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Shiga Toxin/Verocytotoxin-Producing Escherichia coli Infections: Practical Clinical Perspectives

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ABSTRACT Escherichia coli strains that produce Shiga toxins/verotoxins are rare, but important, causes of human disease. They are responsible for a spectrum of illnesses that range from the asymptomatic to the life-threatening hemolytic-uremic syndrome; diseases caused by E. coli belonging to serotype O157:H7 are exceptionally severe. Each illness has a fairly predictable trajectory, and good clinical practice at one phase can be inappropriate at other phases. Early recognition, rapid and definitive microbiology, and strategic selection of tests increase the likelihood of good outcomes. The best management of these infections consists of avoiding antibiotics, antimotility agents, and narcotics and implementing aggressive intravenous volume expansion, especially in the early phases of illness.

INTRODUCTION

Shiga toxin (Stx)-producing Escherichia coli (STEC) cause illness with a spectrum of severity ranging from mild (even asymptomatic) carriage to life-threatening disease (1–3). STEC infections are relatively uncommon; in the United States, extrapolation of data from FoodNet (4) to a nationwide population that exceeds 300,000,000 indicates there are fewer than 4,000 diagnosed cases of E. coli O157:H7 infection per annum. E. coli O157:H7 remains the near-exclusive cause of hemolytic-uremic syndrome (HUS) throughout most of the world, and the single serotype on which most data have been generated. Therefore, we emphasize this particular pathogen in this article. The European Food Safety Authority and the European Centre for Disease Prevention and Control report similar epidemiology: 4,000 confirmed infections caused by Stx-producing E. coli strains (mostly belonging to the O157 serogroup) in 27 European Union member states. The number of reported infections attributed to E. coli strains that produce Shiga toxins has increased since 2008 (5).

Despite their low overall incidence, human infections are medically and epidemiologically actionable. The rarity with which Shiga toxin-producing E. coli infections occur, barriers to timely microbial diagnosis, consequences of missed diagnoses, and the many difficulties in attempts to generate high-quality evidence on which to justify treatments pose challenges for clinicians and public health systems. In this review, we focus on clinical aspects (i) early in illness; (ii) in the intermediate stage of...
illness as HUS evolves in the approximately 15 to 20% of infected children in whom this complication occurs; and (iii) during the HUS phase and its aftermath. When data exist, we cite the appropriate literature, but in other circumstances, we rely on our cumulative experience, as noted.

DEFINITIONS
This field of study has been vexed by multiple nomenclature issues. In this review and in our own papers and practice, we describe the toxins produced by enteric pathogens that cause HUS as Shiga toxins (Stxs). This term is synonymous with verocytotoxins (VT), named for the toxic effect of these proteins on Vero cells, as originally described by Konwalchuk et al. (6) and identified as the key phenotype of these pathogens by Karmali et al. (7). E. coli strains that produce Stx are termed Stx-producing E. coli (STEC), which is synonymous with VT-producing E. coli (VTEC). However, in this text we use the term STEC/VTEC when describing bacteria that produce Stx/VT. This combined term reflects our current misgivings about the term Stx to refer to the cardinal virulence trait of these pathogens. These misgivings are rooted in a practical matter: many physicians, on learning that their patient is infected with a Shiga toxin-producing organism, assume erroneously that the laboratory is describing an infection with Shigella sp. (4). Such misconceptions are, in our experience, preludes to the inappropriate administration of antibiotics.

Enterohemorrhagic E. coli (EHEC) is another term for STEC/VTEC strains that cause human disease. This term is also problematic, because it implies that the diarrhea stools contain visible blood, which is sometimes not the case in E. coli O157:H7 infections, and frequently not the case in infections caused by STEC/VTEC strains belonging to other serotypes. Furthermore, a small subset of patients with HUS will have no diarrhea, but their stool will nevertheless contain E. coli O157:H7 (8, 9).

We also have preferences for clinical descriptors related to STEC/VTEC infection. In lieu of the time-honored term hemorrhagic colitis (coined in the first outbreak report) (10), we prefer the more encompassing concept of “bloody diarrhea.” For HUS, we urge a urinalysis-independent, stringent case definition, consisting of the simultaneous presence of nonimmune hemolytic anemia (hematocrit/packed cell volume <30% with smear evidence of hemolysis and a negative Coombs test), thrombocytopenia (platelet count <150,000 mm3), and azotemia (creatinine > upper limit of normal for age) (11). There is much hazard and little benefit to be gained from using less stringent clinical definitions of this complication of STEC/VTEC infections. For example, reliance on an abnormal urinalysis to define HUS, especially if the serum creatinine is normal, risks consideration of incorrect diagnoses such as urinary tract infections, especially as the possibility of contamination with fecal material is high in the setting of diarrhea. Moreover, these widely available blood tests enable physicians to relate their patient’s course to those described in many other studies during the past 3 decades from multiple countries (12–31).

HISTORY
HUS was first described in the mid-1950s by Gasser et al. (32). In that series of 10 fatal illnesses, cases 3 and 4 had “Brechdurchfall,” which is vomiting plus diarrhea (case 3 had these signs throughout the entire illness, while the diarrhea of case 4 occurred only preterminally). None of the other clinical courses suggested enteric illnesses, and notably none of the reports used the terms bloody diarrhea or dysentery. However, we have found earlier papers describing cases in which diarrhea or dysentery preceded renal failure and death within a time frame that closely resembles that of E. coli-related HUS (33–37).

E. coli O157:H7 and the closely related pathogen E. coli O157:H17 were estimated to have split from the same progenitor about 7,000 years ago (38). This common ancestor acquired a gene encoding Stx2/VT2 before that. However, it was not until the 1970s when E. coli that had been isolated from food was reported to produce Stx/VT (6). This phenotype preceded by several years the first description of STEC/VTEC strains as causes of disease in 1983. In that year, near-simultaneous publications introduced these pathogens to the medical community: Riley et al. described a hamburger-associated outbreak of E. coli O157:H7 infections (10), and Karmali et al. linked fecal STEC/VTEC to HUS (7). Also in 1983, additional investigators demonstrated the production of Stx/VT by E. coli O157:H7 (39–42).

DISTINCTION BETWEEN STEC/VTEC BELONGING TO SEROTYPE O157:H7 AND THOSE BELONGING TO ALL OTHER SEROTYPES
There are important practical reasons to differentiate STEC/VTEC strains that express the O (somatic) 157 and flagellar (H) 7 antigens from all other serotypes, which we collectively term non-O157:H7 STEC/VTEC. Most compellingly, E. coli O157:H7 is the STEC/VTEC
that remains to this day the near-exclusive cause of postdiarrheal HUS \((8, 12, 16, 21, 43–49)\). This serotype is also the one most strongly associated with outbreaks (though most infections are sporadic). If stool specimens are handled adroitly (i.e., immediately transported to the laboratory and inoculated on sorbitol-MacConkey agar on receipt), the microbiologist can often inform the clinician of a presumptive positive or negative for this serotype within 18 to 24 h. That simple piece of information provides valuable clarity to the management of patients with acute diarrhea. However, because a proportion of STEC/VTEC infections are caused by non-O157:H7 STEC/VTEC, there is considerable merit to also determining their presence, but it is much more imperative to exert the greatest effort to confirm or refute the presence of \(E. coli\) O157:H7 in a stool culture. One important exception to this statement exists: sorbitol-fermenting \(E. coli\) O157:H7 is as virulent, or possibly more virulent, than \(E. coli\) O157:H7 \((50)\), and this clone remains endemic in Germany. These organisms, which are closely related to \(E. coli\) O157:H7 \((38)\), are not detected by sorbitol-MacConkey agar screening. \(E. coli\) O157:H7 is best detected in stool by using sorbitol-MacConkey agar with or without cefixime-tellurite \((51)\), because unlike most commensal \(E. coli\) and non-O157:H7 STEC/VTEC strains, \(E. coli\) O157:H7 does not ferment sorbitol after overnight incubation. Hence, the presence of a colorless colony on sorbitol-MacConkey agar plating with or without cefixime-tellurite or cefixime-xime-nime generates diagnostic confidence that the specimen was first cultured for this organism at a point in illness when the pathogen had been eliminated \((44)\).

Table 1 summarizes the \(E. coli\) O157:H7/non-O157:H7 STEC/VTEC acuity pyramid derived from several defined populations (the HUS studies are globally distributed, but the non-HUS cohorts are from the United States). As illness severity increases, inferred from the setting of acquisition of culture (large geographic region to emergency facility to cohorts with HUS), the ratio of non-O157:H7 STEC/VTEC to \(E. coli\) O157:H7 diminishes. Findings from several of these studies are particularly worth mentioning. Of 229 Connecticut patients with infections caused by non-O157:H7 STEC/VTEC who were studied over a decade-long interval \((48)\), HUS developed in only one, while HUS developed in 45 of the 434 patients in this series who were infected with \(E. coli\) O157. In a United States-wide study of 83 patients with HUS \((12)\), 70 patients had stool cultures in which bacteria grew. These specimens were obtained a median of 8 days after illness onset. Of the 30 STEC/VTEC strains identified in these 30 specimens, 25 were \(E. coli\) O157. Of the five patients whose stools yielded non-O157:H7 STEC/VTEC, four had serologic testing in convalescence and three of them had antibody evidence of recent exposure to the O157 lipopolysaccharide antigen. Hence, an EIA (or, increasingly, PCR) \((58, 59)\) to detect an STEC/VTEC strain, when added to sorbitol MacConkey agar screening, is likely to lead to the diagnosis of cases that are at much lower risk of HUS developing. Nonetheless, making a diagnosis in at least a subset of these cases is worthwhile, if for no other reason than to provide etiologic clarity to an

<table>
<thead>
<tr>
<th>Setting and study years</th>
<th>(E. coli) O157:H7</th>
<th>Non-O157:H7 STEC/VTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric emergency facilities (1991–2005) ((1, 16, 142))</td>
<td>Conneciticut: 42%</td>
<td>Connecticut: 58%</td>
</tr>
<tr>
<td>HUS (1984–2010) ((8, 12, 16, 21, 43–49))</td>
<td>95–99%</td>
<td>1–5%</td>
</tr>
</tbody>
</table>
illness that is usually of greater severity than most gastroenteritis. However, data do not exist to calculate the overall value or cost of such policies, but, again, sorbitol-MacConkey agar screening is most crucial to include when performing stool cultures for bacterial pathogens.

CLINICAL MANAGEMENT OF STEC/VTEC INFECTIONS: PRE-HUS PHASE

Our approach to STEC/VTEC infections is based on three overarching principles:

1. Early detection is critical: time is not on your side when treating STEC/VTEC infections.
2. Early and vigorous volume expansion is associated with avoidance of the most severe renal injury.
3. Highly strategic test selection avoids generating misleading and potentially harmful results.

Early identification (and hospitalization) of infected patients is critical because it lowers the risk of secondary cases (60), avoids diagnostic misadventures (for example, we have seen patients started on steroids because of presumed fulminant ulcerative colitis), and facilitates the commencement of intravenous volume expansion. Several lines of evidence suggest that renal perfusion is threatened prior to and during HUS and that diminished kidney blood flow increases the likelihood of severe renal injury. First, there is evidence of prothrombotic abnormalities in the infected host before HUS (and even if HUS does not ensue). Factor 1.2 (the prothrombin activation peptide), D-dimers, plasminogen activator inhibitor, and platelet-activating factor are each elevated during E. coli O157:H7 infections, and von Willebrand factor is also sheared (indicating flow-related rheological stress, probably caused by nascent thrombi) (13, 17, 61). These prothrombotic abnormalities, which are demonstrated at a point in illness when the blood counts are normal, probably produce some degree of renal ischemia, even before there is smear evidence of microangiopathy. Second, if HUS develops, dehydration at presentation (manifest as elevated hematocrit) is associated with less favorable short-term (62–64) and long-term (65) outcomes. Third, intravenous volume expansion early in illness, starting as soon as possible after presentation, is associated with less severe (i.e., nonanuric) HUS, if HUS ensues (20, 21).

The details of our fluid management protocols are provided in reference 66. We have slightly changed our recommendations (articulated in reference 66) to now suggest complete blood counts every 12 h until there is assurance that the hemoglobin is falling with volume expansion, because we have not found other indices of circulating blood volume (BUN:creatinine ratio, skin turgor, or vital signs) to be reliable in this setting (authors’ personal experience). We aim for a decrement in the hemoglobin of 0.5 g/dL per each 12-h period over the first 1 or 2 days. It can be difficult to accurately assess host volume status, and there is a risk of overload with vigorous volume expansion, so we stress the importance of assiduous monitoring of infected children in centers that are adept at pediatric care (20, 66).

Antibiotics were first suggested as potentially increasing the risk of HUS developing in the initial report linking STEC/VTEC infection to this disorder (7). No credible evidence has emerged since then that supports the concept that antibiotics administered to children or adults early in illness reduce the likelihood of HUS subsequently developing. In fact, extensive data from multiple studies, including more than 1,000 patients infected in epidemics and sporadically, demonstrate that antibiotics are at best neutral and quite likely increase the risk of HUS developing (Table 2). Indeed, the largest risk is demonstrated in the studies with the most robust data: large cohorts, interviewed prospectively, with extensive analysis of timing of administration of antibiotics, and representing infections with multiple different strains.

We also urge against the use of narcotics and antidiarrheal agents in patients with infections that could be caused by STEC/VTEC because of their association with higher rates of HUS or neurological sequelae (67, 68). We also do not endorse nonsteroidal anti-inflammatory agents, because, in our experience, they have no value and because of their nephrotoxic potential (69), which might be exacerbated in the dehydrated state (70).

Early in HUS Prognostic Factors

HUS occurs in 15 to 20% of children who are culture positive for E. coli O157:H7. Several indicators apparent early in the course of HUS are associated with a severe course of HUS. A combination of hypocalcemia (≤2 mmol/L) plus oliguria (urine output <0.4 mL kg⁻¹ h⁻¹ for 24 h) within 48 h of hospitalization had the highest predictive value for negative outcomes (death, need for dialysis, hypertension requiring therapy, or central nervous system sequelae at discharge) (71). Multiple seizures, coma, retinal hemorrhages, hyperkalemia (>7.5 mmol/L), acidosis (bicarbonate <8 mmol/L), or a diastolic blood pressure >90 mm Hg are also suggested to be early indicators of poor outcome in HUS (72). An elevated polymorphonuclear leukocyte count in
diarrhea-associated HUS is also a risk factor for poor outcome (73, 74). Unfortunately, these risk factors and biomarkers were measured at different points of illness, often after poor outcomes are becoming self-evident. Nonetheless, the greatest determinant of short- (75) and long-term (62, 76–87) outcome of E. coli-related acute kidney injury remains oligoanuria.

HUS with and without Oligoanuria

There are two categories of HUS: oligoanuric and non-oligoanuric. We emphasize the importance of averting oligoanuria to the extent possible, because of the repeated associations between chronic renal sequelae and presence and duration of oligoanuria during HUS (62, 76–87). In reality, oligoanuric HUS is equivalent to anuric HUS (though there can be a day of oliguria before renal shutdown is complete). Anuria probably reflects acute tubular necrosis. The mechanism of acute tubular necrosis in STEC/VTEC HUS is not completely established but could represent either the effect of Shiga toxin on renal tubules (88–91) or ischemia secondary to thrombotic occlusion of the renal vasculature (92). In view of the abundant evidence of prothrombotic activation before azotemia ensues, and in consideration of examples of diminished renal blood flow preceding anuric renal response in many other clinical situations, we have tended to favor the occlusive/ischemic mechanism as the cause of anuria in HUS. As noted above, oligoanuric HUS has categorically worse short- and long-term implications for patients.

HUS that requires dialysis occurs in up to 71% of patients, according to a summary of HUS series over the past 4 years (Table 3). The median length of stay after the case definition of HUS is attained is 12 days for patients with oligoanuria versus 6 days for patients with nonoligoanuric renal failure (20). Dialysis should be instituted soon after anuria onset to prevent cardiopulmonary overload, avoid electrolyte disturbances, and treat hypertension. Early initiation of dialysis if anuria develops allows the provision of nutrition without exacerbating the above complications.

In our institutions, peritoneal dialysis is the most commonly used modality although intermittent hemodialysis and continuous renal replacement therapies are equally effective. From our perspective, there are several reasons to use peritoneal dialysis in HUS, including avoiding unnecessary care in the intensive care unit (decreasing cost) and allowing direct access to peritoneal fluid, which is helpful if the possibility of bowel perforation is raised. If necessary, home renal replacement can be used in the event of delayed recovery.

Renal replacement therapies, i.e., peritoneal and hemodialysis, are the chief supportive modalities in oligoanuric HUS. A review of these interventions is beyond the scope of this chapter. However, some complications of dialysis seem to be relatively frequent during HUS. First, as we recently reviewed (93), infectious complications of peritoneal dialysis are common. Catheter malfunction, probably related to bowel wall and mesenteric edema, also complicates peritoneal dialysis during HUS. Catheter failure typically presents when a catheter infuses dialysate but does not drain. Catheter malfunction often obligates surgical replacement or conversion to hemodialysis. For hemodialysis, we recommend a dual-lumen catheter of age-appropriate size, preferably in the internal jugular vein. The authors generally use regional citrate anticoagulation of the extracorporeal circuit, but systemic heparin anticoagulation can also be used. Invasive procedures, such as peritoneal dialysis catheter and central vascular line placements, can be performed safely without excessive bleeding during the thrombocytopenia of HUS; platelet transfusions are rarely necessary (94, 95).

Fluid and Electrolyte Abnormalities during HUS

There are numerous electrolyte disturbances associated with acute HUS: Hyponatremia, hyperkalemia or hypokalemia, hypocalcemia, and hypoalbuminemia are common. Notably, however, these abnormalities usually by themselves do not obligate dialysis if urine is still being produced (96). Fatalities in the absence of anuria are exceptionally rare, and recent retrospective data suggesting the value of early renal replacement therapy if children are >10% overloaded probably do not apply to the still urinating child with HUS (97). Hyperuricemia is common, as is elevated lactate, and could be related to diminished renal flow, impaired clearance, and increased production (98).

Hypertension

Hypertension during and after acute HUS is common, with up to 70% of patients affected (99). The mechanism of HUS-induced hypertension is multifactorial and likely related to volume overload and to endothelial and vascular injury. Renovascular hypertension has been suggested to play a role, but plasma renin activity during HUS is below age-appropriate norms (100) (but renal vein renin concentrations have not been determined in this situation). We have had excellent success using calcium channel blockers in acute HUS. If hypertension is present at discharge, we use angiotensin-converting enzyme inhibition even if the creatinine has not yet
**TABLE 2** Summary of antibiotic experience in multiple case control studies of children and adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Year performed, setting</th>
<th>Ages of patients</th>
<th>Predominant antibiotics given</th>
<th>Details provided regarding day of illness on which antibiotics were administered (timing), and comments</th>
<th>HUS rate in group receiving antibiotics</th>
<th>HUS rate in group not receiving antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter ([143])</td>
<td>1985 Outbreak analysis, Canada</td>
<td>16–67 yr old</td>
<td>Amoxicillin, tetracycline</td>
<td>Timing not specified. Outbreak characterized by two phases: primary, contaminate food; secondary, person-to-person transmission. Antibiotic therapy within the 2 days before food exposure (primary phase) did not have increased risk of HUS developing. However, those on antibiotics during the outbreak (secondary phase) had a 10.3 relative risk of HUS developing.</td>
<td>Does not specify</td>
<td>Does not specify</td>
</tr>
<tr>
<td>Pavia et al. ([144])</td>
<td>1988 Outbreak, case-control study, Utah</td>
<td>6–39 yr old</td>
<td>Predominantly trimethoprim-sulfamethoxazole</td>
<td>Timing not specified. Comment: All antimicrobial agents were begun with 72 h after onset of diarrhea.</td>
<td>5/8 (63%)</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>Proulx ([145])</td>
<td>1989–1990 Randomized controlled trial, Canada, antibiotics administered late in illness</td>
<td>5 ± 4 yr (average)</td>
<td>Trimethoprim-sulfamethoxazole (1)</td>
<td>Yes</td>
<td>2/22 (8%)</td>
<td>4/25 (16%)</td>
</tr>
<tr>
<td>Bell et al. ([67])</td>
<td>1993 Outbreak, retrospective cohort, Washington State</td>
<td>&lt;16 yr old</td>
<td>Trimethoprim-sulfamethoxazole (62%), ampicillin or amoxicillin (26%), cephalosporins (12%), metronidazole (8%)</td>
<td>Yes</td>
<td>8/50 (16%)</td>
<td>28/218 (13%)</td>
</tr>
<tr>
<td>Wong et al. ([146])</td>
<td>(superseded by reference 31 described below)</td>
<td>&lt;10 yr old</td>
<td>Trimethoprim-sulfamethoxazole (2/5), β-lactams (3/5)</td>
<td>Yes</td>
<td>5/9 (56%)</td>
<td>5/62 (8%)</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Age</td>
<td>Antibiotics</td>
<td>Timing</td>
<td>HUS Rate</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Dundas et al. (147)</td>
<td>1996</td>
<td>Outbreak, retrospective cohort study, Scotland</td>
<td>18 mo to 94 yr old</td>
<td>Ciprofloxacin</td>
<td>Timing not specified.</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>Smith et al. (148)</td>
<td>1996–2002</td>
<td>Multistrain, age matched, case-case comparison</td>
<td>&lt;20 yr old</td>
<td>β-lactams (22% case, 4% control), sulfonamides (14% case, 24% control), metronidazole (6% case, 2% control)</td>
<td>Timing partly specified. Subjects received antibiotics in two specific periods: within the first 3 days after diarrhea onset and in the first 7 days after diarrhea onset.</td>
<td>27/63c (43%)</td>
</tr>
<tr>
<td>Cimolai et al. (68)</td>
<td>1984–1989</td>
<td>Multistrain, sporadic cases, retrospective cohort study, British Columbia, Canada</td>
<td>Age range not reported.</td>
<td>Agents not specified, but were characterized as “appropriate” if antimicrobial was recognized to be effective in the treatment of shigellosis and if isolate was susceptible in vitro testing.</td>
<td>Timing not specified. Duration of antibiotic use termed “short” if ≤24 h or prolonged if &gt;24 h.</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

*Modified from reference 21 with permission.  
*Risk ratio in lieu of HUS rate was provided, and was 8.5 (95% confidence interval 2.7–27.5) in favor of antibiotics associated with HUS development.  
*Results report the exposure of antibiotics within the first 7 days.  
*Results limited to “appropriate” antibiotics administered for short terms.
normalized, provided the serum creatinine concentration is falling and the patient is not on dialysis.

**Hematologic Complications during HUS**

Almost all patients with HUS require erythrocyte transfusions because of hemolysis. The basis for the hemolysis is presumably physical shearing as red cells course through small vessels in which fibrin thrombi are abundant. Transfusion requirements appear independent of the severity of the renal injury (authors’ personal observations). We use cardiopulmonary compromise or tachycardia as an indication for transfusion, rather than an arbitrary hemoglobin concentration, though in reality it is common to factor in the rate of hemolysis, time of day, vascular access, and point in illness. The transfusion requirement can continue several days beyond resolution of thrombocytopenia and return of creatinine to normal (authors’ personal observations).

Several additional elements should be considered when pondering the need for erythrocyte transfusion. First, erythrocyte life span is short in HUS, ranging between 8 and 24 days (101), and the fibrin debris presumably recedes on a day-by-day basis. Hence, transfused red cells might last longer if transfusion can be delayed until needed. Second, we try to use an entire unit at each transfusion. Third, we have frequently noted hypertension immediately following transfusion, so antihypertensive medications should be readily available. After transfusion needs abate, we usually do not provide iron to correct the residual anemia because the total body iron is not low; reticulocyte counts might be helpful in this situation.

We also rarely transfuse platelets because the underlying process leading to thrombocytopenia is most likely entrapment of platelets in thrombi, and thrombocytes have short circulating half-lives in HUS (101). Also, HUS is a thrombotic process, which is not well served by platelet transfusions. It is also concerning that most HUS-related strokes are thrombotic and not hemorrhagic (102, 103). Fibrinogen turnover is not increased in HUS as it is in classic consumptive coagulopathies (101). We therefore recommend against requesting disseminated intravascular coagulation laboratory tests as they are not likely to provide relevant information.

**Neurologic Complications during HUS**

HUS can be associated with a variety of bona fide neurologic lesions, and signs and symptoms of central nervous system dysfunction have been reported in 20 to 50% of cases. HUS has an apparent predilection for

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**TABLE 3** Severity of HUS in series identified in PubMed published between 2009 and 2013, using search terms hemolytic-uremic syndrome AND children, on September 4, 2013

<table>
<thead>
<tr>
<th>Year of cases, reference</th>
<th>Site</th>
<th>Age group</th>
<th>Dialysis rate</th>
<th>Fatalities</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997–2006 (31)</td>
<td>Washington, Oregon, Idaho, Wyoming, and Missouri</td>
<td>N = 36, &lt;10 yr</td>
<td>31%</td>
<td>0</td>
<td>Many of these patients were well hydrated (i.e., a subset were among those in a single center series [20] at the onset of HUS, which could account for the low dialysis rate).</td>
</tr>
<tr>
<td>2007–2008 (21)</td>
<td>California, Washington, Missouri, Ohio, Wisconsin, Arkansas, Indiana, Glasgow, New Mexico, Tennessee</td>
<td>N = 50 &lt;18 yr</td>
<td>68%</td>
<td>0</td>
<td>This case series employed a case definition of HUS that did not obligate azotemia. Hence, the low dialysis rate might reflect patients who would not have been considered to have had HUS in other series, and demonstrates another reason to avoid urinalysis-dependent definitions of HUS.</td>
</tr>
<tr>
<td>1994–2010 (149)</td>
<td>Alberta, Canada</td>
<td>N = 124 &lt;18 yr</td>
<td>43%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>1998–2008 (150)</td>
<td>Buenos Aires, Argentina</td>
<td>N = 365 Ages not reported</td>
<td>43%</td>
<td>0</td>
<td>94% of patients underwent peritoneal dialysis; 24% peritonitis rate</td>
</tr>
<tr>
<td>1995–2011 (62)</td>
<td>Buenos Aires, Argentina</td>
<td>N = 137 Ages not reported</td>
<td>52%</td>
<td>0</td>
<td>Better hydration during the prodromal phase was associated with lower frequencies of oligoanuria and need for dialysis.</td>
</tr>
<tr>
<td>2011 (30)</td>
<td>Hamburg, Germany</td>
<td>N = 90 &lt;18 yr</td>
<td>71%</td>
<td>1.1%</td>
<td>Outbreak of HUS caused by <em>E. coli</em> O104:H4. Outcomes and severity resembled those of <em>E. coli</em> O157:H7 HUS.</td>
</tr>
</tbody>
</table>

*Only articles with diarrhea associated HUS and dialysis rates are included.*
causing basal ganglia lesions (104), but every structure of the brain can be affected (105, 106). The most common serious neurologic complications of HUS are coma, convulsions, and strokes. These complications are usually poor prognostic signs but are rarely by themselves lethal. Possible mechanisms for these complications include endothelial injury with microthrombotic formation and hypoxia. Neurological dysfunction may be further exacerbated by hyponatremia, hypertension, and uremia. Although involvement of the central nervous system might portend a poor prognosis, it must be appreciated that neurologic recovery can be delayed for weeks or months, even after exceptionally severe HUS (107–110). Indeed, in comprehensive studies of survivors of HUS who were infected during the 2011 outbreak of E. coli O104:H4 infections, children and adults usually made complete neurologic recoveries even after exceptionally severe neurologic abnormalities during the acute phase (30, 111, 112).

Patients infected with STEC/VTEC often are irritable, lethargic, and jittery, and we do not treat these signs. It is possible that the around-the-clock defecations during the pre-HUS phase contribute to their occurrence. The use of sedatives to prevent patient movement is not recommended, because the mental status of patients with HUS is often altered and such sedation might confound clinical assessment. Acetaminophen and, if necessary, fentanyl are our preferred analgesics. Morphine should be avoided because of the neurotoxic effects of its metabolites, which are cleared by the kidneys (113, 114).

Additional nonnephrologic complications of HUS are summarized in Table 4.

**Table 4. Selected nonnephrologic, nonhematologic complications of HUS**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Do not pursue mild (“chemical”) pancreatitis by extensive investigation or withholding oral intake. Hyperlipasemia and hyperamylasemia could be related to intestinal and not biliary injury, emesis, and diminished renal clearance.</td>
<td>151</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Insulin dependence can be transient during acute HUS, or persist following renal improvement, or rarely present in the convalescent phase.</td>
<td>152–157</td>
</tr>
<tr>
<td>Intestinal perforation and necrosis</td>
<td>These complications are often difficult to identify. Acidosis that fails to resolve with dialysis suggests a severe intestinal complication warranting a laparotomy.</td>
<td>158</td>
</tr>
<tr>
<td>Biliary lithiasis</td>
<td>This is usually apparent in the several weeks after HUS resolves and is manifest as right upper quadrant pain and rarely biliary obstruction. This is probably caused by massive hemolysis and subsequent pigment load in the biliary system during HUS.</td>
<td>152, 153</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>This can occur after STEC/VTEC infections, as with other bacterial enteric infections. Its prognosis is good, often resolving within a year.</td>
<td>159</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>These might reflect liver injury or, possibly, arise from hemolysis. There is rarely actionable liver injury during HUS.</td>
<td>160</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>Post-HUS strictures can occur in the small or large bowel. One of the authors is aware of a postinfectious stricture occurring in an adult in whom HUS did not develop, but this complication usually is manifest in the several weeks or months after HUS resolves. These are best detected by contrast studies (small bowel follow-through or barium enema studies).</td>
<td>161, 162</td>
</tr>
<tr>
<td>Cardiac ischemia and/or myocarditis</td>
<td>This complication is unusual but can complicate HUS. Troponin determination and cardiac ultrasound might be helpful. We have noted late in illness, i.e., as HUS resolves, complications in elderly patients with HUS.</td>
<td>9, 163</td>
</tr>
<tr>
<td>Retinal hemorrhages</td>
<td>Ocular abnormalities are rarely sought in young children, so frequency might be higher than has been appreciated. Long-term complications included decreased visual acuity and optic nerve atrophy.</td>
<td>164, 165</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome and pulmonary hemorrhage</td>
<td>Pulmonary hemorrhage is a poor prognostic factor.</td>
<td>9, 64</td>
</tr>
<tr>
<td>Sudden death</td>
<td>This complication is rare. Case reports occurring during the acute phase of illness.</td>
<td>163, 166, 167</td>
</tr>
</tbody>
</table>
analysis indicated the severity of illness and the presence of central nervous system symptoms were associated with worse outcomes. Full renal recovery was not achieved if dialysis exceeded 4 weeks, but we have seen patients who have made nearly complete recoveries after such prolonged anuria. There are profound selection biases in computing chronic sequelae rates if the cohorts are limited to those patients who are still returning to follow-up years after HUS. It is also important to note that it is not clear how clinically relevant many of these sequelae (such as microalbuminuria) are, and in our experience, chronic renal failure later in life after normalization of the serum creatinine is exceedingly unusual. However, it is important to note that a recurring set of data suggests that presence and duration of oligoanuria are major predictors of chronic renal sequelae (62, 76–87), reinforcing the need to avoid this complication during acute HUS, if at all possible.

Use of Plasmapheresis and Eculizumab

Eculizumab administration and therapeutic plasma exchange during the large German outbreak in 2011 ignited debate about using these modalities in E. coli-related HUS. Eculizumab prevents formation of the membrane attack complex by inhibiting C5 function, and its use has been prompted by a letter to the New England Journal of Medicine (115). However, HUS in each of the patients described in that letter was already resolving (decreasing lactate dehydrogenase and/or rising platelet counts) when eculizumab was started. Several in vitro and animal experiments suggest activation of complement after exposure to Stx/VT (116–118), but these experiments employed STEC/VTEC concentrations several orders of magnitude higher than the levels that have ever been documented in humans (119). In contrast, a primate model of lethal STEC/VTEC challenge demonstrated no evidence of complement activation (120). Finding evidence of alternate complement pathway activation in children with HUS is not evidence of a pathogenic role for this branch of the innate immune system (121), as complement is often activated in multisystem organ injury, such as trauma (122). Finally, there are potentially deleterious effects of inhibiting complement during HUS, most notably sepsis (123).

There is similarly no justification for therapeutic plasma exchange in E. coli-related HUS. There is no credible evidence of deficiency in functional ADAMTS13, the enzyme that catalyzes shearing of von Willebrand’s factor into less thrombogenic forms, inhibitors of this enzyme (i.e., an antibody), or circulating ultra-large von Willebrand’s factor multimers, which suggests a lesion that might be treated with plasma therapies (124–126). Analyses of the E. coli O104:H4 outbreak provided no evidence of the value of eculizumab and plasma exchange (127–129). Risks of plasma exchange include complications of catheter insertion, hypocalcemia, and exposure to blood products (130). It is important to remember that patients with HUS often deteriorate after they are initially diagnosed, that the median number of days of anuria (among those whose urine output ceases) is 8 (20), and that gradual spontaneous resolution of the microangiopathy and recovery of renal and neurologic function are the rule and not the exceptions. Creative treatments offer no benefit to standard, assiduous, intensive care monitoring but do carry risks of adverse events. Such interventions should not be conducted outside the context of controlled trials, and only if sufficient data exist to suggest a state of clinical equipoise as to their potential value. Therapeutic plasma exchange and anticomplement therapies do not meet this standard in E. coli-related HUS.

Clinical Pitfalls in HUS

Postdiarrheal HUS overwhelmingly occurs on a tightly choreographed trajectory (131): diarrhea (usually painful) evolves into grossly bloody diarrhea (80 to 85% of the time). All three criteria for HUS are usually met between the 5th and 13th day of illness, with the first day of diarrhea assigned to be the first day of illness. However, opportunities for Type 1 and 2 diagnostic errors arise because many different microangiopathic disorders have at least some laboratory and historic elements in common with E. coli-related HUS, and microbial diagnosis of E. coli-related HUS is often elusive.

Type 1 diagnostic errors (i.e., falsely assuming a patient has E. coli-related HUS when the patient’s microangiopathy is caused by another process) generally occur in patients with aberrant prodromes to renal failure (minimal or no diarrhea, or chronic diarrhea), or laboratory values that are inconsistent with a diagnosis of E. coli-related HUS. This problem is compounded by look-alike disorders that do not have highly stereotypical presentations so are more difficult to recognize. Type 2 diagnostic errors (i.e., incorrectly assuming a patient does not have E. coli-related HUS) generally relate to lost microbiologic diagnostic opportunities. To avoid Type 1 errors, we search for other etiologies of microangiopathy if there is a persistent documented fever in a health care setting; exceptionally long (>10 days)
or short (<5 days) prodromal illnesses; prominent respiratory symptoms or findings; hypotension/shock; family history (especially of distant past episodes) (132); the patient is under 6 months of age, uses specific medications (e.g., oral contraceptives, cyclosporine), is pregnant; or there are discords between renal injury (severe) and hematologic abnormalities (minimal anemia or thrombocytopenia). The gastrointestinal symptoms that accompany thrombotic thrombocytopenic purpura (133) or atypical HUS caused by complement regulatory proteins (134, 135) rarely resemble those of the enteric prodrome of STEC/VTEC-related HUS, and for this reason, we do not routinely seek other disorders if the presentation is typical. Adjunctive tests, which should be requested and interpreted with circumspection, include chest X rays, blood and urine cultures (and testing for Shiga toxin production if an *E. coli* bacterium is isolated), assays for ADAMTS13 activity, and complement regulatory protein gene sequencing (135–137). Tests that are not helpful diagnostically and often misleading include serum C3, C4, and total hemolytic complement. In our experience with HUS, Type 2 diagnostic errors are more common than Type 1 errors, and are often based on the misconception that failing to find evidence of an STEC/VTEC infection proves that such an etiologic agent is absent. It is important to note that microbiology testing early in illness has the highest yield for STEC/VTEC and that many children with HUS are culture negative at the time of presentation with HUS (44). We strive to increase the microbiologic yield by performing a rectal swab culture on admission of all children with HUS, attempting to take possession of specimens the earliest in illness (usually agar plates), and seeking STEC/VTEC in these specimens in our own centers’ microbiology laboratories. Serology, i.e., seeking evidence of circulating immunoglobulins to the O157 lipopolysaccharide (or to the lipopolysaccharide of several other serogroups), can also be used to assign etiology to cases of HUS in patients in whom a pathogen has not been recovered from the stool (138, 139). Antibodies to VT/Stx are less frequently sought, but newer enzyme immunoassays might offer greater ease of performance (140). However, serologic testing is not widely available. Also, absence of diarrhea does not exclude the possibility of an STEC/VTEC infection (8, 9), and finding such a pathogen can avert a much more extensive evaluation and therapeutic misadventures. Therefore, in any atypical presentation of a microangiopathic disorder we nevertheless exclude, to the best our ability, an etiologic agent by either culture or serologic investigation.

**SUMMARY**

*E. coli* O157:H7 remains the most exceptional pathogen among the STEC/VTEC group, in view of its enduring association with HUS worldwide, its leading frequency in case series of STEC/VTEC infections (compared to any other serotype), and its ability to cause epidemics as well as sporadic cases. Agar plating of all incoming stools is the best way to detect this pathogen. Early in illness, aggressive volume expansion is associated with reduced renal injury. Specific therapies directed at this pathogen or its products are either harmful (antibiotics) or unlikely to work (the toxemia is short lived). Therapeutic plasma exchange and complement inhibition are not justified by credible data.

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