# Haemolytic uraemic syndrome

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## Abstract

Haemolytic uraemic syndrome (HUS) is the most common cause of acute kidney injury (AKI) in children. It is categorized by a triad of clinical features, haemolytic anaemia, thrombocytopaenia and AKI. HUS is subdivided into two broad categories, diarrhoea positive HUS (more than 90% of cases) most commonly caused by Shiga toxin (Stx)-producing *Escherichia coli* (also called verotoxin) and the less common diarrhoea negative HUS. HUS is initiated by intestinal colonization with Stx-producing bacteria. HUS results in widespread thrombotic microangiopathy (TMA) in renal glomeruli, the gastrointestinal tract, the brain, and the pancreas. The aim of this review is to summarise the latest developments in our understanding of this condition, focussing on epidemiology, pathophysiology and disease course.

**Keywords** Acute kidney injury; haemolytic uraemic syndrome; pneumococcal haemolytic uraemic syndrome; shiga toxin; thrombotic microangiopathy

## How common? UK and worldwide

The overall incidence of haemolytic uraemic syndrome (HUS) in UK and Ireland is 0.71 per 100,000 children under 16 years of age. A prospective surveillance study of childhood HUS from 1997 to 2001 in UK and Ireland showed the highest incidence rates were in Scotland (1.56 per 100,000). The precise reason for this regional variation is unknown but this difference could be secondary to the relative population densities of livestock and humans and reliance on private water supplies in rural areas. The prevalence of HUS has remained unchanged since 1985. The incidence is similar across Europe, Australia and North America. Argentina is reported to have the highest incidence worldwide, 22 per 100,000.

HUS occurs sporadically in human populations with outbreaks occurring infrequently. The largest outbreak in recent history was in Germany in 2011, and was traced backwards to a rare Shiga toxin producing strain of *Escherichia coli*, *E. Coli* 0104:H4. The majority of affected individuals in this outbreak were adult females. Following post outbreak surveillance consumption of fenugreek sprouts was attributed but other vegetables were also implicated. All sufferers had resided or visited north Germany before becoming symptomatic.

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## Definition

The Swiss haematologist Conrad von Gasser first described HUS in 1955. He used the term to describe the combined symptoms of diarrhoea, haemolytic anaemia, thrombocytopaenia and acute kidney injury (AKI), which he observed in five children.

Haemolytic anaemia is defined as a haemoglobin level less than 100 g/l and fragmented erythrocytes on blood film. Thrombocytopaenia occurs when the platelet count is less than $150 \times 10^9$/l, and AKI with serum creatinine greater than the age-related range (more than 97$^{th}$ percentile) or glomerular filtration rate (GFR) less than 80 ml/min/1.73 m$^2$ by the Schwartz formula.

This description is still valid today however HUS is further subdivided in to two broad categories:

- Typical, usually diarrhoea positive D + HUS (more than 90% of cases)
- Atypical, usually diarrhoea negative D − HUS or aHUS (approximately 5% of cases)

The common causes of each category are listed in Table 1. The D + HUS is the most common cause of AKI in childhood.

## Epidemiology

The incidence of HUS is greatest in children under 5 years old and then peaks again in the elderly. Studies suggest greatest risk of developing HUS is in areas with high density of cattle. There is a seasonal variation with majority of cases occurring in the summer months.

Infections with Shiga toxin (Stx)-producing *Escherichia coli* (STEC; also called verotoxin, VTEC) is the greatest risk factor. *E. coli* 0157:H7 is the most prevalent serotype of STEC associated with human disease worldwide. STEC colonises animals without causing disease. STEC are not part of the normal human gut flora and transmission occurs mainly through ingestion of infected food or water, person to person spread and animal contact. Contaminated ground beef, unpasteurised milk products, vegetables, drinking water and petting of farm animals have been the source of infection in previous outbreaks. Isolated cases can also occur. Inoculation with 100 organisms is sufficient enough to cause disease. The incubation period is 1−8 days, although asymptomatic infection may occur. Shedding of the bacterium may persist for more than 3 weeks after infection.

Approximately 10% of children exposed to STEC will develop gastrointestinal symptoms. Of these children, 3−7% (isolated cases) or up to 20% in outbreaks will develop HUS.

## Pathology, pathogenesis and applied physiology

Understanding of the pathogenesis of HUS provides and explanation for the clinical course and facilitates a logical approach to treatment. Histologically, HUS results in thrombotic microangiopathy (TMA) in renal glomeruli, the gastrointestinal tract, brain and pancreas. TMA is characterized by vessel wall thickening at the arteriolar−capillary junction, with swelling or detachment from the basement membrane and intraluminal thrombosis that leads to partial or complete obstruction of the vessel lumen.

**Some causes of HUS depending on category type**

| Typical HUS | Atypical HUS |
|---|---|
| Infectious causes | Infectious causes |
| • *Escherichia coli* | • *Streptococcus pneumoniae* |
| • *Shigella dystenteriae* | Inherited forms |
| • *Citrobacter freundii* | • Complement abnormalities |
| | • Von Willebrand factor-cleaving protease constitutional deficiency |
| | • Cobalamin metabolism defect |
| | Autoimmune |
| | • Systemic lupus erythematosus |
| | • Scleroderma |
| | • Antiphospholipid syndrome |
| | Drugs |
| | • Cyclosporine A, tacrolimus |
| | • Cytotoxic drugs |
| | • Quinine |
| | • Oral contraceptives |
| | Other |
| | • Autosomal dominant and recessive types |
| | • Cancer associated |
| | • Pregnancy |
| | • Post renal transplant |
| | • HIV associated |

**Table 1**

HUS begins with intestinal colonization of STEC. Attachment of STEC to host intestinal enterocytes is aided by bacterial proteins. This causes destruction of microvilli and the symptom of watery diarrhoea. Further translocation of bacterial proteins from STEC into host enterocytes causes disturbance of cell structure and function.

The role of Stx is vital in the virulence of STEC. The toxin has two subunits, designated A and B. The A subunit has enzyme activity whilst the pentamer B subunit binds specifically to glycosphingolipid receptor (Gb3) on host cells. STEC have bacteriophages that encode Stx, strains can encode for more than one Stx if they process the specific bacteriophage. The *E. coli* 0104:H4 outbreak in Germany in 2011 was caused by an enteroaggressive *E. coli* that had acquired Shiga-toxin producing bacteriophages. Importantly, antibiotics can cause the release of these toxins hence the use of antibiotics is relatively contraindicated in the treatment of HUS

Binding of the toxin to Gb3 causes internalization of the A subunit, this is then cleaved into two parts. The A1 binds to ribosomes and disrupts protein synthesis causing cell death. The Gb3 receptor is found on glomerular endothelium, brain and pancreatic cells. The Gb3 receptor distribution helps to explain some of the clinical symptoms found in HUS. The presence of Stx in the intestinal lumen is also thought to trigger presence of inflammatory mediators (cytokines, interleukins) that cause endothelial damage and further promote platelet adhesion to the subendothelium. Damage to the intestinal epithelium allows Stx to enter the circulation in addition to causing local damage. Stx circulates bound to platelets, monocytes, neutrophils, as well as leucocyte complexes. The leucocytes used for transport are resistant to Stx associated cell damage therefore promote the spread of the toxin to distant sites. The finding of leucocytosis is a poor prognostic factor in HUS.

During the illness, platelets adhere to injured endothelium resulting in TMA. Multiple microthrombi lead to thrombocytopaenia. Stx induces tissue factor expression on endothelial cells, which is a receptor for coagulation factor VII. Via the extrinsic coagulation pathway, factor X is converted to Xa, which in turn promotes clot formation and further platelet activation.

Haemolysis of erythrocytes is less well understood and is assumed as a result of mechanical damage secondary to movement through occluded blood vessels.

Once transported from the intestines the main target organ is the kidney. Glomerular and tubular cells are damaged during the acute infection as Stx has a cytotoxic and apoptotic effect on glomerular endothelial and epithelial cells.

The pathophysiology of atypical HUS depends on the aetiology. Endothelial cell insult and damage is the histopathological manifestation regardless of cause. This may be caused by drugs, autoimmune or genetic mechanisms. In pneumococcal HUS, neuraminidase produced by pneumococcus exposes the T Antigen on erythrocytes which is then bound by pre-existing IgM antibodies and haemolysis.

## Course of the disease

After the initial incubation period D + HUS is usually preceded by gastroenteritis with bloody or watery diarrhoea (90% of cases), abdominal cramps, nausea and vomiting (50% of cases). The intestinal symptoms can lead to haemorrhagic colitis, colonic gangrene or perforation. Within 2 weeks of the intestinal symptoms the child develops pallor and jaundice secondary to haemolysis. Thrombocytopaenia is found on full blood count and clinically may manifest itself as petechiae or bleeding from mucosal surfaces. Renal involvement leads to oliguria/anuria, hypertension (20–30% of cases) and oedema. Renal involvement is typically seen between days 4 and 7 after the onset of diarrhoea. Fever is not usually a presenting symptom but the child may have a history of low grade pyrexia prior to presenting. Central nervous involvement can occur in up to 20% of children. Symptoms range can from irritability, seizures to cerebral encephalopathy.

In a small percentage of children cardiomyopathy and pancreatitis may also be a feature. Please refer to Table 2 for a list of clinical features associated with each system involved.

The duration of symptoms is variable, most commonly lasting 1–3 weeks. Improvement is usually accompanied by a rise in platelet count which typically precedes renal function recovery.

## Diagnosis, history and physical examination

In order to make the diagnosis a standard paediatric history together with emphasis on fluid balance is essential. Specifically ask about gastrointestinal symptoms, the tolerance of oral fluids and ongoing losses including urine output. Exploration of ingestion of infected food products, farm animal contact and person to person spread is essential.