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Recent outbreak of hemolytic uremic syndrome in Germany

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In a recent issue of *Kidney International*, Dr. Sigrid Harendza's diary described how an unprecedented number of patients with hemolytic uremic syndrome (HUS) swamped hospitals in northern Germany in May. As nephrologists we are familiar with patients suffering from HUS; however, HUS is a rather rare event in clinical practice, particularly in adults. Most cases in adults are of noninfectious etiology and due to drug effects or other underlying diseases. By contrast, infection with Shiga toxin-producing *Escherichia coli*, usually associated with prodromal diarrhea, is the primary cause of HUS in children.

HUS caused by enteric infection is statutorily notifiable in Germany, and the national database on notifiable infectious diseases is hosted by the Robert Koch Institute, the federal-level public-health institute. Since 2001, the Robert Koch Institute received between 44 and 118 reports of HUS cases per year, primarily pediatric patients. In May 2011, the situation changed dramatically.

Epidemic profile of the outbreak

An outbreak of Shiga toxin-producing *E. coli* O104:H4 infection started in early May in Germany. The number of HUS cases peaked at 65 on 21 May—as many as would be expected for a whole year in Germany. The outbreak declined afterward, with few cases of HUS occurring after 16 June (Figure 1).

As of 25 July, almost 4000 symptomatic cases, including 50 deaths, had been attributed to the outbreak, of which 732 were confirmed cases and 120 were suspected cases of HUS. In a preliminary report, 89% of these patients were older than 18 years (median age, 43 years), and women were overrepresented.¹ The outbreak occurred primarily in northern Germany.¹ Cases have been reported throughout Germany and from more than 15 other countries; most had a history of travel to northern Germany. The outbreak exhibits novel epidemiological, clinical, and microbiological features. Prominent among them are the unprecedented proportion and total number of HUS cases, and that the majority of HUS patients were adults. Data on prospectively followed patients in this outbreak and German notification data indicate that about 20% of diarrheal Shiga toxin-producing *E. coli* O104:H4 patients in this outbreak developed HUS.¹ This proportion is higher than those in previous reports on large outbreaks all over the world and suggests a high virulence of the outbreak strain.

Character of the *E. coli* strain associated with the outbreak

The outbreak strain is unusual in several ways. It has an enteroaggregative *E. coli* genomic background, with a bacteriophage that carries the Shiga toxin 2 gene integrated into the chromosome. In addition, two plasmids (circular, self-replicating DNA molecules that exist extrachromosomally) carry aggregative adhesion fimbrial operons as well as antibiotic resistance information including extended-spectrum β -lactamases and trimethoprim/ sulfamethoxazole. This genetic combination gives rise to a hybrid pathogen that has the intimate intestinal adherence of enteroaggregative *E. coli* with the toxigenicity of enterohemorrhagic *E. coli* (EHEC) and the added complication of antibiotic resistance.

The outbreak strain belongs to the HUSEC041 (O104:H4, ST678) complex. Another member of this complex was first isolated from a child with HUS in Cologne, Germany, in September 2001 and was extensively characterized.² No other HUSEC041 complex isolates were detected from the more than 700 HUS isolates during the last 15 years until the current outbreak in Germany. We are unaware of

any additional outbreaks caused by this pathogen group in other parts of the world before the onset of the German outbreak. From this we can conclude that this outbreak strain must be extremely rare as a cause of HUS and diarrhea.

Much is still unknown about the HUSEC041 complex strains. The pathogens have not yet been detected in animal groups, and no other evidence has been collected to suggest that the pathogen is of zoonotic origin. This could imply that humans are the sole carriers of O104:H4. Little is known about the persistence of EHEC O104:H4 in both the human and nonhuman environments. The infectious dose is also unknown, though we can speculate that it is low on the basis of the observed high acid resistance. The status of immunity within the human population may also be low, as this strain appears to be a newcomer to the pool of circulating pathogens. The geographic spread of this strain, as well as the extent of its existence within asymptomatic human carriers, is still unknown. But this knowledge would be of high importance in our globally connected world.

Recommendations of German and European authorities

On 10 June, federal public-health and food safety authorities in Germany advised consumers not to eat raw sprouts. The advice was based on analytical epidemiological studies and preliminary food-tracing results. In June, an outbreak of EHEC O104:H4 occurred in the southwest of France, and sprouts were suspected as the vehicle of infection. Despite isolation of the identical outbreak strain, patients from France reported having had no contact with products from northern Germany. The public advice in Germany was tailored to fenugreek sprouts and seeds on 21 July. The European Commission suspended the importation of fenugreek seeds and additional seeds from Egypt until 31 October 2011. The Commission decided to withdraw from the market and destroy all batches of fenugreek seeds imported between 2009 and 2011 from Egypt. But to the best of our knowledge, EHEC O104:H4 has not been isolated from fenugreek seeds or sprouts until now.

Clinical course of hemolytic uremic syndrome in this outbreak

Most patients were admitted with bloody diarrhea, followed by deteriorating kidney function, hemolysis, and thrombocytopenia in about 50% within a few days. In contrast to previous descriptions, more than half of the HUS patients exhibited particular neurological symptoms. Loss of the ability to control the mind horrified those young patients with an unremarkable medical history. Often, focal or generalized epileptic seizure accompanied the disease, but fortunately, computed tomographic or magnetic resonance scans revealed only a few cases with focal infarctions, and most cerebral diagnostic images remained almost normal. In certain cases, neurological symptoms preceded the classical HUS. About 10% of the HUS patients with life-threatening complications, including *E. coli* sepsis or necrotizing enteritis, were admitted to an intensive care unit. The severity of the disease urged a specific therapeutic approach.

Although the clinical course and the pathophysiology of the disease are well characterized, there is a lack of specific therapeutic evidencebased options beyond optimal supportive treatment. At the beginning of the outbreak, an *ad hoc* committee of the German Society of Nephrology recommended treating all HUS patients with renal or neurological and hematological symptoms with plasmaphereses. The rationale behind this recommendation seems to be limited, as cell-bound Shiga toxin may not be effectively eliminated from the circulation by plasmaphereses. Profound clinical evidence is also lacking; a recent analysis concluded that plasmapheresis is a "promising" therapeutic option and not more.³ Just at the beginning of the outbreak, an article reported that treatment with eculizumab improved the clinical course dramatically in three pediatric patients within days.⁴ Eculizumab is a recombinant humanized monoclonal IgG2/4 antibody that specifically binds to the complement protein C5, inhibiting its cleavage by the C5 convertase, which prevents the generation of the terminal complement complex C5b-9. Accordingly, the German Society of Nephrology extended the recommendation to include treatment of all patients who exhibited no short-term improvement after beginning plasmaphereses with this antibody. Finally, a variety of patients have been treated with different antibiotic regimens despite reports that antibiotics might worsen the course.⁵ At the beginning, only eculizumab-treated patients received antibiotics to prevent meningococcal infections, as well as patients with necrotizing enteritis or concomitant systemic bacterial infection. However, on the basis of the specific potency of EHEC O104:H4, some centers liberalized the antibiotic treatment option to eliminate the causative agent earlier.

Conclusion

At the time of this writing, this outbreak seems to be over, and we can observe that the majority of patients survived the disease without any residual organ damage. However, in some patients kidney function did not normalize, and a few patients still suffer from neurological symptoms. To date, 50 patients died. Despite this rather favorable outcome, this outbreak was characterized by the uncertainty of specific therapeutic options. Although not obtained in a randomized fashion, retrospective analyses of this outbreak will hopefully provide reasonable information allowing establishment of an evidence-based and appropriate therapeutic repertoire for patients suffering from hemolytic uremic syndrome.

Disclosure

The authors declared no competing interests.

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In May–June 2011 northern Germany suffered from one of the worst outbreaks of EHEC infection, with a high incidence of severe HUS. About 4000 people were infected and at least 46 died. Dr. Harendza, a staff nephrologist at the Hamburg University hospital, recorded the events in a daily diary, which gives a vivid account of how the epidemic flooded the hospital and strained its dialysis and plasmapheresis abilities, both in terms of technical capability and human resources.

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Figure 1. Epidemic curve of an outbreak of gastroenteritis and hemolytic uremic syndrome caused by Shiga toxin-producing *Escherichia coli* O104:H4 in Germany. The numbers of notified cases of enterohemorrhagic *E. coli* (EHEC)-associated gastroenteritis and of hemolytic uremic syndrome (HUS) are displayed by onset of diarrhea (if reported) during May and June 2011.

