Risk of Hemolytic Uremic Syndrome After Antibiotic Treatment of *Escherichia coli* O157:H7 Enteritis
A Meta-analysis

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HEMOLYTIC UREMIC SYNDROME (HUS) is a complex multisystem disorder characterized by hemolytic anemia, thrombocytopenia, and acute renal failure.[1,2] The classic form of this syndrome often follows a prodrome of acute enteritis, most often caused by Shiga toxin–producing strains of *Escherichia coli*.[3,4] Since the first report by Karmali et al[5] causally linking toxin-producing *E coli* to HUS, *E coli* serotype O157:H7 enteric infection has been recognized as the most common cause of HUS in the United States, with 6% of patients developing HUS within 2 to 14 days of onset of diarrhea.[6] Occurring primarily in children, this serious complication carries a mortality rate of 3% to 5%[1,2,7] and is currently the most common cause of acute renal failure in children in the United States.[8] Approximately half of children with HUS require dialysis,[9] and 5% of patients who survive have long-term renal impairment.[9] No cure exists for HUS, and although management beyond intensive support with needed renal replacement therapy remains controversial, there appears to be a growing consensus that plasma exchange

Context The use of antibiotics for treatment of *Escherichia coli* O157:H7 infection has become controversial since a recent small study found that it may increase the risk of hemolytic uremic syndrome (HUS). However, other larger studies have reported a protective effect or no association.

Objective To determine whether antibiotic therapy for *E coli* O157:H7 enteritis increases the risk of HUS.

Data Sources PubMed and MEDLINE computer searches were performed for studies published from January 1983 to February 2001 using the key words *hemolytic uremic syndrome, risk factor, antibiotics,* and *Escherichia coli* O157:H7. Reference lists of relevant publications were reviewed, and 12 experts in the field were contacted to identify additional reports. No language restrictions were applied to the search.

Study Selection Studies were included if they reported a series of patients with documented *E coli* O157:H7 enteritis, some of whom developed HUS; had clear definitions of HUS; and had adequate data delineating the relationship between antibiotic therapy and the occurrence of HUS. Nine of the 26 identified studies fulfilled these criteria.

Data Extraction Two authors (N.S. and A.S.) independently reviewed each report identified by the searches and recorded predetermined information relevant to the inclusion criteria. A pooled odds ratio was calculated using a fixed-effects model, with assessment of heterogeneity among the studies.

Data Synthesis The pooled odds ratio was 1.15 (95% confidence interval, 0.79-1.68), indicating that there does not appear to be an increased risk of HUS with antibiotic treatment of *E coli* O157:H7 enteritis. Incomplete reporting of data in individual studies precluded adjustment for severity of illness.

Conclusion Our meta-analysis did not show a higher risk of HUS associated with antibiotic administration. A randomized trial of adequate power, with multiple distinct strains of *E coli* O157:H7 represented, is needed to conclusively determine whether antibiotic treatment of *E coli* O157:H7 enteritis increases the risk of HUS.

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therapy brings benefit and should be used.[2,10]

Numerous studies[11-19] have examined risk factors that may predispose patients to development of HUS. Of those risk factors that have been shown in epidemiological studies to predis-

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pose patients to development of HUS following *E coli* O157:H7 infection, the most controversial to date is antibiotic therapy for acute *E coli* O157:H7 enteritis.[20] Studies[11-19] that have addressed this issue have been limited by small sample sizes and use of varying antibiotic regimens for varying periods and have given conflicting results. Although there is no clear consensus on whether antibiotics should be administered as treatment of *E coli* O157:H7, since the report by Wong et al,[14] avoidance of antibiotic therapy for any presumably infectious enteritis appears to be a growing practice.

We report a meta-analysis of published studies undertaken to better understand the association between antibiotic therapy for *E coli* O157:H7 enteritis and the risk of HUS. We critically examine the heterogeneity of the study results, especially the methods used to adjust for severity of illness. Controlling for severity of illness is desirable, since sicker patients are more likely to both develop HUS and receive antibiotics, thus confounding the relationship between HUS and antibiotic use.

METHODS

Using MEDLINE and PubMed database searches, we identified published studies using the key words *hemolytic uremic syndrome, antibiotic, risk factor,* and *Escherichia coli* O157:H7. No language restrictions were applied to the search. The search was limited to reports on human infections published between January 1983 (the year when Shiga toxin–producing *E coli* was first found to be associated with HUS) and February 2002. Reference lists of recent publications, the Cochrane Network, and the National Institutes of Health Web site listings of ongoing trials were reviewed and 12 authorities in the field were solicited to identify unpublished studies.

The following criteria for the inclusion of studies were defined before reviewing specific reports: the study must report on a series of patients with documented *E coli* O157:H7 enteritis, including patients who developed HUS; clear definitions of HUS must be given; and adequate data delineating the relationship between antibiotic therapy and the occurrence of HUS must be reported. Two authors (N.S. and A.S.) independently reviewed each report identified by these searches. Both investigators recorded predetermined information relevant to the inclusion criteria.

Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, using data provided in the studies. Data on both antibiotic use and HUS were abstracted as dichotomous variables. If primary data were not reported, we used the OR and 95% CI reported in the study. Pooled estimates of the OR and 95% CI were obtained using the fixed-effects model of Mantel and Haenszel,[21] and testing for heterogeneity was performed with the Breslow-Day test[22] using SAS statistical software version 8.0 (SAS Institute Inc, Cary, NC). Publication bias was assessed by funnel plot.[23] We did not attempt to calculate a pooled adjusted OR since 3 of the 9 studies did not adjust for severity of illness[13,17,19] and there were substantial differences in the methods used to adjust for confounding among the remaining 6 studies.

RESULTS

Our search yielded 26 reports. Seven studies[7,24-29] were excluded because of lack of a control group, 2 studies[30,31] because of failure to define clear diagnostic criteria for HUS, 4 studies[32-35] for failure to evaluate risk factors for HUS, and 3 studies[36-38] for lack of data on antibiotic use as a risk factor for HUS. One study[39] was excluded because infections with *E coli* serotypes other than O157:H7 were included.

Table. Studies Evaluating the Association Between Antibiotic Therapy of *Escherichia coli* O157:H7 Enteritis and Risk of Hemolytic Uremic Syndrome (HUS)

| Source	Type of Study	Age Range of Patients, y	No. of Patients With *E coli* O157:H7 Enteritis	No. of Patients Developing HUS	Antibiotics Used for Treatment	Interval Between Onset of Acute Diarrhea and Introduction of Antibiotic Therapy, d
Bell et al,[11] 1997	Retrospective cohort	<16	278	36	Trimethoprim, ampicillin, cephalosporins, metronidazole	≤3
Ikeda et al,[12] 1999	Prospective cohort	6-11	292	36	Fosfomycin	≤5
Slutsker et al,[13] 1998	Retrospective case-control	<1-82	93	7	Sulfamethoxazole	≤3
Wong et al,[14] 2000	Prospective cohort	<10	71	10	Trimethoprim-sulfamethoxazole, amoxicillin, cephalosporins	≤3
Proulx et al,[15] 1992	Prospective randomized	<1-17	47	6	Trimethoprim-sulfamethoxazole	7.4*
Cimolai et al,[16] 1994	Retrospective case-control	5 (Mean)	128	27	Not stated	Not stated
Ostroff et al,[17] 1989	Retrospective case-control	<1-78	69	11	Trimethoprim-sulfamethoxazole, erythromycin, ampicillin, gentamicin sulfate, tetracycline	4.3 (1-10)*
Dundas et al,[18] 2001	Retrospective case-control	<1-94	120	34	Ciprofloxacin	≤4
Pavia et al,[19] 1990	Retrospective case-control and randomized trial	6-39	23	8	Sulfonamides, trimethoprim-sulfamethoxazole	≤3

*Data are mean (range).

Figure 1. Relationship Between Antibiotic Therapy for *Escherichia coli* O157:H7 Enteritis and Risk of Hemolytic Uremic Syndrome
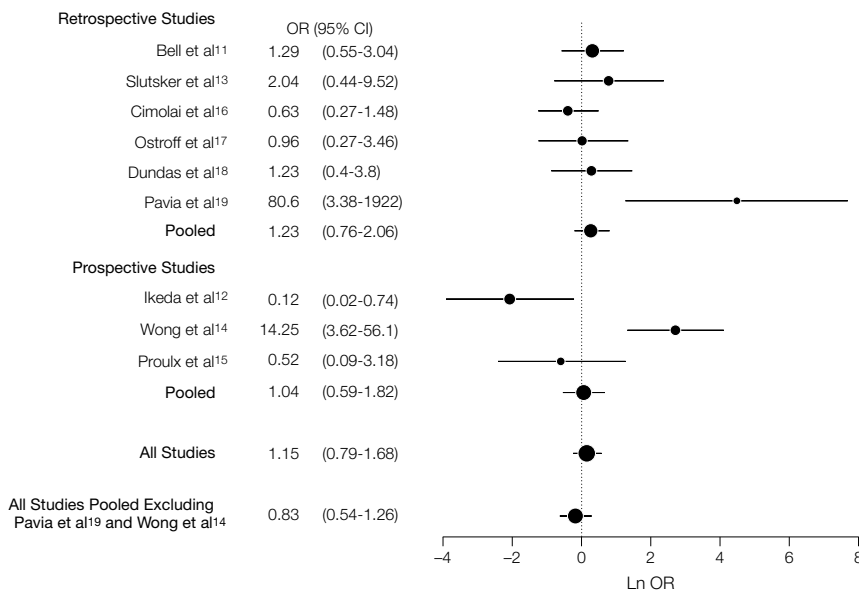
An odds ratio (OR) of greater than 1.0 (ln OR >0) suggests that antibiotic therapy is associated with an increased risk of hemolytic uremic syndrome, and an OR of less than 1.0 (ln OR <0) suggests a decreased risk. CI indicates confidence interval. Sizes of data markers are proportional to sample sizes of the studies.

Figure 2. Funnel Plot of Estimated Ln ORs From 9 Studies
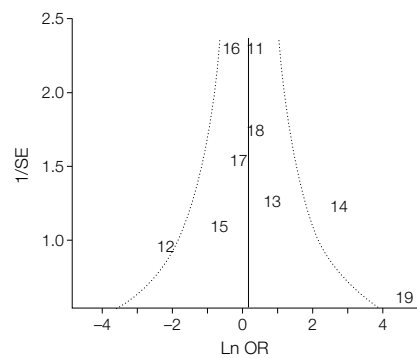
Solid vertical line represents pooled estimated log odds ratio (OR) across the studies. Dotted lines represent 2 SE bounds around the pooled estimate. Studies are represented by their reference numbers.

Nine studies, 6 retrospective and 3 prospective, met the inclusion criteria. Their characteristics are summarized in the TABLE. Only 1 of the retrospective studies showed a statistically significant deleterious effect of antibiotic use and HUS.[19] Four retrospective studies[11,13,17,18] showed no association, and

1 study[16] showed a protective effect, but only in the univariate analysis.

Of the 3 prospective studies, only 1 study[14] reported a statistically significant increased risk of HUS with antibiotic use. One prospective study[12] reported a protective effect of fosfomycin for treatment of *E coli* O157:H7 infection, and 1 prospective randomized study[15] showed no association between antibiotic use and HUS.

The pooled OR was 1.15 (95% CI, 0.79-1.68), indicating a lack of association between HUS and antibiotic use (FIGURE 1). The test for heterogeneity was highly significant ($P<.001$). We examined potential explanations for this heterogeneity. Substantial heterogeneity was observed among studies in the populations studied (adults vs children) and in the types of antibiotics used, the timing and length of therapy, and methods used to control for severity of illness.

Two studies, 1 retrospective[19] and 1 prospective,[14] were found to account for most of the heterogeneity, and when these were removed from the analysis,

the test for heterogeneity was no longer significant. Pavia et al[19] did not control for severity of illness in their analysis, which may have led to an inflated OR. Wong et al[14] did not use physiological measures to control for severity of illness, which may have contributed to an increased magnitude of the association found.

The funnel plot (FIGURE 2) did not show a substantial publication bias.

COMMENT

Antibiotic treatment for *E coli* O157:H7 enteritis has become controversial because a recent epidemiological study[14] suggested that it may increase the risk of HUS. In vitro and animal studies suggest varying effects of antibiotic exposure on toxin production by *E coli* O157:H7.[40-43] Subinhibitory concentrations of trimethoprim-sulfamethoxazole in vitro have been shown to enhance toxin production by *E coli.*[44]

One in vitro study[40] of the effect of 13 different antibiotics on the release of Shiga toxin by 3 different *E coli* O157:H7 strains showed that the response of *E coli* O157:H7 isolates to subinhibitory concentrations of antibiotics seems to be highly dependent on the individual strain involved. This may explain in part the conflicting findings of earlier in vitro studies,[41-43] where in some instances antibiotics were found to decrease toxin production and in others to increase it. Kurioka et al[43] recently reported that norfloxacin, fosfomycin, kanamycin sulfate, ampicillin, and clarithromycin reduced the risk of complications in a murine model of enteritis with a Shiga toxin–producing *E coli* O157:H7; antibiotic therapy shortened the length of *E coli* O157:H7 excretion in stool samples and decreased the amount of toxin in both feces and blood. However, trimethoprim-sulfamethoxazole was associated with increased mortality when given to some of the mice 3 days after initiation of infection.

Similar conflicting results have been found in clinical studies. In a large outbreak of *E coli* O157:H7 enteritis in adult patients, a retrospective case-

control study found that coincidental antibiotic use, defined as antibiotic use in the 4 weeks before development of *E coli* infection, appeared to be associated with an increased risk of HUS (OR, 4.7).[18] However, when patients who received antibiotic treatment for *E coli* O157:H7 enteritis with ciprofloxacin were compared with those who did not, there was no statistically significant difference in risk.

A widely promulgated, recent cohort study of 71 children with *E coli* O157:H7 enteritis, 10 of whom developed HUS, reported a 14-fold increased risk of HUS when various antibiotics were given for treatment of *E coli* O157:H7 enteritis.[14] The relative risk was adjusted for initial white blood cell count and the day the stool sample was collected as markers of disease severity. The authors examined the risk of HUS by class of antibiotic used, and trimethoprim-sulfamethoxazole and β-lactams appeared to be associated with increased risk. An accompanying editorial strongly endorsed the study findings.[45] As a consequence, many US clinicians have become reluctant to give antibiotic therapy to children or adults with acute enteritis, even if they have dysentery and are severely ill. In the study by Wong et al,[14] the reported CI for the adjusted relative risk was very wide (2.2-137). If 2 fewer children who developed HUS had received antibiotics, the association would no longer be statistically significant.

Antibiotic therapy has been shown to be highly beneficial for *Campylobacter jejuni* enteritis,[46] traveler's diarrhea caused by enterotoxigenic *E coli*,[47] and shigellosis.[48] These ubiquitous enteric infections have clinical manifestations indistinguishable from *E coli* O157:H7 enteritis, and withholding antibiotic therapy for these infections until *E coli* O157:H7 infection can be ruled out could be deleterious for many patients.

The paucity of randomized trials does not allow a definitive conclusion to be reached regarding this matter. A prospective study[12] in children with *E coli* O157:H7 enteritis found that administration of fosfomycin within the first 2 days of illness was associated with a significantly reduced risk of HUS. The significant protective effect remained in a multivariable analysis that controlled for severity of illness using the presence of fever as an indicator (adjusted OR, 0.09; 95% CI, 0.01-0.79).

In a case-control study, Slutsker et al[13] reported no association between antibiotic use within 3 days of onset of *E coli* O157:H7 infection and HUS. However, in a subgroup analysis, children younger than 13 years who developed HUS were more likely to have received an antibiotic, primarily sulfamethoxazole (relative risk, 11.5; *P*=.02), than those who did not. However, no adjustment for severity of illness was performed.

In a retrospective cohort study of 278 children with culture-confirmed *E coli* infection, 50 of whom received antibiotic therapy, Bell et al[11] did not find an association between prior antibiotic use and HUS in a multivariate analysis.

A retrospective study by Cimolai et al,[16] using multivariable techniques of data analysis, also did not find an increased likelihood of progression to HUS after antibiotic treatment of *E coli* enteritis. Antibiotic use was defined in this study as being either appropriate or inappropriate. Appropriate antibiotics were arbitrarily defined as those effective against shigellosis, such as ampicillin or trimethoprim-sulfamethoxazole, or the isolate was shown to be susceptible in vitro. Inappropriate antibiotics were those that have not been shown to have therapeutic value for treatment of shigellosis, or the isolate was resistant in vitro. Univariate analysis showed a trend toward a reduced risk of HUS with appropriate antibiotic use, but this variable was not significant in a multivariable analysis.

In a randomized trial of trimethoprim-sulfamethoxazole treatment of *E coli* O157:H7 enteritis in 47 children, no association was found between antibiotic treatment and subsequent development of HUS (2/22 vs 4/25; *P*=.67).[15] Trimethoprim-sulfamethoxazole had no effect on the course of symptoms, duration of excretion of the organism, or likelihood of progression to HUS. However, antibiotic therapy was initiated a mean of 7 days after the onset of diarrhea.

Pavia et al[19] reported an outbreak of *E coli* O157:H7 infection among the residents and staff of an institution for mentally handicapped persons. Eight persons developed HUS and half died. Antibiotics, mainly trimethoprim-sulfamethoxazole, were administered to 5 of the 8 with HUS compared with 0 of the 7 without HUS; however, no adjustment for severity of illness was performed, and it is likely that antibiotics were given to the more severely ill patients, many of whom may have been biologically destined to develop HUS.

A retrospective study performed by Ostroff et al[17] found no association between antibiotic use and HUS. These authors examined differences between patients who received antibiotics for *E coli* O157:H7 infection and those who did not and found similar durations of overall illness in both groups.

In our analysis, we did not use adjusted ORs from the included studies to obtain a summary OR because too few of the 9 studies evaluated possible confounding in their analysis. Three studies[13,17,19] did not assess differences in patients' severity of illness, 3 studies[11,16,18] used multivariate analysis but did not provide sufficient data regarding which factors were adjusted for, 1 study[12] adjusted for severity of illness using the presence of fever, 1 study[14] adjusted for white blood cell count and day of illness on which stool sample was obtained as markers of disease severity, and only 1 study[15] was randomized.

Our analysis does not show an increased risk of HUS after antibiotic treatment of *E coli* O157:H7 infection (Figure 1). Although the included studies differed substantially in the duration and types of therapeutic antibiotics used, we believe our results highlight the ongoing controversy surrounding the use of antibiotics for *E coli* O157:H7 enteritis and the development of HUS. We have focused our analysis on the effect of antibiotic therapy in general on the risk of HUS and have made no

attempt to examine the influence of different antibiotic classes because of wide variation in the type, timing, and duration of antibiotic treatment.

In vitro and animal studies indicate that the timing and duration of antibiotic therapy may have great relevance for the risk of developing HUS. Early in the onset of the enteritis, antibiotic therapy appears, in some studies, to have a protective effect.[49] Of the 9 studies used in our meta-analysis, antibiotics were administered within 3 days of the onset of diarrhea in 3 of the studies.[11,13,14] Of these 3 studies, 2 studies[11,13] did not have a statistically significant increased risk of HUS with antibiotic therapy and 1 study[14] showed an increased risk. In the remainder of the studies, antibiotics were given within 5 days, except in the randomized trial conducted by Proulx et al,[15] in which trimethoprim-sulfamethoxazole was given a mean of 7 days after the onset of acute illness.

The class of antibiotics used for treatment of *E coli* O157:H7 enteritis is also important when assessing the risk of HUS with antibiotic treatment. It is not clear which particular category of antibiotics is most likely to be associated with increased toxin production and which with decreased toxin production by Shiga toxin–producing *E coli*.[42,50-53] Trimethoprim-sulfamethoxazole has been the antibiotic most frequently reported to have a detrimental effect in animal studies.[41,44,54] In their clinical trial, Proulx et al[15] did not show a harmful effect of trimethoprim-sulfamethoxazole. In Japanese studies of antibiotic use for *E coli* O157:H7 infection, fosfomycin is the most frequently used antibiotic and appears to have a protective effect.[30,43]

The major limitation of our meta-analysis is our inability to adjust for severity of illness and to analyze the risk of HUS with various classes and duration of antibiotics and the timing of therapy. Publication bias may also play a role, in that studies showing no effect of antibiotic use on HUS may be less likely to be published. Our assessment of this possibility does not, how-ever, suggest that a substantial publication bias exists.

In summary, we believe that better data are needed—ideally, an adequately powered, nationwide randomized trial in which multiple distinct strains of *E coli* O157:H7 are represented and rapid diagnostic methods for identification of *E coli* O157:H7 infection are used to permit early randomization—before it can be concluded unequivocally that administration of antibiotic therapy to critically ill children or adults with severe, presumably infectious enteritis, especially dysentery that might represent *E coli* O157:H7 infection, is deleterious.

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