Antimicrobial and Antimotility Agent Use in Persons with Shiga Toxin–Producing Escherichia coli O157 Infection in FoodNet Sites

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Antimicrobial and antimotility agents are not recommended for the treatment of Shiga toxin–producing Escherichia coli O157 infection. In our study, many persons with Shiga toxin–producing E. coli O157 infection took antimicrobial (62%) and antimotility agents (32%); 43 (29%) of 146 reported commencing antimicrobial treatment after laboratory confirmation. Efforts are needed to promote practice guidelines.

Shiga toxin–producing Escherichia coli (STEC) O157 are an important cause of illness in the United States [1]. A major complication of STEC O157 infection is hemolytic-uremic syndrome (HUS), which occurs in ~6% of all laboratory-confirmed cases, including 15% of patients <5 years of age [2]. HUS is characterized by hemolytic anemia, thrombocytopenia, and acute renal failure and disproportionately affects young children and older persons. Death occurs in ~3% of children with HUS after STEC O157 infection [2].

The use of antimicrobial agents in treatment of STEC O157 infection is controversial [3]. In vitro and animal studies suggest that some antimicrobial agents, including fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX), increase the risk of developing HUS. Some clinical and epidemiological studies in humans have also found an increased risk of developing HUS associated with the use of antimicrobial agents [4, 5], whereas others have found no association [3, 6].

Practice guidelines for treatment of infectious diarrhea include hydration, clinical and epidemiological evaluation, selected fecal studies and advise that any consideration of antimicrobial therapy be carefully weighed against unintended and potentially harmful consequences [7]. Characteristics of the diarrheal illness that reliably predict the likelihood that the etiology is STEC O157 have not been identified [8]. Practice guidelines advise against the use of antimicrobial agents and antimotility agents when infection with STEC O157 is confirmed or suspected [7, 9]. To determine the extent to which these agents were used in the treatment of laboratory-confirmed STEC O157 infection in the United States, we analyzed treatment data from 2 multi-site case-control studies in the Foodborne Diseases Active Surveillance Network (FoodNet).

METHODS

FoodNet has conducted active, population-based surveillance for laboratory-confirmed STEC O157 infection since 1996. In 1996, FoodNet comprised 5 sites (Minnesota and Oregon and selected counties in California, Connecticut, and Georgia) with a population of 13.2 million. By 2000, the FoodNet catchment area had expanded to include the remaining counties in Connecticut and Georgia and selected counties in Maryland, New York, and Tennessee (population of 30.5 million). Clinical laboratories serving the FoodNet catchment area report all isolations of STEC to FoodNet personnel. Surveillance for HUS began in 1997 and is based on specialty provider networks of pediatric nephrologists and infection control practitioners and a review of hospital discharge data.

STEC O157 risk factor studies were conducted in the FoodNet sites during 1996–1997 (hereafter referred to as study 1) and 1999–2000 (hereafter, study 2). Detailed methods for both studies are described elsewhere [10, 11]. In brief, both studies defined a case as a sporadic, diarrheal illness in a person living in the FoodNet catchment area whose stool culture yielded STEC O157 from March 1996 through April 1997 (study 1) or during a 12-month consecutive period in each site from February through April 1999 (study 2). Case patients were interviewed using a telephone-administered questionnaire within 21 days after the stool that yielded STEC O157 was collected. Methods for case enrollment, criteria for inclusion or exclusion, and
interview protocols in both studies were similar. Case patients were asked about demographic information, symptoms, hospitalization, and treatments, including antimicrobial and antimitoty agents. Study 2 also collected information regarding timing of antimicrobial treatment relative to disease onset. HUS data were only available for case patients participating in study 2. Databases from study 1 and study 2 were merged, standardized, and analyzed using SAS, version 9.1 (SAS Institute). Relative risk (RR) and 95% confidence intervals (CIs) were used to assess differences between groups.

Antimicrobial subclasses were used for data analysis. Aminoglycosides, macrolides, sulfas ("sulf," "sulf drug"; 7 children, 1 older person), macrolides (5 children, 1 older person), aminoglycosides (2 children, 0 older persons), erythromycin-sulfisoxazole (2 children, 0 older persons), otherwise unspecified antimicrobial agents (0 children, 3 older persons), and clindamycin (1 child, 0 older persons).

RESULTS

FoodNet surveillance ascertained 927 laboratory-confirmed STEC O157 infections during the 2 study periods (396 during study 1 and 531 during study 2). Of 678 persons interviewed, 479 (71%) met the inclusion criteria and agreed to participate in the case-control study (196 in study 1 and 283 in study 2). Overall, 293 (62%) of 474 persons reported treatment with an antimicrobial agent (61% in study 1 and 63% in study 2) (Table 1). Among these 293 patients, 47% received fluoroquinolones, 21% received TMP-SMX, 10% received metronidazole, 8% received a β-lactam agent, and 7% received other antimicrobial agents.

Of the 146 patients in study 2 who provided information on the timing of antimicrobial treatment, 43 (29%) reported beginning treatment after their stool culture was known to have yielded STEC O157, including 13 (29%) of 45 children. Among these 43 patients, 53% received a fluoroquinolone, 28% received TMP-SMX, and 12% received other antimicrobial agents.

Overall, treatment with antimicrobial agents was less common among children (110 [44%] of 250) than among older persons (183 [82%] of 224; RR, .48; 95% CI, .41–.57) (Table 1). Treatment with TMP-SMX and β-lactam agents was more common among children than among older persons, whereas treatment with fluoroquinolones was less common among children.

Overall, 146 (31%) of 467 patients reported treatment with an antimitoty agent (Table 1). Most reported receiving loperamide (91%), and 12% received diphenoxylate. Treatment with an antimitoty agent was less common among children (51 [21%] of 245) than among older persons (95 [43%] of 222; RR, .58; 95% CI, .46–.73).

DISCUSSION

Antimicrobial agents, particularly fluoroquinolones and TMP-SMX, and antimitoty agents were frequently used in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proportion (%) of persons</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Took antimicrobial agent</td>
<td>293/474 (62)</td>
<td>0.48 (0.41–0.57)</td>
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<td>Among those who took antimicrobial agent</td>
<td></td>
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<tr>
<td>Fluoroquinolone</td>
<td>139/293 (47)</td>
<td>0.20 (0.13–0.32)</td>
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<td>Trimethoprim-sulfamethoxazole</td>
<td>62/293 (21)</td>
<td>3.34 (2.61–4.28)</td>
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<td>Metronidazole</td>
<td>30/293 (10)</td>
<td>0.69 (.37–1.27)</td>
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<tr>
<td>β-lactam</td>
<td>24/293 (8)</td>
<td>1.50 (1.01–2.24)</td>
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<tr>
<td>Other agent*</td>
<td>21/293 (7)</td>
<td>2.20 (1.65–2.95)</td>
</tr>
<tr>
<td>Missing or unknown agent</td>
<td>53/293 (18)</td>
<td>0.89 (.59–1.33)</td>
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<tr>
<td>Began taking an antimicrobial agent after stool culture yielded E. coli O157b</td>
<td>43/146 (29)</td>
<td>0.97 (.57–1.67)</td>
</tr>
<tr>
<td>Took antimitoty agentd</td>
<td>146/467 (31)</td>
<td>0.58 (0.46–0.73)</td>
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</table>

Abbreviations: CI, confidence interval; RR, relative risk.

* Includes sulfa drugs ("sulf," "sulf drug"; 7 children, 1 older person), macrolides (5 children, 1 older person), aminoglycosides (2 children, 0 older persons), erythromycin-sulfisoxazole (2 children, 0 older persons), otherwise unspecified antimicrobial agents (0 children, 3 older persons), and clindamycin (1 child, 0 older persons).

b Timing of treatment with antimicrobial agents available only for study 2 (n = 146): dicyclomine, diphenoxylate-atropine, atropine-hyoscyamine-scopolamine, hyoscyamine sulfate, and loperamide.

d Antimitoty agents were defined as persons <18 years of age.
treatment of persons with STEC O157 infection. Despite practice guidelines [7, 9], antimicrobial agents were prescribed both empirically and after laboratory confirmation [12]. Empirical treatment of most nonfebrile infectious diarrhea with antimicrobial agents is generally not recommended because of the risk of adverse drug reaction, the potential for development of antimicrobial resistance, the cost of treatment, and the fact that most illnesses are self-limited [13]. The proportion of persons who received antimicrobial agents in this study (62%) was higher than the 40% reported in a multicenter case-control study of sporadic STEC O157 infection during 1990–1992 in the United States [8]. Three nationwide studies of laboratory-confirmed Salmonella and Campylobacter infections conducted during 2002–2004 showed rates of antimicrobial use for diarrheal illness of 50%–72% [14–16]. Publication of practice guidelines in 2001 has not eliminated inappropriate antimicrobial use for treatment of infectious diarrhea.

Almost one-third of patients with STEC O157 infection in our study used antimotility agents. Although these agents can reduce the number of bowel movements and diminish the magnitude of fluid and electrolyte loss in patients with acute diarrhea, their use has been linked to an increased risk of HUS in patients with STEC O157 infection [17] and to complications in other infections [17, 18]. Many antimotility agents are available without prescription. It is not known whether patients in this study used antimotility agents before or after consulting a physician or receiving a laboratory-confirmed diagnosis of the infection. Regardless, physicians should be encouraged to caution patients with bloody diarrhea or suspected STEC O157 infection about the risk of using antimotility agents.

Our analysis has several limitations. Information regarding treatment with antimicrobial and antimotility agents was self-reported. We did not independently verify the type of antimicrobial or antimotility agents received; some patients in the "other agent" category and those in the "missing or unknown agent" category had likely received one of the specified agents. We did not examine why practice guidelines were not observed nor do we know whether clinicians suspected STEC O157 infection before deciding whether to empirically treat with antimicrobial agents. This information would provide additional insight into the clinician’s decision to treat and choice of treatment. In addition, these data were collected in the FoodNet catchment area, which is similar to the US population; however, these findings might not be generalizable to the entire US population [19].

Further efforts are needed to inform clinicians of practice guidelines that advise careful judgment when considering empirical treatment with antimicrobial agents, especially when infection with STEC O157 is confirmed or suspected.

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References