

Diarrhoeal-associated haemolytic uraemic syndrome

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ABSTRACT Diarrhoeal-associated HUS is a common cause of acute renal failure, particularly in young children. The diagnosis is made by the presence of the following triad of findings: haemolytic anaemia (<10 g/dl), thrombocytopenia (<150 ×10⁹/l) and a creatinine value that is above the upper limit of normal for age. Ninety per cent of cases follow a diarrhoeal prodrome, and of these the majority are due to enterohaemorrhagic *E. coli* or VTEC. Sporadic and epidemic cases occur and sources of infection include undercooked meat, contact with farm animals and their faeces, and contaminated water, fruit, or vegetables.

Typically, children under three years of age are affected and present with abdominal pain and diarrhoea. The diarrhoea is often watery and soon becomes bloody. There may also be vomiting. The diarrhoea lasts on average for eight days, and the colitis can be so severe that children may present with an acute abdomen. Perforation, bowel infarction, and intussusception are rare complications. Rectal prolapse is a more common complication. Diagnosis of VTEC infection is by stool culture and serology.

Ten per cent of patients with VTEC infection go on to develop HUS. Of these, 50–60% will develop acute renal failure requiring dialysis. Extrarenal manifestations include seizures and somnolence, with cerebral infarcts and oedema being less common complications. Pancreatitis and altered glucose tolerance can occur and cardiac ischaemia has been reported. On average, dialysis is required for 8–10 days; those requiring dialysis for longer than four weeks are unlikely to make a full renal recovery. Acute mortality is 5–10%, being more common in patients with neurological involvement. End-stage renal failure develops in 3–5%, and up to 25% may be left with renal impairment. At one year after the illness, a normal GFR, normal BP, and absence of proteinuria are predictive of a complete recovery.

KEYWORDS Acute renal failure, diarrhoea, *E. coli* O157, Haemolytic uraemic syndrome

LIST OF ABBREVIATIONS Angiotensin-converting enzyme (ACE), blood pressure (BP), central nervous system (CNS), diarrhoea (D), diarrhoeal-associated HUS (D+HUS) end-stage renal failure (ESRF), glomerular filtration rate (GFR), haemolytic uraemic syndrome (HUS), interleukin-1 (IL-1), membrane cofactor protein (MCP), monocyte chemo-attractant protein-1 (MCP-1), thrombotic thrombocytopenic purpura (TTP), tumour necrosis factor- α ; (TNF- α), verocytotoxin-producing *Escherichia coli* (VTEC), white cell count (WCC)

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Diarrhoeal-associated HUS is a common cause of acute renal failure particularly in young children. The diagnosis is made by the presence of the following triad of findings: haemolytic anaemia (<10 g/dl), thrombocytopenia (<150 ×10⁹/l) and a creatinine value that is above the upper limit of normal for age. Ninety per cent of cases follow a diarrhoeal prodrome, and of these the majority are due to *Escherichia coli* O157. Non-diarrhoea-associated, or atypical HUS, D- HUS, will be discussed briefly later.

Haemolytic uraemic syndrome was first described in 1955, and by 1983 the link was made with enterohaemorrhagic *E. coli* or VTEC. Approximately 10%

of patients with VTEC colitis will go on to develop HUS; it is the young and the elderly who are most susceptible. Of patients developing HUS, approximately 50–60% will require dialysis.

EPIDEMIOLOGY OF VTEC

Verocytotoxin-producing *E. coli* was first isolated from patients during an outbreak of severe bloody diarrhoea in 1982 in Oregon, USA. The outbreak was linked to ingestion of hamburgers and the same organism was also isolated from the ground beef that had been used to make the hamburgers. This new class of *E. coli* was termed

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enterohaemorrhagic *E. coli* and the organism was designated *E. coli* O157:H7. This class of *E. coli* produces a toxin which is similar to that produced by *Shigella dysenteriae* (Shiga toxin), which is lethal to Vero cells in culture, hence the names verocytotoxin- or shiga-toxin-producing *E. coli*. Most, but not all, VTEC are O157:H7; other serotypes are found. In Australia, the major pathogen is *E. coli* O111:H-, with O157 being rare.

The main reservoir for *E. coli* O157 is the intestine and faeces of cattle, although it is also found in sheep and other animals. Infection may follow contact with farm animals or their faeces. The infective dose for humans is small, being only 10–100 organisms, much less than many other enteric pathogens. Most cases are sporadic, but outbreaks do occur, and can be due to eating undercooked or contaminated meat, drinking contaminated water (often private water supplies), fruit or fruit juices, as well as unpasteurised milk. Outbreaks associated with petting zoos have also occurred. Person to person contact has been reported during outbreaks in daycare nurseries, and transmission to staff has also been reported. An outbreak of *E. coli* O157 diarrhoea in Atlanta, Georgia, in 1998 was linked with visits to a water park.

Cases are most common in the summer and autumn, which may reflect seasonal excretion of the organism by cattle. The prevalence of the organism in cattle varies between 10–20% or higher. Rates of up to 44% have been reported in Argentina, which has a high incidence of HUS in children.

Non-O157 strains of *E. coli* have been associated with bloody diarrhoea and HUS, e.g. O111:H-. Haemolytic uraemic syndrome may also be associated occasionally with other *E. coli* infections, such as urinary tract infections.

PATHOGENESIS

In the large bowel, VTEC binds to the gut epithelial cells. Shiga toxins can enter the circulation bound to polymorphic mononuclear cells. The main target of the toxin is the endothelium. The toxin binds to the Gb3 receptors on endothelial cells and the bound toxin is internalised by receptor-mediated endocytosis, a process that eventually leads to cell death. Organ damage is assumed to be due to the resultant tissue ischaemia that follows vascular injury. Interaction of the toxin with monocytes and macrophages causes release of IL-1 and TNF- α , which in turn increases the expression of toxin receptors on endothelial cells, thus causing further damage. The main target is the renal endothelium, but other organs can be affected.

In addition to the direct effect of the toxin, the pathogenesis of HUS also involves increased expression of chemokines and cytokines. Circulating levels of IL-1 and -8, TNF- α , and MCP-1 are elevated and the magnitude

of the increase has been shown to correlate with disease severity. A high WCC at presentation is a well-recognised adverse prognostic factor in HUS.

SYMPTOMS

It is typically children under three years of age who are infected, and they present with abdominal pain and diarrhoea. The diarrhoea is often watery and soon becomes bloody. There may also be vomiting. The incubation period is 1–8 days after contact. The diarrhoea lasts on average for eight days, and the colitis can be so severe that children may present with an acute abdomen. Perforation, bowel infarction, and intussusception are rare complications. Rectal prolapse is a more common complication. If HUS ensues, within a few days children are noted to be pale and to have a reduced urine output. The platelet count and haemoglobin levels fall, and the urea and creatinine levels rise.

Extrarenal manifestations include CNS involvement, which may be seen in 25% of patients. Somnolence and seizures are the most common symptoms, but extensive CNS involvement may occur, with infarction or cerebral oedema. Mild elevation of liver enzymes is very common; pancreatitis and cardiac ischaemia are less frequent complications.

INVESTIGATIONS

Initial blood tests are required to check a full blood count, renal and liver function, as well as glucose and amylase levels. A blood film will confirm thrombocytopenia and typically shows the presence of schistocytes and helmet cells (red blood cells destroyed by fibrin thrombi) representing a microangiopathic haemolytic anaemia. Coombs' test will be negative. Blood should also be sent for *E. coli* O157 IgM antibodies, should stool microbiology prove to be negative. Other family members and close contacts should be screened for *E. coli* O157, as infection can be asymptomatic. The Public Health department should be contacted, and contact with the public avoided until two stool samples are negative on culture. *E. coli* O157 is detected in the laboratory by the fact that it does not ferment sorbitol. However recent outbreaks have been caused by organisms that do ferment sorbitol.

Verocytotoxin-producing *E. coli* in the stool can be isolated on culture, or detected by more detailed methods to detect the O157 lipopolysaccharide or the type 1 or 2 Shiga toxins themselves.

CLINICAL COURSE

The platelet count usually falls to less than $50 \times 10^9/l$, but haemorrhagic complications are rare. The haemoglobin

can fall swiftly and most children with HUS will require one or more blood transfusions. Dialysis is required in 50–60% of children with HUS. Anuria lasts on average 8–10 days. The first sign of recovery is an increase in the platelet count.

TREATMENT

No treatments have been shown to be effective in preventing the progression of VTEC infection to HUS. The use of antibiotics in treating the diarrhoeal illness is associated with a worse outcome, and is not recommended. Similarly, the use of anti-motility agents may worsen outcome and should be avoided. Unfortunately, a trial of an oral agent that binds Shiga toxin did not show any benefit in terms of preventing the need for dialysis, nor was there a reduction in the incidence of death or serious extrarenal events.

Treatment is therefore supportive. Initial assessment of fluid balance is critical as patients are often fluid depleted, and therefore require fluid resuscitation. However, once the intravascular volume has been restored, renal function should be monitored carefully, and fluid input should only equal insensible losses plus any other output, in an effort to avoid fluid overload. Inappropriate administration of fluid can be associated with hypertension, fluid overload, and hyponatraemia. The combination of the latter and hypertension can precipitate seizures, which may occur in up to 10–20% of patients.

Red cell transfusion is commonly needed, but platelet transfusion rarely so, and should be avoided where possible, as there is a theoretical risk of increasing microthrombi formation in the renal vasculature.

Of the children who develop HUS, 40% become anuric and 50–60% require dialysis. Most children are managed with peritoneal dialysis, but if the abdominal symptoms are severe or if there is significant neurological involvement, then haemodialysis is the treatment of choice. For the latter group, plasma exchange may be employed. There is no controlled evidence of benefit in HUS, but experience of its use in TTP in adults is encouraging in this group of patients whose outlook can be poor. Treatment with anticoagulants, steroids, and other agents have been tried without benefit.

OUTCOME

There remains some uncertainty over the long-term outcome of diarrhoeal-associated HUS, as most of the studies in the literature involve small numbers of patients followed up for relatively short periods of time. A meta-analysis and review of the literature suggests an acute mortality rate of 5–9%; death is due to CNS involvement, hyperkalaemia, congestive heart failure, and pulmonary haemorrhage.

In the majority of patients, renal function will recover, but some will be left with a reduced GFR, hypertension, or proteinuria. Approximately 3–5% will not recover renal function acutely, and will remain on renal replacement therapy, but it is clear from prolonged follow-up studies, that a greater percentage will be left with some degree of renal impairment (up to 25%), which results in chronic renal failure over time. Patients who are left with renal sequelae may benefit from treatment with ACE inhibitors.

Adverse prognostic factors at presentation are oligoanuria, dehydration, an elevated WCC $>20 \times 10^9/l$, and haematocrit of $>23\%$. The severity of the acute illness, especially the presence of CNS involvement, is strongly associated with poorer outcome. Anuria and dialysis for greater than eight days is associated with a worse renal prognosis; namely reduced GFR, proteinuria, or hypertension. No patient requiring dialysis for more than four weeks has been reported to make a full renal recovery.

The prognosis for patients with mild HUS who do not require dialysis is much better, but some of these patients have been reported to develop renal sequelae and even chronic renal failure, with prolonged follow-up.

Taking four studies together, however, a normal GFR, normal BP, and absence of proteinuria a year or so after an episode of D+ HUS are associated with complete recovery.

For patients with D+ HUS who develop ESRF, the disease should not recur in a renal transplant.

ATYPICAL HUS

Approximately 5–10 % of cases of HUS are not associated with diarrhoea, so-called D– HUS. D– HUS comprises a heterogeneous collection of conditions, most of which have a worse outcome than D+ HUS. The condition may follow a relapsing course. Acute mortality can be up to 25% and nearly 50% develop end-stage renal failure. Haemolytic uraemic syndrome can be associated with a number of medications (anti-neoplastic agents, anti-platelet agents, and the calcineurin inhibitor immunosuppressants ciclosporin and tacrolimus) and underlying conditions, such as connective tissue disease, malignancy, transplantation, and pregnancy. Some cases may be idiopathic. Some cases are familial and autosomal recessive, and dominant forms have been described. The underlying causes include abnormalities of complement regulatory proteins, such as Factor H, MCP, and Factor I.

Another infective cause is HUS associated with pneumococcal infection, which is reported to be increasing in incidence, and which is associated with a higher morbidity and mortality than D+ HUS.

KEYPOINTS

- Ten to fifteen per cent of patients who develop colitis due to *E.coli* O157, go on to develop HUS. The young and the elderly are most likely to be affected.
- The diagnosis of HUS is made by the combination of diarrhoea, which is often bloody, anaemia, thrombocytopenia, and elevated creatinine.
- Acute mortality is 5–10%, and 50–60% will require acute dialysis.
- Neurological involvement can occur in 25% and is associated with a worse outlook.
- Up to 25% may be left with renal sequelae including hypertension, proteinuria, and reduced glomerular filtration rate. This is more likely in those requiring dialysis for more than eight days.
- There are no proven treatments for HUS, but plasma exchange is thought to be beneficial in those with severe neurological involvement.

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