Increasing Evidence That Certain Antibiotics Should Be Avoided for Shiga Toxin–Producing \textit{Escherichia coli} Infections: More Data Needed

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(See the Major Article by Freedman et al on pages 1251–8.)

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Shiga toxin–producing \textit{Escherichia coli} (STEC) causes gastrointestinal manifestations ranging from mild nonbloody diarrhea to severe hemorrhagic colitis. Some strains can cause life-threatening post-diarrheal hemolytic uremic syndrome (HUS). Despite the medical community’s nearly 35-year experience with these pathogens, the optimal clinical management to decrease the likelihood of HUS remains unsettled. Most concur that current best practices for managing STEC O157 infections include early diagnosis, supportive care (especially ensuring adequate hydration), monitoring for early evidence of HUS, and avoidance of antibiotic treatment unless required for another infection [1–3]. However, the question of possible risks and benefits of antibiotic treatment of STEC, especially O157, diarrhea has been debated for decades.

Early observations of patients with STEC O157 infection noted that those who had received antibiotics seemed more likely to develop HUS [4]. However, proof of a causative association has not been well suited for randomized clinical trials because patients are often empirically treated with antibiotics before STEC is diagnosed, and by the time a diagnosis is made the events that lead to HUS are likely already under way. Observational studies have all struggled with ways to account for (or have simply ignored) the fact that sicker patients are probably both more likely to get treated with antibiotics and more likely to develop HUS, regardless of any causal effect. The proposed mechanism for harm is increased production of toxin stimulated by the antibiotic, release of toxin from stimulated or dying bacteria, or both. These theories have been supported by in vitro [5–10] and animal model [6, 11] studies showing that exposure of certain STEC strains to certain antibiotic classes (eg, fluoroquinolones, trimethoprimsulfamethoxazole [TMP-SMX], β-lactams, and others) at certain doses can increase production and release of Shiga toxins or worsen severity of infections. However, some in vitro studies have shown that certain antibiotics (eg, macrolides, rifaximin, tigecycline, fosfomycin, and others) at certain doses can reduce or not alter Shiga toxin production by certain STEC strains [5, 7, 10, 12], and studies of mice and pigs have suggested that certain antibiotics (eg, azithromycin and fosfomycin) may improve or, at least, not worsen outcomes [6, 11, 13]. Better information about the effects of treatment with various antibiotic regimens could inform treatment decisions, not only for diarrheal illness, but also for those now rare patients with invasive STEC infections, such as O80:H2 reported from France [14].

In this issue of \textit{Clinical Infectious Diseases}, Freedman et al describe a rigorous meta-analysis that attempted to quantify the risk that any form of antibiotic treatment of diarrhea caused by all varieties of STEC confers for the development of HUS. They thoroughly searched for applicable data and objectively graded the risk of bias (RoB) of all 17 studies in their analysis. In addition, the authors appropriately classified studies into those that did (12 studies) and did not (5 studies) apply widely accepted laboratory-based HUS case definitions.

However, in our opinion, the dearth of good data made it an impossible task. The published literature is simply not broad enough to provide a definitive answer about the entire universe of STEC infection and antibiotic combinations, especially when considering important factors including antibiotic class, dose, duration, and timing of treatment. The large majority (14 of 17) of studies in their primary analysis and all of the studies in their subanalysis of best studies (ie, the 5 low-RoB studies that used a strict HUS case definition) were exclusively of STEC O157 infections. Moreover, the amount of data on individual antibiotic classes was limited. For example, only 2 of the 5 best studies included patients treated with macrolides and only 9 patients in those studies were reported as...
having been treated with that antibiotic class [15, 16].

Nevertheless, Freedman et al proved successful in better quantifying the collective risk that administration of some common antibiotic classes poses for infections caused by the most clinically relevant portion of the STEC universe. Their key finding, based on the 5 best studies, was that treatment of the diarrheal phase of STEC O157 infection with certain antibiotics (primarily cefotaxime and other β-lactams, fluoroquinolones, metronidazole, and TMP-SMX) is associated with an increased odds of developing HUS (odds ratio, 2.24 [95% confidence interval, 1.45–3.46]). This is important given that about 95% of STEC-associated HUS in the United States is caused by serogroup O157 [17] and this serogroup is a predominant cause of HUS in many other countries as well. Their subanalysis of all 6 low-RoB (not limited to those using a stringent HUS case definition) studies suggests that their key finding can be extended to infections caused by STEC O111 strains that produce Shiga toxin 1 and 2 and use the same adherence mechanism as STEC O157 [18, 19].

The many subanalyses in Freedman et al’s supplementary material assure the reader that the authors made every effort to identify appropriate subsets for analysis. Some of the analyses are intriguing. For example, although the data on individual antibiotic classes are limited and the results not statistically significant, there is a hint of a stronger deleterious effect of β-lactams than quinolones or TMP-SMX. A differential effect of various antibiotics could be one reason for the lack of a significant effect of antibiotic administration on development of HUS when all studies were included. Unfortunately, the data did not allow Freedman et al to perform a subanalysis of the 4 studies that tried to control for disease severity in a way that would have allowed them to calculate a pooled adjusted odds ratio. Analyses unadjusted for severity of illness tend to overestimate the magnitude of association between antibiotic administration and HUS risk [15, 16].

Prothrombotic events leading to HUS are thought to usually begin early in the diarrheal illness [20]. To this point, Freedman et al found that restricting attention to 5 studies that specifically evaluated antibiotic administration in the first 3 days increased the strength of association between antibiotic treatment and HUS. The finding bordered on statistical significance; each of the analyzed studies reported an elevated odds ratio for this association. One of the studies reported that the risk of HUS among patients treated with antibiotics in the first 3 days of illness was greater than that observed for a wider time window (≤7 days) [15]. The large variability in timing of the start of antibiotic administration across the studies, some extending to quite late in the diarrheal phase of illness (≥7 days), may have decreased the observed risk in their overall analysis.

Little comment is needed on the 11 studies that did not contribute to the key findings of the meta-analysis. However, it can be useful to examine the 2 studies that reported a reduced risk of HUS with antibiotic treatment. Geerdes-Fenge et al reported that ciprofloxacin reduced the risk of HUS among patients with STEC O104:H4 infection. This finding was based on a nonadjusted analysis of 24 patients, in which all 6 children and 13 of the 18 adults developed HUS [21]. Given that ciprofloxacin is generally contraindicated in children, there is no way of knowing without age adjustment if the observed protective association was merely an artifact of confounding by age. Furthermore, the O104:H4 strain differed greatly from most other STEC strains by its enterogaugregative intestinal adherence mechanism. HUS has also complicated diarrheal illnesses caused by a handful of other enterogaugregative E. coli serotypes (O111:H2, O111:H21, and O127: H4) that have acquired Shiga toxin–encoding phases [22]. Given their unique intestinal adherence factors, it is plausible that antibiotics affect these pathogens differently than they do more traditional STEC serotypes, whose adherence to enterocytes is mediated by intimin. Ikeda et al also reported a reduced risk of HUS with antibiotic treatment, specifically that treatment with fosfomycin on the first 2 days of diarrhea decreased the odds of HUS in children with STEC O157:H7 infection compared with children who were almost all treated with other antibiotic regimens [23]. Thus, it cannot be determined if the apparent protective effect of fosfomycin was due to a (more) harmful effect of other antibiotics. However, fosfomycin may deserve further evaluation. A study published after the meta-analysis was completed found that administration of this bacteriostatic agent in the first 5 days of STEC (almost all O157) diarrhea reduced the odds of HUS [24].

Freedman et al raise a valid point about clinical practice that may lessen the practical significance of the fact that their key findings are not generalizable to the entire universe of STEC infections. They rightly explain that the decision to treat diarrhea is typically made at the time of initial clinical presentation, well before an etiology is precisely determined. Because many patients with non-O157 STEC infection present similarly to those with classic STEC O157 infection (with abdominal pain, bloody diarrhea, and little or no fever), a decision to withhold antibiotics because of concern about possible STEC O157 infection (based on presentation, early detection of Shiga toxin, or both) would result in the same management for patients with virulent non-O157 as for O157 STEC infection. Thus the bigger clinical issue becomes finding ways to better ensure that patients with virulent STEC (eg, all O157 and STEC that produce Shiga toxin 2) are not empirically treated with antibiotics that may increase the risk of HUS. Newer multiplex culture-independent diagnostic tests (CIDTs) have the potential to quickly identify such infections [25].

In the past decade, increasing use of first-generation CIDTs for detection of Shiga toxins has enabled detection of a full spectrum of non-O157 STEC infections [26], many of which cause relatively
mild infections and presumably would not be frequently treated empirically with antibiotics. We are unaware of any data to evaluate the risks or benefits associated with antibiotic treatment of these less virulent STEC strains. If such studies were conducted, the questions asked would differ from those addressed by the current meta-analysis. Arguably, the most feared “complication” of these less virulent infections is not the extremely rare development of HUS, but rather local statutory requirements that may mandate that patients, including convalescent patients still asymptptomatically shedding STEC, be excluded from certain venues (such as attending childcare facilities) until the illness is resolved and they are no longer shedding STEC. These requirements serve important public health functions but can be very burdensome to patients and their families [27]. Although there are documented outbreaks of non-O157 STEC infection in which no patients developed HUS, published reports lack data on the frequency of antibiotic administration among these patients and whether they limit the duration of illness or shedding of STEC.

In summary, the findings of Freedman et al support the avoidance of the antibiotics best studied (β-lactams, fluoroquinolones, metronidazole, and TMP-SMX) among patients with STEC O157 infection. It seems wise to extend this recommendation to other virulent STEC strains. The lack of evidence of a protective effect of these antibiotics against development of HUS in multiple subanalyses further adds to the strength of this recommendation. These are the best data we have to inform clinical practice until more studies are conducted that assess various STEC and antibiotic class combinations, have low RoB, use a strict definition of HUS, and determine whether antibiotics were administered early in the course of illness. A randomized controlled trial, aided by the earlier detection of STEC infection through newer CIDTs, could be conducted if the data showed strong evidence of a protective effect for a particular antibiotic regimen, or if a way to halt the progression of HUS were discovered.

Notes
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