EDITORIAL COMMENTARY

Escherichia coli O104:H4 and Hemolytic Uremic Syndrome: The Analysis Begins

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(See the Major Article by Loos et al, on pages 753–9.)

Although tragic, epidemics provide opportunities to obtain information that can advance medical practice. In the case of rare infections for which little clinical guidance exists, outbreaks can provide data on a scale that would be otherwise unfeasible. The German pediatric community [1] provided such an analysis of last year’s epic Shiga toxin (Stx)–producing Escherichia coli (STEC) O104:H4 outbreak by focusing on the informative group of infected children who developed hemolytic uremic syndrome (HUS). Loos et al are to be commended for their collegiality and functionality in producing such a thorough report so expeditiously and especially for using an appropriate case definition for HUS. Some publications from this outbreak and other cohorts have employed nonstringent and imprecise case definitions rather than the more exact, clinically pertinent, and urinalysis-independent criteria used in multiple North American, European, and Japanese series [2–21]. By adhering to simple and relevant criteria for case inclusion, Loos et al enable physicians worldwide to relate their past and future experiences to the patients in this report. We hope that subsequent publications from this outbreak emulate this disciplined standard.

Definitional attributes aside, the most enduring lesson from this article will be the contrasts it provides: children with HUS received standard supportive care, whereas infected adults were treated very differently with unproven (in this illness) technologies; children with HUS had relatively good outcomes, whereas adults did not do as well.

The events that unfolded last year put this contrast in perspective. On 19 May 2011, Hamburg pediatricians informed the Robert Koch Institute of a cluster of children with HUS [22]. Their stools did not contain E. coli O157:H7, prompting an intense search for other STEC. Within a week of receiving the pathogen, Bielaszewska et al, in a microbiologic tour de force, identified the causative pathogen as an E. coli O104:H4, determined that it possessed STEC and enter-aggregative E. coli traits, and developed and disseminated molecular diagnostic protocols [23].

Because of concern that the virulence of E. coli O104:H4 exceeded that of the quite formidable but reasonably familiar E. coli O157:H7, and because of the large proportion of infected patients who were adults, on 1 June 2011, the German Society for Nephrology recommended initiating therapeutic plasma exchange (TPE) as early as possible in severely affected patients, although the society did qualify this advice by noting the absence of controlled trials [24]. Their definition of severely affected relied largely on a platelet count <100 000/mm3 (which is a fairly common abnormality in STEC infections in patients who have no evidence of renal insufficiency), if accompanied by the nebulously described “presence of renal and/or neurologic involvement.” A justification for using TPE was that it might remove circulating Stx. We understand that the preponderance of adults with HUS in the outbreak underwent TPE.

If patients did not improve after TPE, many physicians turned to eculizumab, a monoclonal antibody that neutralizes the fifth component of complement. This off-label use appears to have been prompted by a letter to the New England Journal of Medicine [25] published early in the outbreak, describing 3 children with typical HUS who improved after eculizumab administration. Eculizumab is remarkably useful in atypical HUS, a disorder caused by genetic defects in components or regulators of the
alternative pathway of complement as well as antibodies to the complement regulator factor H [26] and characterized by uncontrolled complement activation. There are similarities between atypical and typical HUS: each is accompanied by renal failure, thrombocytopenia, and hemolyisis. Stx activates complement and inhibits the alternative pathway regulator factor H in vitro. Also, complement deposits are present on HUS patients’ platelets and blood-cell derived microparticles [27–29]. A third intervention, immunoadsorption, was tried on at least a small group of patients in Germany [30] to remove a hypothetical pathogenic autoantibody.

Except for concern that the hypervirulence of *E. coli* O104:H4 warranted interventions beyond those that are reasonably successful for *E. coli* O157:H7 HUS, there was in June 2011 (as there remains today) scant justification for TPE, eculizumab, or immunoadsorption in treating typical HUS. Typical HUS, thrombotic thrombocytopenic purpura (TTP), and atypical HUS are different forms of thrombotic microangiopathies with distinct mechanisms of causation and treatments that relate to their respective pathophysiology. For typical HUS, which is a consequence of STEC infection in which there is no evidence for persistent free toxin in plasma, assiduous monitoring and supportive care are almost always sufficient treatment. TTP is associated with deficient function of the von Willebrand factor (VWF) cleaving metallocuprotease ADAMTS13, which cleaves ultra-large (pathologic) circulating VWF multimers. Antibodies to or congenital absence of (Upshaw Schullman Syndrome) ADAMTS13 underlies TTP. Both mechanisms of TTP respond to TPE, and Upshaw-Schulman Syndrome responds to plasma infusion alone. Before and during typical HUS, there is normal ADAMTS13 function, no circulating inhibitors of (eg, antibodies) to this metalloprotease, and no evidence of ultra-large multimers of VWF [4, 31, 32], as confirmed during the outbreak [30]. A single paper claimed the value of TPE during an outbreak of STEC O157:H7–related HUS in Scotland in 1996 [33]. This treatment was, however, withheld from the most ill patients, and their deaths contrasted with survival of the less ill were offered as evidence of the value of TPE. Indeed, the American Society for Apheresis assigns to TPE the lowest grade of evidence in support of efficacy for typical HUS [34]. Nonetheless, based on an uncontrolled case series of 5 patients [35], a Lancet commentary endorsed plasmapheresis for typical HUS [36].

The rationales for using eculizumab and immunoadsorption in this outbreak are similarly unclear. Each patient described in the letter to the *New England Journal of Medicine* had objective evidence of improvement by the time the antibody was infused: platelet counts were rising, and/or serum LDH concentrations were falling. Although, as noted above, Stx activates complement in vitro and inhibits regulators of the alternate complement pathway, these experiments used concentrations of Stx 1000–1 000 000 times greater [27–29] than has ever been documented in infected humans (17 pg/mL) [37], and nonhuman primates are severely injured by administering 100 ng/kg of Stx2 [38]. Also, by inhibiting complement, an antibacterial arm of the innate immune system is compromised, which could be risky in STEC infections. The single description in 1988 of antiendothelial antibodies in HUS [39] has not been repeated, and no other autoantibody in typical HUS has subsequently been identified, thus raising questions about the value of immunoadsorption.

Therapeutic plasma exchange, eculizumab, and immunoadsorption could be counterproductive in typical HUS. Fifteen percent of adults undergoing TPE in a recent 3-year period had major complications related to this treatment [40]. Because plasma VWF is already sheared in typical HUS [4], TPE using plasma containing VWF multimers of normal size might even be thrombogenic. Indeed, a case series published after the outbreak independently associated plasma therapy during HUS and worse long-term renal function in multivariable analysis [41], although it is difficult to remove clinical severity as a confounder in such an analysis. Host defense interference by complement inhibition or iatrogenic hypogammaglobulinemia should not be undertaken lightly in patients who have compromised gut integrity or ongoing bacterial infection, undergo invasive procedures during HUS, and are at risk of hospital-acquired infections.

By outbreak end, 842 German patients developed HUS, and 49 adults as well as 1 child died (32 with HUS; [http://www.rki.de/DE/Content/Service/Presse/Pressemeldungen/2011/11_2011.html](http://www.rki.de/DE/Content/Service/Presse/Pressemeldungen/2011/11_2011.html)), a mortality greater than in most recent pediatric HUS series and greater than that in the children infected by the same strain in this outbreak. Until a complete description of the causes of adult deaths is published, we can only speculate if adult fatalities are explained by deaths before HUS developed [42] or by circumstances that are difficult to manage, such as infections occurring in individuals with comorbidities, withholding of medical care at patient or family direction [43], differential virulence as a function of age of host, consequences of novel interventions, or hypervirulence of this pathogen. The work of Loos et al makes this last explanation less probable. The physicians who used TPE, complement inhibition, and immunoadsorption during the outbreak are now obligated to communicate patient outcomes associated with these interventions, so as to confirm or refute the postulated benefits of these modalities in typical HUS.

This editorial is not the forum to judge value or harm of plasmapheresis, eculizumab, or immunoadsorption in typical HUS. We await comprehensive and critical peer-reviewed analysis of the experience with these modalities in the *E. coli* O104:H4 outbreak, superseding the small series and personal
communications have appeared to date describing the use of TPE, eculizumab, and immunoadsorption [30, 35, 44], and hope that the data offer new options to treat typical HUS. However, unless and until their benefit and safety are demonstrated, physicians should be advised that TPE, eculizumab, and/or immunoadsorption might cause more harm than good in typical HUS at any age. Finally, physicians treating adults with STEC-related HUS would do well to draw on the expertise of pediatric nephrologists like Loos et al, whose quite impressive track record in typical HUS, which is caused largely by E. coli O157: H7, can now be extended to E. coli O104: H4.

Notes

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References


