The Pathogenesis and Treatment of Hemolytic Uremic Syndrome

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The assignment of patients with hemolytic uremic syndrome (HUS) to diarrhea-associated (D+ HUS) and atypical D− HUS subgroups (1) is no longer valid (2). In this review, we use the abbreviation Stx for the Shiga toxin protein (3). To conform with this new terminology, we use the term Shiga toxin-associated HUS (Stx HUS) for cases either caused by, or presumed to be caused by, Stx-producing bacteria (Table 1). However, D+ HUS and Stx HUS are used interchangeably in those instances in which the authors cited in this review may not have determined whether their patients had evidence of infection with Stx-producing Escherichia coli.

The supposition that atypical (non-diarrhea-associated) HUS is a heterogeneous subgroup of HUS that differs from diarrhea-associated HUS on epidemiologic, clinical, laboratory, histologic, and prognostic grounds (1) is not entirely correct because some patients with HUS caused by Stx-producing Escherichia coli do not have diarrhea (4). In addition, because individuals with inherited types of HUS were included under the rubric of atypical D− HUS, we propose that idiopathic HUS is a more appropriate term than atypical D− HUS. There are many causes of the hemolytic uremic syndromes (5,6) (Table 2), but the purpose of this review is to describe the pathogenesis and treatment of Stx-associated HUS, of idiopathic HUS (atypical HUS), and of the important subset of the inherited forms of HUS. Inherited HUS is reviewed briefly because people with autosomal recessive or autosomal dominant inheritance of HUS share many of the clinical and histopathologic features of idiopathic HUS (atypical D− HUS).

Shiga Toxin-Associated HUS

Stx HUS is the most common type of HUS (7,8). It is a clinicopathologic entity with a well defined cause, pathogenesis, and clinical course. This is the typical, classical, sporadic, and epidemic form of HUS that occurs mainly in childhood but can also affect infants and adults. Stx HUS is characterized by the sudden onset of hemolytic anemia (with fragmented erythrocytes), thrombocytopenia, and acute renal injury, after a prodromal illness of acute gastroenteritis, often with bloody diarrhea. However, Stx HUS can occur without diarrhea (4) and in association with a urinary tract infection (9). The manifestations of acute renal failure predominate over those of brain involvement. The pancreas, lungs, heart, and other organs may be injured (10). Stx-producing Escherichia coli, unlike Shiga dysenteriae type 1 (11), is an uncommon cause of HUS in black people. More than 95% of patients with HUS caused by Stx-producing Escherichia coli recover from the acute illness, and recurrences are unusual.

Epidemiology

Stx HUS occurs sporadically and in epidemics. Prompt recognition of an outbreak and identification of the source can prevent serious illness in many individuals and save lives while leading to a better understanding of risk factors for Escherichia coli O157:H7 infection (12). Outbreaks may be traced to a single source of contaminated food or water, but the importance of person-to-person spread of Escherichia coli must be emphasized (13). The infective dose of Escherichia coli O157:H7 is 50 to 100 organisms, and the incubation period to onset of diarrhea is 1 to 8 days. Younger children may continue to excrete the bacteria for more than 3 weeks after the infection. Asymptomatic, prolonged carriage of Escherichia coli O157:H7 is unusual.

Pathogenesis

Vascular endothelial cell injury is central to the pathogenesis of all forms of HUS, but there is increasing evidence that renal tubular cells are injured in Stx HUS (Table 3) (14). Shiga toxin-producing Escherichia coli (STEC) are the major cause of hemorrhagic colitis and are responsible for most cases of HUS (2). STEC toxins are also called Shiga-like toxins because they are related to Shiga toxin (Stx), the exotoxin produced by Shigella dysenteriae type 1. Human STEC strains produce Stx1, Stx2, and variants (Stx2c, Stx2e). STEC colonize colonic mucosa, adhere to mucosal villi, and release Stx. It is unclear whether Stx is released in a single wave, as multiple waves, or continuously, because Stx cannot be detected in the serum. The five B subunits of Stx bind to the glycolipid receptor glycosphingolipid globotriosyl ceramide (Gb3) on endothelial cells. The A unit is internalized by receptor-mediated endocytosis and causes cell injury by inactivating the 60S ribosomal subunit (15). Gb3 receptors are present in greater density in the cortex than medulla of human
kidney endothelial cells. The central role for endothelial cell injury is based on histologic and ultrastructural demonstration of swollen, detached endothelial cells. Endothelial cell injury exposes the thrombogenic basement membrane, and this causes platelet activation and local intravascular thrombosis. The predominant lesions seen in patients who die within days of the onset of Stx HUS are glomerular thrombi that appear to extend into the arterioles (16).

Endothelial cells may be injured by inflammatory and non-inflammatory mechanisms (17). Evidence for a role of inflammation is derived from the marked leukocytosis that occurs in the early phase of the illness, the finding of a transient leukocyte infiltration in glomeruli, and the demonstration of neutrophil activation. STEC-derived lipopolysaccharide (LPS) activates neutrophils that in turn release tumor necrosis factor-α (TNF-α), interleukin-1, elastase, and free radicals (18,19). Leukocyte adhesion is stimulated by Stx1 under dynamic flow conditions (20). Stx1 influences the interaction between leukocytes and endothelium in vitro and increases leukocyte adhesion possibly by upregulation of adhesive proteins on the surface of endothelial cells (18). The concept of “rolling” leukocytes may explain leukocyte–endothelial interactions without histologic demonstration of leukocytes in glomeruli (20). TNF-α or LPS or both prime the endothelial cells to undergo apoptosis when exposed to picomolar amounts of Stx (15,21). TNF-α or LPS together with Stx may act synergistically to damage the vascular endothelium.

Coagulation studies usually reveal normal prothrombin and partial thromboplastin times, normal or elevated factors V and VIII, normal fibrinogen turnover, and elevated fibrin split products (14). There are perturbations in the antithrombotic system with reduced prostacyclin, thrombomodulin, tissue plasminogen activator, and heparin-like molecules that activate antithrombin III. In addition, the serum levels of prothrombotic substances are increased. These include tissue factor, platelet-activating factor, tissue plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor, and thrombomodulin A2. Thrombocytopenia is caused by increased platelet consumption and destruction, and is characterized by intravascular activation of platelets. Infused autologous platelets are taken up by the spleen and liver. Platelet survival is shortened and platelets circulate in an exhausted, degranulated state. Platelet activation may persist for weeks after the platelet count has returned to normal. Platelet activation may decrease local glomerular fibrinolysis by producing PAI-1. Increased PAI-1 levels are detected in the sera of patients with HUS (22). Erythrocyte fragmentation, an important feature of HUS, is caused in part by neutrophil release of free radicals that mediate lipid peroxidation of the red blood cell membranes (23). Erythrocyte membranes become more rigid and undergo increased shear stress as they pass through fibrin-lined microvessels. In addition, leukocytes may release cytokines that damage erythrocyte membranes. Ultrastructural studies of Buffy coats from patients with HUS reveal leukocytes with projections in intimate contact with erythrocytes that suggest the possibility of site-directed cytokine release.

Renal Histopathologic Findings

The earliest histopathologic changes in the kidneys of these patients are leukocyte infiltrates and thrombi. These resolve over a period of several weeks. Biopsies performed more than 2 weeks after onset show ectatic glomerular capillaries, swollen endothelial cells, and varying amounts of necrosis. Crescents are uncommon and there may be patchy cortical necrosis. The importance of tubulointerstitial injury in Stx HUS has been stressed (14), especially in view of the fact that many patients are anuric. Patients who initially have oligoanuria followed by persistent proteinuria, hypertension, and/or chronic renal insufficiency develop focal segmental glomerulosclerosis (FSGS) more often and later than the less frequently observed changes of diffuse mesangial proliferative glomerulonephritis or diffuse glomerulosclerosis (24). Patients with a poor outcome have

<table>
<thead>
<tr>
<th>Table 1. New nomenclature for Shiga-like toxin (verotoxin) family</th>
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<tbody>
<tr>
<td>Current Names</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Shiga toxin (Stx)</td>
</tr>
<tr>
<td>Shiga-like toxin I (SLT-I) or verotoxin I (VT1)</td>
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<tr>
<td>Shiga-like toxin II (SLT-II) or verotoxin II (VT2)</td>
</tr>
<tr>
<td>Shiga-like toxin IIc (SLT-IIc) or verotoxin IIc (VT2c)</td>
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<tr>
<td>Shiga-like toxin IIe (SLT-IIe) or verotoxin IIe (VT2e)</td>
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</table>

Infections

*Escherichia coli* O157:H7 and other serotypes, *Shigella dysenteriae* type 1, *Streptococcus pneumoniae*, *Aeromonas*, HIV

Hereditary HUS

autosomal recessive, autosomal dominant; inborn error of cobalamin metabolism

Drug- and treatment-associated HUS

cyclosporin A, tacrolimus, mitomycin C, oral contraceptives, quinine, ticlopidine hydrochloride, irradiation, OKT3

HUS associations

pregnancy, solid organ transplant, bone marrow transplant, malignancy, systemic lupus erythematosus, systemic sclerosis, Sjögren’s syndrome, poststreptococcal glomerulonephritis, membranoproliferative glomerulonephritis

Idiopathic HUS (atypical D– HUS)

with recurrent episodes, without recurrent episodes; with complement deficiency, without complement deficiency (14,19).
Table 3. Pathogenesis of Stx HUS: a theoretical succession of inter-related, overlapping, synchronous, and asynchronous events

<table>
<thead>
<tr>
<th>Event</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Stx-producing Escherichia coli infection</td>
<td>colonic injury</td>
</tr>
<tr>
<td>entry to circulation of Stx</td>
<td>attachment of Stx to Gb3 receptor on glomerular endothelial cells</td>
</tr>
<tr>
<td>inhibition of endothelial cell protein synthesis</td>
<td>cell injury and death—necrosis and apoptosis</td>
</tr>
<tr>
<td>Access of LPS</td>
<td>LPS stimulates production of cytokines, TNF-α and IL-1 Stx, LPS, and cytokines synergistically injure endothelial cells</td>
</tr>
<tr>
<td>Neutrophil leukocytosis</td>
<td>LPS activates leukocytes</td>
</tr>
<tr>
<td>leukocytes release TNF-α, IL-1, elastase, free radicals</td>
<td>Stx stimulate leukocyte adhesion</td>
</tr>
<tr>
<td>transient leukocyte infiltration in glomeruli</td>
<td>Stx upregulate adhesive proteins on endothelial cells</td>
</tr>
<tr>
<td>Activation of platelets</td>
<td>local procoagulant state</td>
</tr>
<tr>
<td>early, transient thrombi in glomeruli, afferent arterioles</td>
<td>removal of platelets by spleen and liver</td>
</tr>
<tr>
<td>Endothelial cell injury</td>
<td>perturbed endothelial cell functions—prostacyclin, von Willebrand factor, endothelin, nitric oxide, PAI-1</td>
</tr>
<tr>
<td>exposure of collagen</td>
<td>endothelial cell swelling, injury, detachment</td>
</tr>
<tr>
<td>Tubulointerstitial injury</td>
<td>acute renal failure</td>
</tr>
<tr>
<td>Hemolysis, thrombocytopenia</td>
<td>secondary to vascular injury</td>
</tr>
<tr>
<td>secondary to peroxidative damage</td>
<td></td>
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</tbody>
</table>

* Updated from reference 50. Stx, Shiga toxin; HUS, hemolytic uremic syndrome; Gb3, globotriosyl ceramide; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; PAI-1, plasminogen activator inhibitor-1.

higher PAI-1 activity than those with a good outcome (22). A potential role for PAI-1 in the pathogenesis of the FSGS in HUS can be inferred from studies of patients with idiopathic FSGS (25).

Classification of Severity

We have classified patients with D+ HUS into two groups: those who are mildly affected and those who are severely affected (26). Mildly affected patients have the triad of features, whereby HUS is defined, but they never develop anuria. Severely affected patients are anuric for more than 24 hours. Mildly affected patients almost never have seizures, are rarely hypertensive, and do not require dialysis. Their outcomes are uniformly excellent. Severely affected patients may have seizures, often develop hypertension, require dialysis for optimum management, and may progress to end-stage renal failure.

Treatment Algorithm (Figure 1)

Supportive treatment is responsible for the dramatic decline in the acute mortality rate from more than 30% before 1970 (26) to current rates of below 5% (27). Meticulous attention to salt and water management is important. Patients dehydrated from diarrhea and vomiting must be rehydrated, but, because oliguria may be developing, overhydration must be avoided. In euvoletic patients, fluids are limited to insensible losses plus urine output. Hyponatremia commonly results from a combination of the kidney’s inability to excrete free water and the intravenous administration of hypotonic solutions to correct the dehydration. Because hyponatremia may cause neurologic manifestations, the serum sodium concentration must be corrected by careful water restriction and, in rare cases, careful use of hypertonic saline. Hyperkalemia, hyperphosphatemia, and severe metabolic acidosis should be managed medically, but if this fails, dialysis or hemofiltration is indicated. The value of early dialysis has not been evaluated in a prospective controlled study. There are no specific indications for dialysis in a patient with Stx HUS (D+ HUS) who is not anuric, hyperkalemic, volume overloaded, or severely acidemic. Azotemia is not an indication for dialysis, especially in nonoliguric patients (28). Nutrition must be maintained because patients with HUS have a high catabolic rate, and to avoid a negative nitrogen balance, the administration of carbohydrates and an essential amino acid preparation is recommended. Inanition may be a relative indication for dialysis in a highly catabolic oliguric patient.

Packed red blood cells are transfused slowly if the hemoglobin decreases below 6 g/dl. Blood must be given slowly because the blood pressure can increase markedly during or after transfusion. Platelet transfusions are rarely required unless there is active bleeding or the patient needs an invasive procedure. Hypertension may respond to fluid removal if the patient is volume overloaded, but specific treatment is usually required. This may be achieved with calcium-channel blockers or hydralazine, whereas nitroprusside is used in refractory cases.

There is no specific treatment for the colitis. Agents that retard peristalsis may be harmful because toxic megacolon is one of the complications of the enterocolitis. Most patients have been given antibiotics, but these are not indicated and may be harmful. Commercial immune globulin preparations contain anti-cytotoxin-neutralizing antibodies, but not anti-Stx2 antibodies, and are ineffective in ameliorating the disease. Colectomy is indicated if ischemic bowel lesions are suspected. Hyperglycemia, ketonemia, and acidosis secondary to islet cell necrosis are treated with insulin. Convulsions are treated with intravenous administration of diazepam or phenytoin. Unless there are recurrent seizures or cerebral infarcts, long-term anticonvulsant treatment is not indicated.
Specific Treatment

The current acute mortality rate of less than 5% and the recognition that there are different causes of HUS make it difficult to interpret the results of many studies. Rigorous criteria are needed for the design of therapeutic trials because it is impossible to evaluate the importance of results obtained.
from studies in which several kinds of treatment were used in the experimental and control groups. Heparin is not effective and may even be harmful. Fibrinolytic agents, prostacyclin, antioxidants, and intravenous immunoglobulin infusions have no apparent value. Angiotensin-converting enzyme inhibitors may be indicated for patients who have persistent proteinuria or hypertension, or both, after recovery from the acute stage of HUS. These agents must be used cautiously because some patients develop hyperkalemia.

**Fresh Frozen Plasma or Plasmapheresis**

Patients with Stx HUS (D+ HUS) have been treated with fresh frozen plasma (FFP) infusions (29–32) or plasmapheresis (33) with no apparent benefit (Table 4). Potential risks of FFP infusions are volume overload, transmission of infections, and renal injury. There are no controlled, randomized, stratified, prospective studies on plasmapheresis for D+ HUS. A retrospective study attempted to show that patients over 5 years of age who were treated with plasmapheresis had a better renal outcome (33), but this study is imperfect. The patients were not randomized to treatment and control arms, there were no entry criteria for using plasmapheresis, the prognostic scoring system was invalid, there were no details about the length or severity of acute renal failure, and the types of dialysis and other treatments were not described. The evaluation of treatment regimens in adult patients is subject to the same criticisms as those in children. In addition, patients with many types of HUS and thrombotic thrombocytopenic purpura are included, and the presence of comorbid conditions is not taken into account.

**Renal Transplantation**

Posttransplant HUS occurs in four clinical contexts: inherited HUS, idiopathic HUS, de novo occurrence of HUS after renal transplant, and de novo HUS associated with cyclosporin A, tacrolimus (FK 506), or OKT3 treatment. It can be difficult to distinguish recurrence from rejection or cyclosporin A toxicity (34). Recurrences after transplantation are uncommon with Stx HUS (D+ HUS) regardless of the origin of the donor kidney or treatment with cyclosporin A (35).

**Immediate Outcome**

There are no consistent correlations of outcome in relation to age of onset in childhood. However, adults with D+ HUS have a poorer outcome than children (4). The occurrence of hemorrhagic colitis is a favorable prognostic sign because this is a hallmark of D+ HUS (even in adults), but patients with a prolonged diarrheal phase have a worse outcome than those with a short period of diarrhea. Prolonged anuria is associated with a poorer outcome (36). Patients with intestinal gangrene or rectal prolapse have a poorer outcome. Data compiled from five series (including our own) of 468 patients with D+ HUS reveal that 3% had colonic infarctions and 40% of these patients died. The longer the length of anuria, the worse the outcome. Hypertension during the acute phase of D+ HUS does not necessarily mean that antihypertensive treatment is required in the future. Minor neurologic dysfunction does not predict outcome. Major central nervous system involvement, especially coma, is a major predictor of poor outcome. The initial neutrophil count is significantly higher in patients with poor outcomes (37), as is the plasma concentration of PAI-1 (22).

**Long-Term Prognosis**

Before the introduction of early peritoneal dialysis, as many as 30% of children with HUS died of fluid overload, metabolic derangements, and uremia. After early intervention with short-term dialysis was initiated in Johannesburg, South Africa, the mortality rate in that center improved from 30% to 5% (26,27), and the most recent series report an acute mortality rate of 4 to 12%. This is mainly due to better management of acute renal failure. Higher mortality rates of up to 60% have been reported in *Shigella dysenteriae* type 1 HUS (11), possibly because of the severity of the illness and the lack of sophisticated medical services. D+ HUS now has the same long-term outcome in Argentina (38) as in the rest of the world. The long-term prognosis may be correlated with the appearance of the pathology in the initial biopsy specimen (39). Late sequelae occur in 90% of patients with cortical necrosis and in 60% who have thrombi in more than 50% of their glomeruli (39). However, we do not advocate performing renal biopsies to determine the

<table>
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<th>Table 4. Plasma therapy for D+ HUS</th>
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<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>Multicenter, randomized, controlled</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Multicenter, randomized, controlled</td>
</tr>
<tr>
<td>Retrospective, case control</td>
</tr>
<tr>
<td>Retrospective</td>
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* Ref., reference.
prognosis. End-stage renal failure occurs in a small number of patients after apparent recovery (40). The length of the period of anuria is an important predictor of chronic renal failure. Patients who were anuric in the acute phase should receive follow-up care for many years to monitor protein excretion, hypertension, and elevation of serum creatinine.

Prevention
In the future, irradiation of meat, vaccines, or both, may help to prevent Stx HUS. Synsorb Pk, a synthetic oligosaccharide receptor for Stx attached to diatomaceous earth, is currently being evaluated (41). However, it is imperative to wash hands and food well, to observe scrupulous hygienic measures around infants, children, and the elderly, and to cook food, especially meat, thoroughly.

Idiopathic HUS (Atypical D−HUS)
Idiopathic HUS excludes all patients who have a cause for HUS or a well defined diarrheal prodrome, especially if bloody. What remains is a heterogeneous group of patients (42). There is no etiologic agent or seasonal pattern. The onset is insidious and may be preceded by features of the nephrotic syndrome (43). Compared with Stx (D+ HUS), there are more frequent chronic sequelae with proteinuria, severe hypertension, an increased incidence of end-stage renal failure, and a higher mortality rate. However, many patients recover completely. Recurrences may occur before or after renal transplantation, or both (Table 5) (1,42,44). The pathogenesis is unknown. The histopathologic findings often differ markedly from those seen in D+ HUS, with collapsed ischemic glomeruli and afferent arteriolar intimal hyperplasia (43).

Treatment of Idiopathic HUS
The principles of treatment of these patients are the same as in patients with Stx HUS, with some exceptions. Plasmapheresis may be beneficial in idiopathic (atypical) forms of HUS, especially when symptoms of neurologic involvement are present, but the effect on the renal disease is less encouraging (1). Furthermore, these cases raise additional difficult management decisions. The patient and family must be informed of the possibility that the disease may recur before and/or after transplantation, and that the HUS may be inherited even if there is no apparent history of it having occurred in another family member.

Renal Transplantation
HUS may recur after transplantation in idiopathic (atypical) cases, but a recurrence cannot be predicted in someone who has never had one or whose family history has been negative for HUS. Bilateral nephrectomies may be helpful in selected patients with uncontrollable malignant hypertension (45). Recurrent episodes of HUS may occur in living-related or cadaver donor kidneys, and in some, but not all, allografts. Recurrences do not always result in graft loss. It is prudent to be cautious in the use of living-related donors in patients with atypical HUS and in adults with HUS because of a high recurrence rate and a poor 2-year graft survival rate of only 35% (46).

Inherited HUS
Fewer than 5% of cases of HUS are inherited either by autosomal recessive or autosomal dominant modes. In autosomal recessive inheritance of HUS, the onset in siblings is separated by more than 1 year, and children are more often affected than neonates and adults. The prognosis is poor, with a mortality rate of approximately 65%. Patients may have recurrences before and/or after renal transplantation, regardless of the donor source of the kidney or the use of cyclosporin A (47).

Most affected people with autosomal dominant inheritance of HUS are adults (48), recurrences can occur, and the prognosis is poor, with a combined morbidity and mortality rate of more than 90%. A diagnosis of inherited HUS cannot be made in the first affected case in the kindred. Clues to the diagnosis include a family member who was affected at a remote time, a non diarrheal prodrome or no prodrome, a progressive course, and recurrences. The histologic changes are predominantly renal arteriolar changes with intimal proliferation, thrombi, and collapsed ischemic glomeruli. These findings are similar to those of atypical D−HUS (idiopathic HUS) (43). Treatment with FFP and plasmapheresis is recommended but is of unproven value. Genetic counseling should be offered, but there are no markers to determine the heterozygote state or whether a fetus is affected. There is preliminary evidence of linkage to the factor H locus on chromosome 1 in autosomal dominant inheritance of HUS (49).

Conclusions
The assumption that HUS is a syndrome and that there are many causes and associations of the disease is widely accepted. There have been enormous advances in defining the etiology, epidemiology, pathogenesis, and histopathologic features of Shiga toxin-associated HUS. However, although the acute mortality rate has declined, patients continue to die, in part because there is no specific treatment of the endothelial injury and its consequences. Attempts to prevent the disease by vaccines and pharmacologic agents show promise, but public and personal health measures are of paramount importance in preventing the contamination of foods and fluids and person-to-person transfer. Similar advances have not been made in the

Table 5. Outcomes in atypical D−HUS (idiopathic HUS)

<table>
<thead>
<tr>
<th>No. of Cases and Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Atypical D− HUS cases</td>
<td>20</td>
</tr>
<tr>
<td>death in acute phase</td>
<td>3</td>
</tr>
<tr>
<td>full recovery</td>
<td>4</td>
</tr>
<tr>
<td>recurrences</td>
<td>11</td>
</tr>
<tr>
<td>end-stage renal failure</td>
<td>4</td>
</tr>
<tr>
<td>renal transplant</td>
<td>2</td>
</tr>
<tr>
<td>posttransplant recurrence</td>
<td>2</td>
</tr>
<tr>
<td>deaths</td>
<td>5 (25%)</td>
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</tbody>
</table>
idiopathic and inherited forms of HUS. Although these forms constitute a small percentage of the total, they continue to have very high mortality and morbidity rates.

References


34. Miller RB, Burke BA, Schmidt WJ, Gillingham KJ, Matas AJ, Mauer M, Kashtan CE: Recurrence of haemolytic-uraemic syn-