

Outbreak of hemolytic uremic syndrome caused by *E. coli* O104:H4 in Germany: a pediatric perspective

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Abstract In May–June 2011, an unprecedented outbreak of hemolytic uremic syndrome (HUS) caused by Shiga toxin-producing *E. coli* (STEC) O104:H4 affected >800 adults, in whom this disorder is usually rarely seen. Over 90 children were also affected in the largest STEC-associated HUS outbreak in children to date. Despite high patient numbers and chronic staff shortages in pediatric institutions, almost all patients were treated locally, mainly because of maximally increased staff input. Epidemiologic features were characterized by relatively high age at presentation, possibly related to the isolated etiologic agent, raw bean sprouts. Fortunately, in children, other clinical features, including neurological complications, dialysis requirement, and short-term outcome, were comparable to previous historical series. Only one child died, compared to 35 adults. Differences in treatment recommendations and approaches between adults and children were noted. Treatment with eculizumab was available, but handled more restrictively in children. Despite treatment differences, children and adult clinical outcomes were comparable, pending a final analysis. In summary the STEC O104:H4 HUS outbreak was challenging for pediatric resources but clinical presentation and complications were comparable to previous experience. Acute outbreak onset made structured approaches to treatments impossible, however,

ongoing analysis may provide evidence for improving care of children with STEC HUS.

Keywords Hemolytic uremic syndrome · Shiga toxin · Children · *E. Coli* · STEC · Eculizumab · Epidemiology

Introduction

May and June are usually quiet months in Germany, partially because of the many public holidays that result in many short-term breaks, e.g., by dialysis nurses as well as pediatric nephrologists. In 2011 these months turned out to be dramatic, since a previously unprecedented hemolytic uremic syndrome (HUS) epidemic occurred in northern Germany, which is now regarded as the largest reported outbreak with Shiga toxin-producing *E. coli* (STEC) leading to HUS including neurological problems.

More than 800 cases of HUS were reported to the authorities and quite unexpectedly and (in contrast to previous STEC HUS epidemics) more than 90% of affected patients were adults. However, it was not exclusively limited to this age group and more than 90 children contracted *E. coli* O104:H4-associated HUS, which is the largest pediatric HUS epidemic known.

This editorial tries to recapture important experiences and highlight specific epidemiologic aspects, as well as some characteristic clinical features of affected children. Since not all clinical data have yet to undergo a final analysis, only an overall view will be presented.

Epidemiology

STEC-associated HUS is the most frequent cause of acute kidney injury in Germany in children, and since 2001,

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between 44 and 118 patients per year have been reported to the Robert Koch Institute in Berlin (usually adults are not affected by enteropathogenic HUS making it a classical pediatric disease). In our center, an average of ten patients with typical HUS are treated per year; fortunately, only one patient has died in the last 20 years. In 2011, three patients with “typical” diarrhea-associated HUS had been admitted from January to April; one can see from Fig. 1 that in May and June 2011 a dramatic increase occurred that must have had a special cause.

As indicated in the “HUS diary” of Sigrid Harendza [1], the first adult patient in Hamburg with HUS presented May 18. The first two children in May (with STEC O104:H4) were already admitted in our unit on May 17, but this was not regarded as unusual since summer is usually “HUS-time”; thus it did not result in any activity above that which was expected. However, in the following days, more and more children with HUS were admitted and already after 1 week 14 patients and after 2 weeks 24 children were hospitalized; a total of 33 HUS cases caused by STEC O104:H4 were treated in Hamburg in May and June alone.

As reported by Frank et al. [2], a total of 3,816 cases of *E. coli* O104:H4 (including 54 deaths) were diagnosed in Germany, 845 of which (22%) involved HUS. The peak of the infection was around May 21–22, and 88% were adults with a median age of 42 years with an overrepresentation of women (68%). The outbreak strain was typed as an enteroaggregative Shiga toxin-producing *E. coli* O104:H4, producing extended-spectrum beta-lactamase and HUS in adults occurred in more than 20% of the identified cases, which indicated the aggressiveness of the strain.

Search for etiology

After identification of the enteroaggregative *E. coli* serotype O104:H4, genome-wide comparisons were performed,

which showed that the genome of the German outbreak strain could be distinguished from those of other O104:H4 strains because it contained a prophage encoding Shiga toxin 2 resulting in distinct virulence and antibiotic-resistance factors [3].

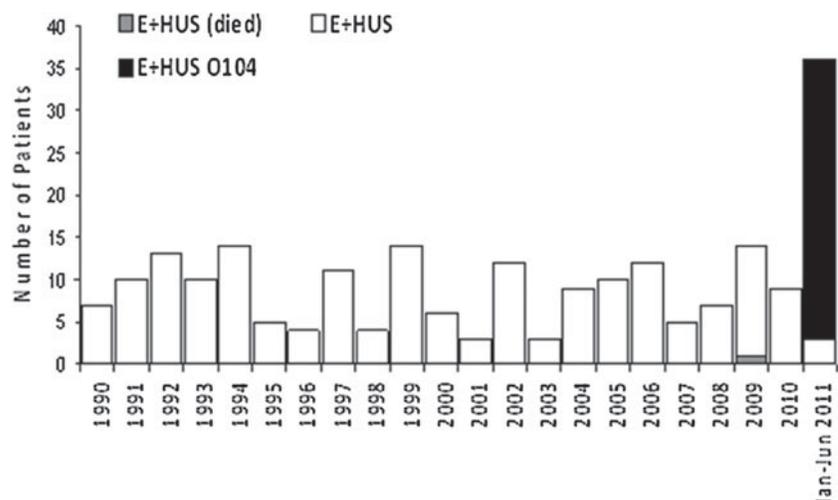
This led to an intensive search for the source of the infection and initially almost daily suspected candidates were discussed, from cucumbers to tomatoes and other products. Finally, a recipe-based study found that bean sprout ingestion explained 100% of cases and trace-back investigations identified the producer [4].

Specific pediatric details in comparison to published series

Since quite an unusual number of adults patients were affected, the high rate (22%) of patients developing HUS as well as the extended spectrum beta lactamase (ESBL) production led to the concern that this STEC O104-HUS epidemic resulted in an unfavorable and aggressive course. This impression was aggravated after neurological complications were noted in adults and the first patients died.

Regarding children, the clinical course of the individual patients seemed comparable to the long-term experience. The large number of patients who needed simultaneous treatment was challenging, especially on resources, but the initial rate of complications was not unusual. Especially when looking at the published pediatric series from the US [5], Australia [6], Great Britain [7], and Germany [8], it seems that most pediatric patients with STEC O104:H4 HUS had a comparable course compared to historic controls. Two special features compared to the past, however, were the fact that patients were from a high socioeconomic status and that age at presentation was relatively high. Most patients were older than 10 years, which is considerably higher than for *E. coli* O157 and O111, where patients are usually under 3 or

Fig. 1 *E. coli* hemolytic uremic syndrome (STEC HUS) prevalence at the University of Hamburg Children’s Hospital since 1990. The numbers for 2011 are from January to June



under 5 years of age, respectively. As mentioned, in the adult population, a preponderance of the female sex was noted, but this could not be confirmed in children, where the male/female ratio was similar to previous series, nationally and internationally.

Fortunately, mortality in children was extremely low, since only one child died compared to more than 35 adult patients by the end of June. Thus, pediatric mortality again was in the range of published historical series that document a mortality rate in children ranging from 2.3–3.6%. The higher rate in adults may be related to additional morbidity, especially in elder patients. Whether differences in treatment, e.g., use of antibiotics, have had an impact, cannot be proven.

More than two-thirds of children required dialysis, while in the remainder of patients renal failure could be managed conservatively. This again compares to previous studies, where 47–90% required dialysis, although the need for dialysis has been reported to be higher in STEC O111H compared to O157H. The most frequent modality was peritoneal dialysis, however, about 40% were treated by extracorporeal modalities, sometimes for logistical reasons, e.g., during one weekend no more Tenckhoff catheters were available.

Concerning the neurological complications, about a quarter of the children had neurological complications, including convulsions or altered mental status including coma, or both. This again compares to published series since neurological complications are frequent in children with HUS and have been reported for 13–45% of patients. The approach towards treatment of neurological complications included anti-epileptic drugs and plasma exchange (PE) in most centers, while one pediatric center only used eculizumab.

Plasma exchange and eculizumab

As mentioned above, plasma exchange for HUS in children in our unit is reserved for patients with neurological complications. For exchange albumin, 5% is used for typical HUS and FFP for atypical HUS. For adults, however, the German Society of Nephrology recommended PE for all patients with HUS with renal and/or neurological symptoms and thrombocytopenia $<100,000 \text{ mm}^3$ to be performed daily for 5 days. The use of FFP was recommended for exchange. As a result, the number of plasma exchanges increased dramatically and resulted in considerable logistical problems (supply of staff, machines, FFP). As a consequence, many adult patients had to be referred to other centers, and in Hamburg included many private dialysis practices that were recruited to dialyze and plasmapheresis patients.

On May 26, i.e., in the middle of the epidemic, a letter in the New England Journal of Medicine appeared [9] reporting the benefits of using eculizumab in enteropathogenic HUS, especially for patients with neurological complications that were resistant to plasma exchange. During the following days and weeks, eculizumab became available and was used in many adult patients with STEC-HUS but also in individual children.

Comparison to adults

The differences in the clinical approach and treatment for the adults were considerably more aggressive than for the children. In addition to PE and eculizumab, also antibiotic treatment was used frequently for adults, as well as intestinal decontamination. Surprisingly, there was little communication between pediatric nephrologists and (adult) nephrologists, despite the long experience of pediatricians with this disorder. Instead, because of the intensive media coverage and also due to the fact that often more than one generation was affected within one family, treatment recommendations of adult nephrologists were also suggested for children, directly and indirectly.

Other aspects and summary

Since many children were treated simultaneously, communication between parents was common, resulting in both anxiety and solidarity. Fortunately, the course of the disease was as anticipated, but if for instance ten patients are in the hospital, e.g., with neurological complications at the same, this implies a significant stress factor for patient families and staff.

A favorable outcome in most children was achieved because of excellent efforts by the pediatric staff who were competent and experienced in the treatment of this acute disorder. Logistical problems were overcome by increased activities: no extra personnel were provided although the number of patients increased by 300% for HUS alone. Last but not least, it should not be forgotten that routine care for children with kidney disease was continued.

Despite the favorable short-term outcome for the majority of patients, it should be kept in mind that HUS is a life-threatening disease. One child has died and chronic kidney disease is present in a small proportion of the patients at the time of writing. Long-term observation is therefore required in order to define the ultimate burden. The lack of controlled data on treatment of enteropathogenic HUS has become evident and it is surprising in this respect that treatment recommendations are already published, before evidence is produced [10].

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