Fecal Shedding of Shiga Toxin–Producing *Escherichia coli*: What Should Be Done to Prevent Secondary Cases?

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(See the Major Article by Vonberg et al on pages 1132–40.)

Keywords. shedding; STEC; HUS.

Much of what is known about the shedding and person-to-person transmission of Shiga toxin–producing *Escherichia coli* (STEC) infection is specific to a single serogroup, O157 (H7 and nonmotile). In many countries, it accounts for the greatest number of severe STEC infections, including those associated with life-threatening postdiarrheal hemolytic uremic syndrome (HUS) [1–6]. Secondary cases, transmitted person-to-person through fecal shedding, are estimated to account for 11% of infections [7]. In certain settings, such as childcare centers, outbreaks result nearly entirely from person-to-person spread [8].

Ever since the association was first made between STEC and HUS in 1983, it has been known that some non-O157 STEC can also cause HUS [9]. However, non-O157 STEC strains are diverse; some are just as virulent as STEC O157, others tend to cause only mild diarrheal illness, and others are not human pathogens. This spectrum of virulence is governed in part by the type of Shiga toxin expressed [10–12] and the presence of genomic pathogenicity islands that contain virulence genes, including those for intestinal adherence [13, 14]. STEC strains that produce specific Shiga toxin (Stx) 2 subtypes, especially Stx2a, Stx2c, and Stx2d, tend to be more virulent [15–18]. Person-to-person transmission is an important mode of spread for at least some of the common non-O157 serotypes [19–27].

Over the past decade, the increasing use of assays that detect Shiga toxins or genes that encode them has markedly increased the detection of non-O157 STEC infections in the United States [28, 29] and has improved the detection and investigation of outbreaks worldwide [24, 30, 31]. With this surge in detection comes increasing questions from physicians, institutions, and health officials about reasonable and practical measures to prevent secondary transmission.

The 2 primary strategies for preventing secondary cases can be challenging to implement and burdensome. First, patients and their caregivers are advised to practice careful hygiene. Second, statutory requirements that vary by location usually mandate exclusion of infected persons, including those who are asymptomatic, from situations that may facilitate transmission (such as attending childcare facilities) until the diarrheal illness is resolved and they are no longer shedding STEC. In many jurisdictions, lack of shedding is defined as documentation of 2 negative stool cultures on specimens collected at least 24 hours apart (and, when relevant, at least 48 hours after cessation of antibiotic therapy) [32]. Because shedding can be prolonged, this policy can be onerous for patients and families.

Modifications could improve these strategies. Even in the most attentive households, preventing fecal-oral spread can be difficult, especially when young children are present. Hospitalization of patients acutely ill with virulent STEC strains can reduce secondary transmission through contact isolation [33, 34]. Return-to-work and return-to-school

Received 20 December 2012; accepted 21 December 2012; electronically published 8 January 2013.

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Clinical Infectious Diseases 2013;56(8):1141–4
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2013.
DOI: 10.1093/cid/cis1222

polices tailored to the virulence of the STEC strain may lessen burden on persons who are asymptomatically shedding low-virulence organisms [22, 27]. Infections caused by less virulent strains could be handled more like salmonellosis, in which persons with good hygiene can often return to work or school when no longer symptomatic [32].

It is possible that antibiotic therapy could further reduce both the risk of secondary transmission and the social impact of exclusion policies. Findings from observational studies suggest that antibiotic treatment of STEC O157 diarrhea may increase the risk of HUS [35, 36], and this caution has been extended to other STEC strains. However, harm from such treatment has not been proven through randomized controlled trials, and observational studies suffer from biases such as greater likelihood of antibiotic treatment of patients presenting with more severe illness. Nevertheless, the lack of strong data supporting a benefit from treatment of the diarrheal illness, coupled with the physician's injunction to do no harm, cautions against antibiotic treatment. However, antibiotic treatment of persons in later stages of STEC infection may carry a lower risk. For example, one study reported better outcomes among patients with HUS who received antibiotics [37]. Additionally, the authors of a small case series of persons treated with antibiotics for asymptomatic carriage of a variety of non-O157 STEC strains concluded that it may be a safe eradication method for less virulent STEC strains [38].

Studies of the massive, tragic outbreak of STEC O104:H4 infections in Germany in 2011 have yielded information on the effectiveness of antibiotics in shortening the duration of shedding. In this issue of *Clinical Infectious Diseases*, Vonberg et al make elegant use of limited data to study how shedding of this rare enteroaggregative Stx2a-producing *E. coli* strain was affected by antibiotic (primarily azithromycin) administration. This analysis was made possible in large part by the experimental use of eculizumab to treat HUS. Administration of this immunosuppressive drug requires antibiotic prophylaxis for the prevention of meningitis. The German Society of Infectious Diseases recommended azithromycin for this purpose because it was less likely to induce Stx release than antibiotics of other classes in vitro [39, 40].

Vonberg et al report the following: (1) the median duration of shedding was 17–18 days among mostly adult patients treated at tertiary care hospitals, a large percentage of whom had HUS; (2) shedding can persist for >150 days; and (3) factors associated with shorter shedding duration included age >15 years, HUS, and receipt of antibiotics during hospitalization. After adjustment for other factors, treatment with antibiotics was found to reduce median shedding duration by 30% (Table 3 of Vonberg et al). As the authors mention, their findings should not be generalized to all STEC. Different mechanisms of intestinal adherence may result in differing shedding dynamics between the enteroaggregative strain studied and the far more common non-enteroaggregative STEC. Of note, the direction of impact of HUS and antibiotic treatment on shedding duration demonstrated in some small analyses of STEC O157 [41, 42] was different from that reported by Vonberg et al.

The findings of Vonberg et al expand upon those of a single-center study [43] by more rigorously assessing the independent effects of antibiotic treatment and HUS on shedding duration. However, it is still possible that the association between antibiotic treatment and decreased shedding duration remained partially confounded by disease severity. Although the authors rightly chose accepted criteria to define HUS, HUS cases exhibit a wide spectrum of severity. Furthermore, some patients with severe illness (eg, colitis) do not have HUS [44]. In this outbreak, eculizumab, and hence antibiotics, were administered to patients with the most severe manifestations of HUS [37]. Therefore, simply adjusting for the presence of HUS likely did not fully control for disease severity. The authors strengthen their argument by examining patients who did not receive antibiotics and finding no difference in shedding duration among patients with and those without HUS. However, a similar concern about the spectrum of HUS applies: Patients with HUS who did not receive eculizamub (and therefore antibiotics) generally had milder HUS, and the severity of their illnesses may have been similar to hospitalized patients without HUS. In future analyses, inclusion of additional markers of disease severity, such as leukocyte count, may more fully control for disease severity [45–47].

Additional information that would aid in the interpretation of the data presented by Vonberg et al includes the following: (1) a description of discordant results between culture and culture-independent tests for STEC infection, (2) the effect of antibiotic treatment on the duration of diarrhea, (3) a summary of illness status (eg, diarrhea, HUS, or convalescence) and day of illness at the time of antibiotic administration, (4) the number of patients evaluated for intermittent shedding and results of those tests, and (5) specific assessment of the effect of azithromycin on shedding duration. We highlight the value of the first 2 factors.

Although it was reasonable to aggregate culture, polymerase chain reaction (PCR), and enzyme immunoassay (EIA) results to evaluate shedding, the sensitivity and specificity of each test in this setting are uncertain. Because all stool samples were cultured, a subanalysis that evaluated shedding as confirmed by culture might have provided specific information on a single, widely accepted measure. We also do not know if strains isolated late in the shedding periods continued to be Shiga toxin positive; STEC

can lose toxin genes in vivo [48, 49]. A summary of the frequency of discordant results between culture and culture-independent tests and how such discordance varied by time would have added valuable data about the relative duration of positivity of different tests. This is of practical importance. Clinicians and health departments are increasingly asking if culture and culture-independent tests can be used interchangeably for exclusion decisions. If EIA or PCR were more sensitive than culture, it is possible that an important proportion of the patients with prolonged positivity of these tests were no longer shedding viable organisms in numbers sufficient to detect in culture; these patients may pose less risk of disease transmission. Nevertheless, the authors and medical centers deserve praise for culturing all stools and not relying solely on culture-independent tests [28].

Presumably, persons with active diarrhea are more likely to spread STEC than asymptomatic shedders. Therefore, including resolution of diarrhea as a secondary endpoint would have been interesting. Further research is needed to understand the actual risk of asymptomatic shedders' transmitting illness in various settings and how the risk varies by the number of organisms shed. At some threshold, the risk of transmission from these persons likely approaches the risk of transmission from undetected shedders. In some areas, 1% of healthy persons' stools yield STEC [50], a reason to reinforce routine handwashing.

We commend the authors for cautiously interpreting their findings. From the public health–based and evidence-based medicine perspectives, many questions remain before antibiotic-mediated eradication could be considered an effective strategy for safely preventing secondary transmission of STEC infections. Randomized controlled trials are needed and should begin with patients infected with low-virulence strains who are beyond the period of highest risk for developing HUS. Such studies should include long-term follow-up to ensure that short-term antibiotic-mediated elimination of STEC is not followed by increased likelihood of long-term carriage, as has been observed with nontyphoidal *Salmonella* [51].

The most important and effective means of preventing secondary cases will likely always remain early identification of primary cases with rapid implementation of hygienic and isolation precautions. Development of point-of-care tests that can identify virulence factor profiles associated with severe disease could aid in early implementation of these measures. Ongoing efforts are needed to more fully understand the bacterial and host factors that determine virulence so that tiered exclusion policies that protect the public while minimizing costs to individual patients and families may continually be refined [13].

From the perspective of the individual patient whose diarrhea has resolved, decisions regarding the use of antibiotics to shorten time away from work or school should be made on a case-by-case basis by the patient (or parent) and physician, all fully informed of the virulence characteristics of the infecting strain and the possible risks and benefits of treatment [52, 53].

Notes

Financial support. The Centers for Disease Control and Prevention.

Potential conflicts of interest. Both authors: No reported conflicts.

Both 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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