MAJOR ARTICLE

An Outbreak of Shiga Toxin–Producing *Escherichia coli* O104:H4 Hemolytic Uremic Syndrome in Germany: Presentation and Short-term Outcome in Children

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(See the Editorial Commentary by Tarr and Karpman, on pages 760–3.)

Background. In May and June 2011 the largest known outbreak of hemolytic uremic syndrome (HUS) occurred in northern Germany. Because, quite unusually, a large number of adults was affected and the causative *Escherichia coli* strain, serotype O104:H4, showed an atypical virulence factor pattern, it was speculated that this outbreak was associated with an aggressive course and an unfavorable prognosis also in children.

Methods. Retrospective analysis of medical records of 90 children and comparison to previous outbreak and sporadic case series.

Results. Median age was unusually high (11.5 years) compared with that in historical series. Only 1 patient (1.1%) died in the acute phase. Most patients (67/90 [74%]) received supportive care only. Renal replacement therapy was required in 64 of 90 (71%) of the children. Neurological complications, mainly seizures and altered mental stage, were present in 23 of 90 (26%) patients. Ten patients received plasmapheresis, 6 eculizumab, and 7 a combination of both.

After a median follow-up of 4 months, renal function normalized in 85 of 90 (94%) patients, whereas 3 patients had chronic kidney disease stage 3 or 4, and 1 patient (1.1%) still requires dialysis. Complete neurological recovery occurred in 18 of 23 patients. Mild to moderate and major residual neurological changes were present in 3 patients and 1 patient, respectively, although all patients were still improving.

Conclusions. *E. coli* O104:H4 caused the largest HUS outbreak in children reported in detail to date and most patients received supportive treatment only. Initial morbidity, as well as short-term outcome, due to this pathogen, is comparable to previous pediatric series of Shiga toxin–producing *E. coli* HUS.

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Hemolytic uremic syndrome (HUS) was first described by Gasser and colleagues in 1955 [1]. It consists of an acute onset of hemolytic anemia with the appearance of schistocytes, thrombocytopenia, and subsequent renal failure due to severe thrombotic microangiopathy [2]. Although HUS is a rare disease, it typically occurs in childhood and is mainly associated with infections, especially due to enterohemorrhagic *Escherichia coli*

(EHEC) through ingestion of contaminated food. HUS is a major cause of acute kidney injury in childhood [2, 3].

Escherichia coli serotype O157:H7 is frequently found in stool cultures, but several other serotypes are also known to cause HUS (eg, O26 or O111) [4]. The production of Shiga toxin 1 and/or especially Shiga toxin 2 (Stx2) by the causing pathogen plays a key role in inducing HUS [5]. Shiga toxins can induce microvascular damage in the kidney and other organs (eg, pancreas and brain). Thus, neurological symptoms in the acute phase of typical HUS are common and have been described in 20%–25% of patients [6, 7]. Clinical and epidemiological data on HUS in children are available from large surveillance studies of sporadic cases [6–10] and a few reports on outbreaks or clusters [11–13], usually including 10–45 cases of HUS. The biggest outbreak of HUS so far occurred in Sakai, Japan, in 1996 with 121 cases, but clinical data were only published on smaller subcohorts [14].

At the beginning of May 2011, a large outbreak of infections with Shiga toxin–producing *E. coli* (STEC) started in the northern part of Germany. More than 3800 cases of *E. coli*–positive infections were reported, including 845 patients with HUS [15]. The *E. coli* strain that caused the 2011 outbreak has the serotype O104:H4. It produces Stx2 and is resistant to any β-lactam antibiotics and cephalosporins (extended-spectrum β lactamase–producing [ESBL] phenotype) [16]. Further analysis revealed an atypical virulence factor pattern of this strain with genotypic and phenotypic characteristics of STEC as well as enteroaggregative *E. coli* (EAEC) [17]. Genetic comparison of the strain showed that it could be classified as EAEC that acquired Shiga toxin and other virulence factors [18].

Surprisingly, 88% of the patients with HUS were adults, with an overrepresentation of women. However, a very high number of children also developed HUS, making it the largest HUS outbreak ever reported [19]. The large number of adults affected in the outbreak with severe renal and neurological complications led to intensified treatment protocols, including routine plasmapheresis and use of eculizumab in adult patients [20].

We describe the natural history of *E. coli* O104:H4–associated HUS in children and evaluate the role of treatment with supportive care only. Data on the clinical presentation and short-term outcome of 90 children are shown, representing an almost complete pediatric cohort of *E. coli* O104:H4–induced STEC-HUS in Germany.

METHODS

Case Definition

HUS was defined as the combination of hemolytic anemia (hemoglobin <10 g/dL with signs of red cell fragmentation), thrombocytopenia (thrombocytes $<150 \times 10^9$/L), and acute renal impairment (creatinine above the age-dependent normal range). Five of 90 patients showed incomplete forms based on these criteria: 1 patient had normal hemoglobin levels and 1 patient had normal thrombocytes, but both had acute kidney injury and 1 of these patients needed dialysis. Three patients had creatinine levels within the normal range but fulfilled all other criteria, and 2 of these showed halved creatinine at discharge. All 5 patients were included in the study.

Evidence of *E. coli* O104:H4 infection was based on local microbiologic analysis. Stool cultures for EHEC were done with further serotyping and/or testing for the antibiotic resistance, as the outbreak strain had an ESBL phenotype. Stx2 or *stx2* was detected by immunoassay or polymerase chain reaction (PCR) in an enriched stool culture. If the results were negative, but the medical history strongly supported an outbreak-related case (eg, family members also suffered from diagnosed HUS or enterocolitis with the outbreak strain), the patient was included in the study.

Data Collection

A German Pediatric HUS Registry was initiated. All pediatric nephrologists and the 16 pediatric dialysis centers in Germany were contacted to provide HUS patients aged ≤18 years who presented during the outbreak period from May to the beginning of July 2011. Patients with HUS due to *E. coli* O104:H4 were admitted in 13 centers, including 9 pediatric dialysis centers, and data collection in these centers was completed. The local ethical committee approved the study and informed consent was obtained from the guardians. Clinical data of 90 patients could be collected, including all patients who required renal replacement therapy. Ten patients in these centers with STEC-HUS due to other serotypes (O145, O157, and O80) during the same period were excluded from the analysis. Ninety-nine pediatric patients with STEC-HUS due to *E. coli* O104:H4 were reported to the Robert Koch Institute in accordance with the federal infection protection act. Nine patients were not reported to the registry, as they had not been treated in the established pediatric dialysis centers.

Statistical Analysis

Descriptive statistics are presented for continuous variables (mean, median, standard deviation, and ranges) and for categorical variables (patient counts and percentages). Continuous variables were compared by Mann-Whitney *U* test. *P* values <.05 were considered statistically significant.

RESULTS

Patient Characteristics

Ninety children were treated in 13 pediatric departments throughout Germany (Figure 1). The first child was diagnosed on 16 May 2011. From the beginning of June, the number of

Figure 1. The pediatric departments and the numbers of patients with hemolytic uremic syndrome during the outbreak in Germany. (**X** indicates the probable source of the contaminated sprouts from a single sprout producer located in northern Germany.)

new cases rapidly declined. The last patient was admitted on 5 July 2011. Hospitalization was necessary for a median of 17 days (range, 2–103). Median age of the patients was 11.5 years (range, 0.6–17.5); 18 children (20%) were aged 5 years or younger. Forty-nine patients (54%) were girls and 41 (46%) boys. The median duration of the prodromal phase from the beginning of the first gastrointestinal symptoms to the onset of HUS was 5 days (range, 0–14). One patient (1.1%) died in the acute phase on dialysis due to cardiomyopathy, severe hemolysis, and neurological involvement.

Laboratory Results

Laboratory data are shown in Table 1. A trend toward normalization of serum creatinine, full blood count, and lactate dehydrogenase at discharge could be demonstrated.

Microbiology

In 75 of 90 patients (83%), stool cultures were EHEC-positive and further analysis showed either serotype O104:H4 and/or the typical antibiotic resistance of the outbreak strain with an ESBL phenotype. In addition, Stx2 was detected in 67 of these 75 patients either by immunoassay or PCR depending on the approach of local laboratories. In 7 of 90 patients (8%), only Stx2 was detectable. In 8 cases (9%), neither the stool culture was positive nor was Stx2 demonstrated.

Clinical Data

An overview of selected clinical data and a comparison to previous series is presented in Table 2. For detailed assessment, see the Discussion.

Gastrointestinal Symptoms

In the prodromal phase, all of the patients showed mild to severe gastrointestinal symptoms. Diarrhea was present in 86 of 90 patients (96%), and 66 of 90 (73%) developed bloody diarrhea (Table 2). Vomiting occurred in 64 of 90 (71%) and abdominal pain was documented in the medical records of 62 of 90 patients (69%). Fourteen of 90 children (16%) had fever before the diagnosis of HUS according to parental report. One patient had severe gastrointestinal complications including perforation of the colon, resulting in peritonitis and multiple abscess formation requiring repeated surgery including colectomy.

Renal Complications

Dialysis therapy was required in 64 of 90 (71%) patients, and oligo-/anuria was reported in 59 of 90 (66%) patients. After 4 weeks, 60 of 63 survivors were removed from dialysis. In 2 patients, dialysis could be terminated subsequently. The median time period of dialysis was 11 days (range, 2–199) in 62 patients who survived and in whom dialysis could be

Table 1. Laboratory Data of 90 Patients on Admission and Discharge

	Admission	Minimum/Maximum	Discharge (n = 89)
Serum creatinine, mg/dL[a]	3.6 (3.14)	6.6 (4.4) (max)	1.3 (1.1)
Hemoglobin, g/dL	10.8 (1.6)	6.4 (1.2) (min)	8.6 (1.3)
Thrombocytes, $\times 10^9$/L	72 (79)	35 (23) (min)	286 (124)
Lactate dehydrogenase, U/L	1729 (869)	2523 (1720) (max)	429 (216)

All values are mean (standard deviation).

[a] To convert values for creatinine to μmol/L, multiply by 88.4.

Table 2. Epidemiological and Clinical Data of 90 Patients and Comparison to Previous Series

	Current Study	Previous Studies	References
Epidemiology			
Age, median, years	11.5	2–3.5	[6, 7, 10, 22]
Male/female, %	46/54	48/52	[6]
Mortality, %	1.1	1–5	[7–9, 25]
Gastrointestinal symptoms			
Diarrhea, %	96	86–100	[6–9, 12, 22, 25, 26]
Bloody diarrhea, %	73	57–73	[6, 8–10, 22]
Vomiting, %	71	75–85	[9, 25, 26]
Renal complications			
Dialysis, %	71	47–90	[6, 7, 9, 12, 22, 25, 28]
Duration of dialysis, median, days	11 (n = 62)	8–15	[6, 9, 12, 14, 25, 29, 30]
Neurological symptoms			
Total with neurological symptoms, %	26	19–25	[6, 7, 9, 10]
Seizures, No. (%)	16/23 (70)		
Impaired consciousness including coma, No. (%)	17/23 (74)		
Visual disturbances, No. (%)	7/23 (30)		

terminated (Figure 2). Thirty of 64 patients (47%) underwent hemodialysis or hemofiltration, and 26 of 64 patients (41%) received peritoneal dialysis. Eight patients were switched from peritoneal dialysis to hemodialysis/hemofiltration for technical or logistical reasons. Twenty-six patients (29%) could be managed conservatively and did not need dialysis. Arterial hypertension, defined as blood pressure >90th percentile, was seen in 32 patients (36%) at presentation. Maximum white blood cell count during the course of illness was significantly higher in patients who required dialysis treatment versus those who did not (15.8×10^9/L [±5.6] vs 12.4×10^9/L [±7.1], $P < .005$).

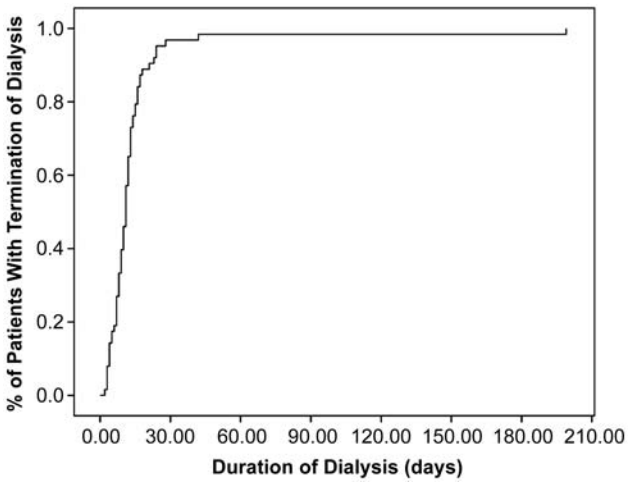

Figure 2. Duration of dialysis in 62 patients in whom renal replacement therapy could be terminated.

Neurological Complications

Severe neurological symptoms occurred in 23 of 90 (26%) children. The median duration from diagnosis of HUS to the onset of neurological symptoms was 2 days (range, 0–10). Most had seizures (16/23 [70%]) and/or double or blurry vision (7/23 [30%]). Seventeen patients (17/23 [74%]) had impaired consciousness, including 5 patients, 1 of whom died, with complex symptomatology, including coma, encephalopathic state, paresis, and aphasia. Patients with neurological involvement showed a significantly lower minimum thrombocyte count during the course of HUS (28.6×10^9/L [±22.0] vs 37.5×10^9/L [±24.4], $P < .004$).

Treatment Modalities

Sixty-seven patients (74%) received supportive care only, including renal replacement therapy. Red blood cell transfusions were given to 59 of 90 patients (66%). Only 6 patients received >5 transfusions. Despite only low-grade evidence to support its use, plasmapheresis was performed in 17 of 90 (19%) patients, mainly for neurological complications (n = 16), but also for severe renal involvement (n = 1). Exchange was done against albumin (n = 12) or fresh frozen plasma (n = 5), with a median of 4 exchanges (range, 2–7). Albumin was used to eliminate proaggregating/proinflammatory factors, whereas use of fresh frozen plasma additionally replaces coagulation and complement factors. The treatment with plasmapheresis included 7 patients with neurological complications for whom an additional subsequent treatment with anti-C5 antibody eculizumab was used. Eculizumab alone was given to 6 patients, making a total of 13 of 90 (14%) patients in whom eculizumab was used. This includes 3 patients with neurological complications, who were pretreated with protein C. Seven eculizumab-treated patients were enrolled in an open-label single-arm study, including 3 after plasmapheresis pretreatment. The rationale for the treatment with eculizumab was a single report on its effect in 3 children with STEC-HUS and neurological complications [21]. Four patients with neurological complications, including 1 with convulsions and 1 with double vision and impaired consciousness, were treated with supportive care only.

Short-term Outcome

After a median of 4 months of follow-up (range, 3–6 months), 4 patients (4.4%) still suffered from chronic kidney disease, including 3 with stage 3-4 disease with an estimated

glomerular filtration rate of 25, 29, and 40 mL/min/1.73 m^2, respectively. One patient was still on chronic hemodialysis after 6 months of follow-up.

Of the children with neurological complications, 18 of 23 (78%) showed a complete recovery. Mild symptoms were still present in 3 patients (fine motor disturbances, n = 2; concentration deficits, n = 1). One child although improving, still had major motor disturbances with dyskinesia after severe cerebral edema.

DISCUSSION

STEC-HUS is a serious disorder leading to acute kidney injury and neurological complications in many children. In this series, the largest to date, of a pediatric STEC-HUS outbreak associated with *E. coli* O104:H4, initial morbidity and mortality as well as short-term outcome results are in line with those of previous pediatric reports of STEC-HUS. In the majority of patients, STEC-HUS seems to be a self-limiting disorder.

Some epidemiological differences could be noted in this *E. coli* O104:H4 outbreak. The median age at presentation was 11.5 years and thus significantly higher than previously reported for STEC-HUS cases in France [22], Great Britain [7], the United States [10], and Germany and Austria [6], with an average age <5 years. In this series only 20% of the patients were ≤5 years of age. This could be related to the route of transmission—for example, ingestion of sprouts [23], which are rarely consumed by young children. In contrast to the outbreak in adults, we did not see any predominance of female patients [15]. This outbreak was associated with a high rate of progression from enterocolitis to HUS in 20% of the infected adult individuals [15]. Usually a progression rate of 10%–15% to HUS has been documented for sporadic and outbreak cases in children [24].

STEC-HUS is a life-threatening disease also in children, and unfortunately 1 child in our series did not survive the outbreak, resulting in a pediatric mortality rate of 1.1%. Fortunately, in comparison to previous reports this is actually low. Mortality rates in pediatric STEC-HUS range from 1% to 5% in sporadic cases [7–9, 25]. In some outbreaks higher rates of 6.7% [11] and even up to 11% with *E. coli* O157:H(-) in Germany have been reported [26, 27]. One should note that in small series, overrepresentation of complications might occur. During this outbreak, mortality associated with STEC-HUS in adults was 36 of 845 (4.2%) patients [15].

Gastrointestinal symptoms had a frequency comparable with previously published studies of sporadic and outbreak cases. In these studies, diarrhea was seen in 86%–100% [6–9, 12, 22, 25, 26], bloody diarrhea in 57%–73% [6, 8–10, 22], and abdominal pain and vomiting in 75%–85% [9, 10, 25, 26] of patients. A trend toward higher frequency of bloody diarrhea has been seen in some outbreaks [12, 25]. In addition, the observed median period from onset of clinical symptoms until the development of HUS was in the range of previously published series of 5–6.5 days [8, 10, 12, 22, 28] and is consistent with the findings of Frank et al during this outbreak [15]. However, in a retrospective analysis of medical records, the frequency of symptoms might be underestimated owing to incomplete history taking.

The most prominent complication in children was acute kidney injury, requiring renal replacement therapy in 71% of patients. This number seems high compared to previous reports, where it was between 47% and 68% [6, 7, 9, 22, 25, 29]. For *E. coli* non-O157 and O111, dialysis rates of 65% and 90%, respectively, have been reported [6, 12, 25], so the actual figures in the current outbreak seem comparable for STEC-HUS in general. It should be noted that all pediatric dialysis centers contributed to this series, and underreporting of milder cases could have occurred. Most children required dialysis only for a short time (median, 11 days) and most children were removed from dialysis after 4 weeks; this compares to previous reports in which patients were on dialysis for an average period of 8–15 days [6, 9, 12, 14, 25, 29, 30]. Interestingly, we were able to confirm in this large cohort that elevated white blood cell count is associated with an increased need for dialysis [6, 31, 32].

Severe neurological symptoms occurred in 26% of the children; this included seizures, paresis, visual disturbances, and/or impaired consciousness. Mild symptoms (eg, agitation and irritability) have not been included, since they are often present in intercurrent disease in children (eg viral gastroenteritis). Again, results match with those of previously published studies reporting neurological complications in up to 19%–25% of cases [6, 7, 9, 10]. Other studies suggest that there might be even a higher incidence of neurological complications in other HUS outbreaks [12, 25, 28]. The majority of the patients showed a complete restitution. Neurological complications remain a major challenge in the clinical care of children with typical HUS, as shown by the series of Nathanson et al, in which 52 children were described and 9 children died. This is especially important since no controlled data on prevention or treatment are available, although plasmapheresis is often performed [33].

The short-term outcome of the pediatric cases is encouraging, although in a small proportion of patients chronic renal impairment seems to be prevalent. Again, this is not in contradiction with previously published studies [12, 28, 34, 35]. Some children have not completely recovered from their neurological complications; therefore, long-term follow-up will be important regarding more subtle renal changes such as proteinuria and hypertension [36, 37], but also to determine neurological long-term morbidity [33, 38].

Plasmapheresis was mainly reserved for patients with neurological symptoms. This is in contrast to the outbreak in adult patients, in which initially almost all patients received plasmapheresis [39], although there is a lack of controlled studies [36]. In the middle of the outbreak a report on the effect of eculizumab, an anti-C5 antibody, in 3 children with STEC-HUS and neurological complications was published [21]. The drug has been used successfully in cases of atypical HUS, for example, to prevent recurrences after renal transplantation [40]. Eculizumab was used frequently in adults in this outbreak and an open-label single-arm trial has been initiated. Seven children have been enrolled and results of this study will be published elsewhere. From our study, however, it does not seem justified to recommend plasmapheresis and/or eculizumab for all patients with STEC-HUS, given that 74% of the patients recovered with supportive treatment alone.

In conclusion, these data show that HUS due to *E. coli* O104:H4 is a multiorgan disease with acute onset and significant complications, but short-term outcome is comparable to previous pediatric cohorts. As the majority of patients with STEC-HUS have a favorable outcome with supportive therapy alone, this indicates that it is often a self-limiting disease. Additional treatment efforts only seem justified in complicated cases, for example, when neurological complications occur. This should be evaluated by randomized controlled studies.

Note Added in Proof: One further patient was entered into the registry after submission of the manuscript, a 13-year-old girl with acute kidney injury (max. creatinine 3,1mg/dl) who did not require dialysis.

Notes

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Potential conflicts of interest. Three centers (Hannover [T. A., L. P., M. K., D. H.], Hamburg [S. L., J. L., G. H., J. O., M. J. K.], and Erlangen [K. B.]) enrolled 7 patients in a single-arm multicenter trial on eculizumab treatment, which is sponsored by Alexion. Comprehensive data on the treatment effect in these patients will be published elsewhere. L. P. and U. V. received support for travel and/or honoraria for consultancy by Alexion.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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