


To the Editor—In their article, Jelacic et al. [1] describe the bacterial genotypes of Shiga toxin–producing Escherichia coli (STEC) and clinical profiles of patients in Montana. In a statewide surveillance project that spanned 2 years, all stool samples (~6300) were tested for the presence of Shiga toxin. In 82 patients, STEC was isolated as the only organism, and 32 (39%) of them expressed the lipopolysaccharide antigen O157. Although the difference was not statistically significant, bloody diarrhea tended to be reported more often by patients whose stool cultures yielded STEC of serogroup O157, compared with those infected with a non-O157 strain (P = .061).

In Germany, a nationwide case-control study of risk factors for sporadic STEC-associated illness was conducted from 1 April 2001 to 31 March 2003 (D. Wer- ber, unpublished data). In that study, a case patient was defined as a person who showed clinical symptoms and was not part of a recognized outbreak and whose stool sample contained a Shiga toxin gene (stx) detected by polymerase chain reaction. Among all the patients in the study for whom we could obtain the information, the proportion of STEC being O157 was 16% (n = 48); yet, among the 57 pa-

tients who reported bloody diarrhea, this proportion was 39% (n = 22) (P < .001).

In a multivariate analysis, bloody diarrhea was associated with STEC O157 and with the stx subgroup gene but not with stx or eae or hlyA or with other STEC serogroups (table 1).

Of importance is that in a multivariate analysis that, in the study design [2], controlled for serogroup as a risk factor, both the presence of an stx and the presence of eae gene were associated with severe disease (defined as bloody diarrhea or as clinical signs of hemolytic-uremic syndrome). When bloody diarrhea is chosen as the outcome for statistical analysis, our data agree with this set of virulence loci in the case of stx but not in the case of eae. A recent Danish study found that, in addition to STEC O157 and O103, both the stx subgroup gene and the eae gene were associated with bloody diarrhea [3]. Surprisingly, Jelacic et al. found no statistical association with any virulence loci [1]. Thus, although the genomic basis seems to be unclear, the latter 3 studies (all uncontrolled, in the study design, for serogroup) all find that STEC O157 confers a greater risk of bloody diarrhea than do non-O157 strains.

These studies, however, are limited in at least 2 ways. First, STEC O157 is strongly associated with several known or putative virulence genes; for example, the stx subgroup gene was found in 100% and 96% of pa-

tients in Montana and Germany, respec-

Table 1. Risk factors for bloody diarrhea (BD) in a case-control study of risk factors for sporadic Shiga toxin–producing Escherichia coli–associated illness in Germany.

<table>
<thead>
<tr>
<th>Determinant</th>
<th>No. (%) of patients</th>
<th>No. (%) with BD</th>
<th>Univariate analysis, OR (95% CI)</th>
<th>Multivariate analysis, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virulence loci</td>
<td></td>
<td></td>
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<tr>
<td>stx2</td>
<td>110 (38.6)</td>
<td>36 (59.0)</td>
<td>2.92 (1.63–5.22)</td>
<td>2.35 (1.11–4.94)</td>
</tr>
<tr>
<td>stx1</td>
<td>212 (74.6)</td>
<td>33 (54.1)</td>
<td>0.28 (0.16–0.53)</td>
<td></td>
</tr>
<tr>
<td>eae</td>
<td>150 (68.5)</td>
<td>27 (69.2)</td>
<td>1.04 (0.49–2.20)</td>
<td></td>
</tr>
<tr>
<td>hlyA</td>
<td>188 (86.2)</td>
<td>33 (84.6)</td>
<td>0.85 (0.32–2.24)</td>
<td></td>
</tr>
<tr>
<td>Serogroup</td>
<td></td>
<td></td>
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<tr>
<td>O157</td>
<td>48 (16.4)</td>
<td>22 (38.6)</td>
<td>5.08 (2.59–9.93)</td>
<td>3.51 (1.54–7.98)</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; OR, odds ratio.

* O145, O111, O103, O26, and the group of the remaining STEC were not statistically significant.
respectively, who were infected with STEC O157. These correlations need to be taken into account, ideally in the study design, or when these data are analyzed. It is noteworthy that the results reported by Boerlin et al. [2] predict that STEC O157 more frequently causes bloody diarrhea (or clinical symptoms of hemolytic-uremic syndrome) than do non-O157 STEC strains, given the recently reported strong association of this serogroup with stx and eae [1, 3–6]. Yet, even when these virulence loci are controlled for in the analysis—as Jelacic et al. [1], Ethelberg et al. [3], and we did—STEC O157 was associated with bloody diarrhea; this may indicate that additional (unmeasured) virulence loci that are exclusively or predominantly present in strains of this serogroup contribute to the occurrence of bloody diarrhea.

A second limitation is that the clinical spectrum of bloody diarrhea may range from a few visible traces of blood to “all blood and no stool” [7]. Conceivably, the former condition is less likely to precipitate urgent medical evaluation than is the latter. In this respect, patients in Montana infected with STEC O157 more frequently had their stool cultures obtained in emergency departments than did patients infected with non-O157 strains (P = .022) [1]. The authors plausibly attribute it to the increased occurrence of bloody diarrhea in patients infected with STEC O157 and to the generally less-severe illness associated with non-O157 strains [1]. However, if the degree of bloody diarrhea or the accompanying symptoms are more pronounced in patients with STEC O157 infection, then there is likely a difference between the rate of presentation to points of care by STEC O157–infected patients with bloody diarrhea and that by non-O157 STEC–infected patients with bloody diarrhea. Consequently, such a difference would account for at least some of the association between STEC O157 infection and bloody diarrhea. Therefore, some caution is warranted when these results are interpreted.

Furthermore, it would be of interest if presentation to an emergency point of care depends on the set of virulence loci rather than on the serogroup of the infecting strain. Regardless, in patients with hemolytic-uremic syndrome—a life-threatening condition that should inevitably lead to admission to a hospital—bloody diarrhea also was more frequently reported by patients with STEC O157:H7 infection [8], supporting the hypothesis that STEC O157 more frequently causes bloody diarrhea.

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References

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Reply
To the Editor—We thank Dr. Werber’s group for sharing their data on Shiga toxin genotyping and clinical profiling of patients infected with Shiga toxin–producing Escherichia coli (STEC) [1]. We, too, were struck by the lack of association between the presence of the stx2 gene and the occurrence of bloody diarrhea in the patients from whom these organisms were isolated. This curious finding is related, in part, to the unexpectedly high frequency of bloody diarrhea in patients infected with E. coli belonging to serogroup O26 that do not contain the stx2 gene, at least not as detected by the primers used in our study. The reason for the high frequency of bloody diarrhea in these patients infected with E. coli O26 remains unknown.

As mentioned in our Discussion, the conclusions derived from any single population may not be applicable to all populations of patients infected with STEC. Nonetheless, it is almost certain that serogroup and associated genotypes (with known and/or yet-to-be-discovered virulence genes) play an important role in the clinical illnesses that result. Thus, serogroup might be a surrogate for the “set of virulence loci,” as emphasized by Werber et al.

The data set in our article has unique characteristics, because it was based on isolates that were recovered from a geographically well-defined population and that were collected prospectively, over a fixed interval, by use of a standardized re-