections may include Rocky Mountain spotted fever and microtubercles



<http://foodpoisoning.pritzkerlaw.com/archives/cat-hemolytic-uremic-syndrome.html>

Viral infections may include the following:

Human immunodeficiency virus (HIV)

Coxsackievirus

Echovirus

Influenza virus

Epstein-Barr virus

Herpes simplex virus

Fungal infections can include *Aspergillus fumigatus*.

Vaccinations may include the following:

Influenza triple-antigen vaccine

Typhoid-paratyphoid A and B (TAB) vaccine

Polio vaccine

Causes of the secondary or sporadic form may include the following:

Pregnancy and puerperium

Oral contraception

Cancers (chiefly mucin-producing adenocarcinomas)

Chemotherapeutic agents (mitomycin-C, cisplatin, bleomycin, gemcitabine)

Immunotherapeutic agents (cyclosporine, tacrolimus, OKT3, interferon [IFN])

Antiplatelet agents (ticlopidine, clopidogrel)

Malignant hypertension

Collagen vascular disorder (eg, SLE)

Primary glomerulopathies

Transplantation (eg, of kidney, bone marrow): This can be de novo or recurrent. It occurs in 5-15% of renal transplant patients who receive cyclosporine and in about 1% of patients who receive tacrolimus.

An immunodeficiency-related cause includes thymic dysplasia.

Familial causes account for 3% of all cases of hemolytic-uremic syndrome (HUS), and both autosomal dominant and autosomal recessive forms of inheritance have been reported. Autosomal recessive HUS occurs in

childhood, and patients have a poor prognosis with frequent recurrences and a mortality rate of 60-70%. Autosomal dominant HUS occurs mostly in adults, who have a poor prognosis; the cumulative incidence of death or ESRD is 50-90%.

No cause is identified in about 50% of all cases of sporadic non-Stx HUS.

Drugs implicated in causing non-Stx-HUS are as follows:

Anticancer agents: These include mitomycin, cisplatin, bleomycin, and gemcitabine. The risk for hemolytic-uremic syndrome (HUS) after mitomycin therapy is 2-10%, and onset may be delayed, occurring almost 1 year after the patient starts treatment. The prognosis is poor, with a 75% mortality rate at 4 months.

Immunotherapeutic agents: Examples are cyclosporine, tacrolimus, OKT3, and IFN.

Antiplatelet agents: Examples are ticlopidine and clopidogrel.

Posttransplantation hemolytic-uremic syndrome (HUS) is reported with increasing frequency and may be primary (de novo) or recurrent. It is often a consequence of the use of calcineurin inhibitors or of humoral (C4b positive) rejection. This condition occurs in 5-15% of renal transplant patients treated with cyclosporine and in about 1% of patients treated with tacrolimus.

Pregnancy-associated hemolytic-uremic syndrome (HUS) occasionally develops as a complication of preeclampsia. Patients may progress to full-blown hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Postpartum HUS usually occurs within 3 months of delivery. The prognosis is poor, with a 50-60% mortality rate, and residual renal dysfunction and hypertension occur in most patients.

Idiopathic hemolytic-uremic syndrome (HUS) accounts for 50% of all cases of sporadic non - Stx-HUS.

Reference: <http://emedicine.medscape.com/article/201181-overview#a0104>