Bloody Diarrhea and Shiga Toxin–Producing Escherichia coli Hemolytic Uremic Syndrome in Children: Data from the ItalKid-HUS Network

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Objective To analyze the results of an enhanced laboratory-surveillance protocol for bloody diarrhea aimed at identifying children with Shiga toxin–producing Escherichia coli (STEC) infection early in the course of the disease toward the early identification and management of patients with hemolytic uremic syndrome (HUS).

Study design The study (2010-2019) involved a referral population of 2.3 million children. Stool samples of patients with bloody diarrhea were screened for Shiga toxin (Stx) genes. Positive patients were rehydrated and monitored for hemoglobinuria until diarrhea resolved or STEC-HUS was diagnosed.

Results A total of 4767 children were screened; 214 (4.5%) were positive for either Stx1 (29.0%) or Stx2 (45.3%) or both Stx1+2 (25.7%); 34 patients (15.9%) developed STEC-HUS (0.71% of bloody diarrheas). Hemoglobinuria was present in all patients with HUS. Patients with Stx2 alone showed a greater risk of STEC-HUS (23.7% vs 12.7%) and none of the patients with Stx1 alone developed HUS. During the same period of time, 95 other patients were diagnosed STEC-HUS but were not captured by the screening program (26 had nonbloody diarrhea, 11 came from areas not covered by the screening program, and 58 had not been referred to the screening program, although they did meet the inclusion criteria). At HUS presentation, serum creatinine of patients identified by screening was significantly lower compared with that of the remaining patients (median 0.9 vs 1.51 mg/dL).

Conclusions Nearly 1% of children with bloody diarrhea developed STEC-HUS, and its diagnosis was anticipated by the screening program for Stx. The screening of bloody diarrhea for Stx is recommended, and monitoring patients carrying Stx2 with urine dipstick for hemoglobinuria is suggested to identify the renal complication as early as possible. (J Pediatr 2021;237:34-40).

The epidemiology of acute bloody diarrhea in children is not clearly known both in high- and low- to middle-income countries. What is known is that a wide array of pathogens can cause bloody diarrhea in children, with varying incidence by geography, season, age, socioeconomic conditions, and hosts' immune status.

In Western countries, culture-proven bloody diarrhea is mostly due to Campylobacter, Salmonella, Shigella, Yersinia, and Escherichia coli, especially Shiga toxin (Stx)-producing Escherichia coli (STEC). STEC infections can be complicated by the hemolytic uremic syndrome (HUS), that, besides being the most common thrombotic microangiopathy (TMA) in children, is the leading cause of acute kidney injury in children beyond the neonatal age. STEC-HUS is characterized by platelet consumption, mechanical non–immune-mediated hemolysis, and renal, as well as multiorgan, damage with severe and life-threatening consequences.
Detailed knowledge of the local epidemiology is of paramount importance for identifying new and effective prevention strategies as well as for driving the optimal diagnostic approach. Moreover, the patient’s early clinical management can be modified by knowledge of epidemiologic data (virulence profiling and risk of complications). We describe the results obtained from the 10-year experience with a centralized screening program of bloody diarrhea for Stx in children that was promoted in a large area with more than 12 million general population. The study presents the general epidemiology of Stx + bloody diarrhea in children with special regard to HUS development and the impact of the screening program in anticipating the diagnosis and the management of HUS.

Methods

The present analysis includes all tested children (up to 20 years of age) with bloody diarrhea obtained from 2010 through 2019 within a network of 63 pediatric units in Northern Italy (ItalKid-HUS Network), with a referral pediatric population of 2.3 million. We present all STEC-HUS cases diagnosed during the analyzed period including those not screened before the diagnosis of HUS, either because they were not tested (n = 58) due to the rapid course of the disease or because they came from areas not covered by the screening program (n = 11) or because they did not exhibit bloody diarrhea at all (n = 26) (Figure 1).

The network was developed for the identification of STEC infections aimed at the early diagnosis and management of STEC-HUS. Exclusion criteria were history of chronic diarrhea due to any cause. Stool specimens (occasionally, fecal or rectal swabs) were obtained either from the emergency department or upon patient’s admission, and only 1 sample was recorded for each patient. Samples were delivered at room temperature and accepted 24 hours a day/7 days a week, and the results were made available during the subsequent day since sample receipt. All the patients/parents were informed about the investigations and gave their written consent to the diagnostic procedures. The study received the approval by the ethical committee of our institution.

Objectives and End Points

The present study was carried out on an intention-to-diagnose basis. The study was aimed at anticipating the diagnosis and the management of STEC-HUS while evaluating the prevalence of STEC infection among children with bloody diarrhea. Primary end points of the study were the measurement of the proportion of Stx-positive patients among children with acute bloody diarrhea, the distribution of Stx, and STEC serotypes involved. The secondary end point were the comparison of laboratory (serum creatinine [sCr], platelet counts, and hemoglobin) at presentation and the outcomes of HUS in patients identified by screening and/or diagnosed with HUS (with or without prodromal bloody diarrhea).

Definitions

Bloody diarrhea was defined as: acute (<10 days) diarrhea with visible blood in at least one bowel movement either seen by health professionals or reported by caregivers. STEC-HUS was defined as the concomitant presence of platelet consumption (platelet count <150 000/mm³ or more than 50% acute reduction of platelet count), non–immune-mediated (Coombs negative) hemolysis (anemia or undetectable haptoglobin or lactate dehydrogenase above upper limit of normal), and renal damage (sCr above the upper normal limit for age and sex or proteinuria or hematuria) in a patient with evidence of STEC infection (Stx genes in stool or anti-lipopolysaccharide positivity against the “top 6” serotypes). The “top-6” serotypes are O157, O26, O103, O111, O145, and O104. Cases with negative Stx and negative anti-lipopolysaccharide were further investigated to exclude complement dysregulation. The same was done in cases of atypical course and/or with poor outcome. Positive urine dipstick or urinalysis for hemoglobinuria was defined as ≥+ (small) or ≥20 mg/mL, respectively. Positive urine dipstick or urinalysis for hematuria (presence of red blood cells) was defined as ≥+ (small) or ≥5 red blood cells/per high-power field, respectively.

Laboratory Procedures

The biological samples are centralized at our Center, where the test for the detection of STEC-related genes was performed using the Reverse Dot Blot Assay (Genotype EHEC; Arnika) until 2018 and subsequently a real-time polymerase chain reaction (PCR) (RIDA Gene-Relab). In detail, 50 μL of feces or rectal swabs are inoculated on the MacConkey broth and incubated at 37°C for 18-24 hours. DNA from bacteria is extracted (Genta Puregene blood kit) and quantified (NanoDrop 1000 spectrophotometer). A reverse dot blot (Genotype EHEC-Arnika) was used to identify the following genes: Stx1, Stx2, intimin (eae), and invasion plasmin antigen H gene (ipaH). The target DNA was amplified with 5’ biotinylated primers and hybridized to specific oligonucleotides immobilized on the membrane strips. Hybridization is detected by adding streptavidin–horseradish peroxidase to the membrane, hence obtaining a colorimetric reaction.

Since 2018, STEC-related genes were detected by multiplex real-time PCR performed by the RIDA Gene-EHEC/EPEC (R-biopharm) screening kit. If the screening was positive for Stx, a second multiplex real-time PCR was performed using the RIDA Gene E. coli Stool Panel I kit (R-biopharm) to discriminate between Stx1 and Stx2 genes. The amplified targets are revealed with probes marked at the ends, respectively, with a quencher on one side and with a fluorescent dye (fluorophore) on the other. In the presence of a target, the probes hybridize with amplicons. The main serotypes of STEC were identified using a real-time multiplex PCR for the serogroups most frequently associated with human infection: “top 6.” The procedures required a maximum of 6 hours for reverse dot blot and 2 hours for real-time PCR.
Statistical Analyses
Data are provided in absolute numbers and percent with 95% CIs or as median and IQR. Correlation between variables was analyzed by means of the Pearson correlation coefficient. The $\chi^2$ test was used to compare categorical variables. The Student t test was used to compare discrete variables. Statistical significance was set at a $P$ value of < .05 (2-tailed). Data analysis was performed using StatView (Abacus Corp).

Results

Bloody Diarrhea
In total, 4767 patients with bloody diarrhea have been screened for the presence of Stx genes during the past 10 years. Male sex was significantly ($P < .001$) over-represented (56.9%) compared with the expected 48.8% of the general population. The median age of screened patients was 3.4 years (IQR 1.5-7.0). Bloody diarrhea was more common in younger children, with the greatest relative frequency in the age group <1 year. More than 60% of screened patients were in the age range 0-5 years. In addition, as known and expected, bloody diarrhea was more common during summer with a peak relative frequency in August and the nadir in February.

Stx Gene Positivity
Of the 4767 screened samples of bloody diarrhea, 214 (4.5%) were positive for either Stx1 ($n = 62$; 29.0%) or Stx2 ($n = 97$; 45.3%) or both genes ($n = 55$; 25.7%). Moreover, 741 (15.5%) patients with bloody diarrhea were positive to the eae gene either in association with Stx genes ($n = 124$) or without ($n = 617$); in 85 samples (1.8%), the ipaH gene was identified.

The rate of Stx gene positivity among children with bloody diarrhea per year ranged from as low as 2.5% in 2010 to 5.6% in 2016, with a positive slope of the regression line suggesting...
an increasing incidence of STEC infection over time (Figure 2). During the same period of time, 95 children also were tested because of ongoing HUS associated with either bloody diarrhea (n = 69) or nonbloody diarrhea (n = 26); thus, the total of Stx gene–positive children identified during the 10 years increased to 277.

Although the age group more commonly affected by bloody diarrhea is <1 year, this age group seems relatively less affected by STEC infection compared with other age groups. From age 1 year onward, the percentage of Stx+ among bloody diarrheas remains fairly constant across ages, ranging from 7% to 9% thus demonstrating that no age is exempt from STEC infection. However, more than 50% of STEC infections were recorded at younger than age 5 years (Table I).

Bloody diarrhea is more common in late summer and autumn, and the rate of Stx+ positivity among children with bloody diarrhea is greater from July through October. In September, the rate of Stx+ positivity for bloody diarrhea observed, was well above 10% (almost 3-fold the average). In addition, no difference was observed in the sex, age, or seasonal distribution of identified Stx genes (1, 2, or 1+2).

Among Stx+ patients captured by the screening program, the most frequently identified serotype was O157 (25.3% of cases), followed by O26 (24.9%), O103 (7.0%), O111 (6.1%), O145 (4.4%), O127 (1.3%), and O104 (0.4%). Non–top-6 serotypes accounted for 30.6% of cases positive for Stx at the time of screening for bloody diarrhea.

**STEC-HUS**

Of the 214 patients who were Stx+ identified through the screening program, only 34 developed HUS (15.9% of Stx+ and 0.71% of screened bloody diarrhea). Only patients with STEC carrying either Stx2 gene (with or without Stx1) developed STEC-HUS. Thus, if the analysis is restricted to the 152 patients carrying the Stx2 gene (either alone or in combination with Stx1), the subjects at actual risk of STEC-HUS was 3.2% of bloody diarrheas (152/4767). The risk of Stx+ gene infection to turn into STEC-HUS was significantly different according to the isolated Stx gene: 0% for Stx1, 23.7% for Stx2, and 12.7% for Stx1+2 (P < .0001).

Of 63 patients who were Stx2+ that were tested with urine dipstick or urinalysis for hemoglobinuria, all those with HUS, had a positive urine and only 7 positive tests were not associated with HUS. The median number of days between presentation and the detection of hemoglobinuria was 4.8 (IQR 3.3-6.0) and whenever the urine turned positive for hemoglobinuria the diagnosis of HUS was confirmed by blood tests within the subsequent 24 hours. None of the patients persistently negative for hemoglobinuria developed HUS. Thus, the sensitivity of hemoglobinuria for the development of HUS was 100% (95% CI 95-100) with a specificity of 85% (95% CI 77-91); the positive predictive value was 68% (95% CI 55-79), the negative predictive value was 100% (95% CI 93%-100%), and the accuracy was 89% with a likelihood ratio of 6.7.

Although Stx gene positivity (as percent of bloody diarrheas) does not change with age (ranging from 2.6 to 4.3), the risk of conversion of Stx+ into STEC-HUS decreased with age, being as high as 26.4% in children younger than 5 years old (P for trend: .10) (Table I).

With regard to Stx genes involved in the 129 patients who developed HUS, Stx1 alone was found in 0.8% only, and the most common association was with Stx2 and Stx1+2 (details are provided in Table II). The most frequent STEC serotype identified among children with HUS was O26 (34.1%), and O157 was detected in 17.8% of cases. The distribution of serotypes was significantly different in patients whose STEC infection did or did not turn into HUS (Table II).

The median creatinine level (and IQR) at presentation of STEC-HUS in children who were identified as STEC infected by the screening program before the development of the renal complication (n = 34) was significantly (P < .001) lower (0.9 mg/dL; IQR 0.4-1.5) compared with that of patients

**Table I. Distribution of bloody diarrhea, of Stx 2 and Stx1+2 positivity, and of STEC-HUS by age groups including only patients being tested at the stage of bloody diarrhea (before the development of STEC-HUS)**

<table>
<thead>
<tr>
<th>Age groups, y</th>
<th>Bloody diarrhea (%)</th>
<th>Stx2 and 1+2 pos. (%) of bloody diarrhea</th>
<th>STEC-HUS (%) of Stx pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>3078 (64.6)</td>
<td>87 (2.8)</td>
<td>23 (26.4)</td>
</tr>
<tr>
<td>5-10</td>
<td>1012 (21.2)</td>
<td>40 (4.0)</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>10-15</td>
<td>491 (10.3)</td>
<td>21 (4.3)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>15-20</td>
<td>186 (3.9)</td>
<td>4 (2.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>4767 (100)</td>
<td>152 (3.2)</td>
<td>34 (22.4)</td>
</tr>
</tbody>
</table>

Figure 2. Changes in the rate of Stx2- and Stx1+2-positive bloody diarrheas over time in the area of the ItalKid-HUS Network (figures include all patients identified positive including patients with ongoing HUS referred to our Center during the analyzed period: screened and unscreened).
diagnosed with ongoing STEC-HUS (n = 95; 1.5 mg/dL; IQR 0.9-2.9). As shown in Figure 1, no significant differences were observed in the rate of short-term complications (need for renal-replacement therapy or central nervous system involvement) between the 2 groups. The overall long-term outcome was more favorable in patients diagnosed with STEC infection before HUS development (any adverse long-term outcome: 2.9% vs 15.8%). Moreover, the distribution of Stx type and of serotypes were not different in patients whose STEC infection was identified before or following the diagnosis of HUS. Finally, out of 129 children with HUS managed at our Center during the 10 years of activity of the screening program, only one died (0.8%; 95% CI 0.02-4.3).

**Discussion**

Bloody diarrhea is not uncommon in children and, when caused by STEC, it can be complicated by the development of STEC-HUS, with possible life-threatening consequences, including severe acute and chronic renal damage. No specific treatment for STEC-HUS is available, and the management of patients is centered on supportive care.

In 2010, we became increasingly aware that control of STEC-HUS required strong preventive measures. Thus, we decided to move our attention from overt HUS to the early (prodromal) phase of the infection when the kidney is not yet involved. The target of our intervention was to decrease the incidence of STEC-HUS while ameliorating its course and outcome. This ambitious target was supported by the increasing availability of reliable diagnostic tools as well as by new evidence that well hydrated children exhibited better outcomes.20 The working hypothesis behind the activity of the ItalKid-HUS Network was that the screening of bloody diarrheas for Stx could lead to the early identification, referral and inpatient management of STEC infected children at high risk for STEC-HUS.

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**Table II. Virulence profile and serotypes in patients infected with STEC and in those who developed STEC-HUS (includes all patients: screened and unscreened)**

<table>
<thead>
<tr>
<th>Stx, n (%)</th>
<th>STEC infected without HUS (n = 180)</th>
<th>STEC-HUS (n = 129)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61 (33.9)</td>
<td>1 (0.8)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>2</td>
<td>72 (40.0)</td>
<td>71 (55.0)</td>
<td></td>
</tr>
<tr>
<td>1+2</td>
<td>47 (26.1)</td>
<td>21 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>—</td>
<td>36 (27.9)</td>
<td></td>
</tr>
<tr>
<td>Eae+, n (%)</td>
<td>124 (68.9)</td>
<td>78 (60.5)</td>
<td>P = .12</td>
</tr>
<tr>
<td>Serotype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O157</td>
<td>35 (19.4)</td>
<td>23 (17.8)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>O26</td>
<td>15 (8.3)</td>
<td>44 (34.1)</td>
<td></td>
</tr>
<tr>
<td>Other top 6</td>
<td>22 (12.2)</td>
<td>22 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Non-top 6</td>
<td>42 (23.3)</td>
<td>28 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>66 (36.8)</td>
<td>12 (9.3)</td>
<td></td>
</tr>
</tbody>
</table>

Our efforts did not decrease the incidence of STEC-HUS, which has remained fairly stable in our area (around 5-6 cases/million age-related population). We also observed that the disease often has a rapid course from the development of bloody diarrhea to STEC-HUS; thus, only one-third of STEC-HUS were identified at the stage of bloody diarrhea before the development of the TMA (Figure 1). More than 20% of STEC-HUS cases did not have bloody diarrhea or bloody diarrhea was not noticed, so the screening did not capture them.

Nevertheless, the program has provided evidence of a positive impact on the disease. First of all, we now have a much better understanding of the local epidemiology of the disease that leads to more detailed individual risk assessment with important clinical implications. For instance, we are now aware that 4.5% of all children with bloody diarrhea are Stx+. Furthermore, we confirmed that Stx1 is a very rare cause of STEC-HUS and Stx2 alone is associated with a greater (double) risk than when present in combination with Stx1 as previously hypothesized from both human21-25 and experimental data.26,27 In addition, although bloody diarrhea is not nearly as common in very young children (<1 year old), these seem relatively less likely to be Stx+ compared with other age groups.

Our screening program clearly identified only a portion of bloody diarrheas occurring in the area, and this is among the reasons why a substantial number of HUS cases were not captured before the development of the renal complication. Nevertheless, because of the screening program and the consequent awareness among pediatricians of bloody diarrhea presenting as a prodromal phase of a subsequent severe disease, the diagnosis of STEC-HUS was significantly anticipated in patients who entered the screening program compared with unscreened patients. For example, the median level of sCr at STEC-HUS presentation in the screened patients was 0.9 mg/dL compared with 1.5 mg/dL in unscreened patients. Furthermore, the sCr level during the years immediately before the initiation of the screening program of bloody diarrhea for Stx at our Center was 2.0 mg/dL (IQR 1.1-3.3).28 In addition, if we analyze some recently published series of STEC-HUS, the sCr of our patients at presentation is significantly lower: in Belgium, Keenswijk et al reported a median of 2.98 mg/dL in 34 patients.28 In Argentina, Alconcher et al reported a median sCr at presentation of 2.39 mg/dL in 466 patients,29 and that reported by Balestracci et al was 2.35 mg/dL in 153 patients.30 Finally, in a series from France, Netherlands, and the United Kingdom, altogether involving 270 patients, sCr at admission was well above 2 mg/dL (unpublished data kindly provided by Chantal Loirat, Veronique Fremeaux-Bacchi, Nicole van der Kar, and Sally Johnson, 2020).

Finally, among the major results of anticipating the diagnosis and the management of STEC infections and of STEC-HUS, we observed an important drop of the case-fatality rate from 5.2% to less than 0.8%. However, as
shown in Figure 1, early diagnosis did not affect the acute phase of the disease (both in terms of need for renal-replacement therapy and overt central nervous system involvement) but early diagnosis did reduce the overall long-term sequelae of the disease. Given the relatively small numbers of bloody diarrhea in children, the severity of the possible complications and their rapid development, we believe that all patients with bloody diarrhea should be closely monitored and managed as if any of them could evolve into STEC-HUS until Stx testing excludes the diagnosis. In our setting, close monitoring and appropriate management means stool analysis for Stx, weight restoration (if dehydrated), generous administration of maintenance fluids, and urine dipstick every 12 hours aimed at identifying upcoming TMA (Figure 3).

Only patients carrying Stx2 (alone or in combination with Stx1) (3.2% of bloody diarrheas) will continue to require the described measures (generous fluid supplementation and urine dip stick every 12 hours) until diarrhea resolves. Almost 15% of this subgroup will develop STEC-HUS. This becomes particularly relevant during late summer and early fall, when the probability that bloody diarrhea is associated with Stx rises well above 10%.

We thank the members of the ItalKid-HUS Network (Appendix). We are also very thankful to “Progetto Alice–Associazione per la lotta alla SEU” for their funding together with support and continuous commitment to our research.

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Data Statement


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Appendix

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