Province-Wide Review of Pediatric Shiga Toxin-Producing *Escherichia coli* Case Management

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Objective To identify the gaps in the care of children infected with Shiga toxin-producing *Escherichia coli* (STEC), we sought to quantitate care received and management timelines. Such knowledge is crucial to the design of interventions to prevent the development of hemolytic uremic syndrome (HUS).

Study design We conducted a retrospective case-series study of 78 children infected with STEC in Alberta, Canada, through the linkage of microbiology and laboratory results, telephone health advice records, hospital charts, physician billing submissions, and outpatient antimicrobial dispensing databases. Outcomes were the time intervals between initial presentation and reporting of positive culture result and symptom onset to HUS and to describe the proportions that had baseline blood work performed and received antibiotics.

Results Seventy-eight children infected with STEC were identified; 13% (10/78) developed HUS. Median time from initial presentation to laboratory stool sample receipt was 33 hours (IQR 18, 42); time to positive culture was 120 hours (IQR 86, 205). Time from symptom onset to HUS diagnosis was 188 ± 37 hours. Baseline blood tests were obtained in 74% (58/78) of infected children. Antibiotics were administered to 50% (5/10) of those who developed HUS and 22% (15/78) of those who did not; $P = .11$. The provincial telephone advice system received 31 calls regarding 24 children infected with STEC; 23% (7/31) of callers were recommended to seek emergency department care.

Conclusions A significant proportion of children developed HUS following multiple interactions with the health care system. Delays in the confirmation of STEC infection occurred. There are numerous opportunities to improve the timing, monitoring, and interventions in children infected with STEC. *(J Pediatr 2017;180:184-90).*

Children infected by Shiga toxin-producing *Escherichia coli* (STEC) are at risk for developing hemolytic uremic syndrome (HUS).[1-7] Because STEC pathogens, most notably *E coli* O157:H7, have the potential to cause outbreaks, infections constitute medical and public health emergencies.[8] There is a need for rapid and accurate diagnosis and treatment[9]; identifying the presence of STEC infection should encourage the avoidance of antibiotics,[4,10] monitoring of laboratory measures, attention to hydration status,[11] and precautions to reduce spread.[12]

Understanding of the typical pattern of illness and transitional stages from *E coli* O157:H7 infection to HUS is important. After exposure, the typical history begins with a brief incubation period (typically 3-4 days)[13] followed by 2-3 days of nonbloody diarrhea. Subsequently 70% of children infected with *E coli* O157:H7 develop bloody diarrhea,[14] typically appearing on the third day of illness and persisting for 3-5 days.[15] A total of 10%-15% of patients infected with STEC develop HUS after a median interval of 7 days (IQR 5, 8) from the start of diarrhea,[16] and two-thirds of patients with HUS require renal replacement therapy (eg, dialysis).[7]

Because STEC progression to HUS includes a phase between first presentation and overt deterioration, there is an opportunity to intervene. An emerging

ED	Emergency department
HUS	Hemolytic uremic syndrome
NM	Nonmotile
PHN	Personal health number
PIN	Pharmaceutical Information Network
ProvLab	Provincial Laboratory for Public Health
STEC	Shiga toxin-producing *Escherichia coli*

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therapeutic consideration is the provision of intravenous hydration to prevent the development of dehydration, which is associated with poor outcomes in children with HUS.[11,17,18]

If significant delays or time gaps are identified, quality improvement efforts could target these intervals, enabling the provision of intravenous hydration or other therapies that may prevent the development of renal failure. In the summer of 2014, there was an increase in the number of STEC cases in the province of Alberta, Canada. As the initial stage of a quality improvement initiative, a review of all pediatric STEC cases during the period from June 1 to October 31, 2014 was conducted.

Methods

This project was a part of the APPETITE (ie, Alberta Provincial Pediatric EnTeric Infection TEam) initiative and was endorsed by Pediatric Emergency Research Canada.[19] The University of Calgary's research ethics board deemed this project to be a quality assurance evaluation and hence outside of their mandate for ethics review. Ethical considerations were assessed by the province's A pRoject Ethics Community Consensus Initiative (ARECCI)[20] process for quality improvement project evaluation.

We sought to quantify among the children infected with *E coli* O157:H7 (1) the time interval between initial health care presentation for the illness until a positive culture result; (2) number of health care visits before stool sample submission for testing; (3) the number of health care visits before the development of HUS; (4) the duration of symptoms before the development of HUS; (5) the proportion of children with baseline and follow-up blood tests; and (6) the proportion of infected children who received antibiotics.

A health care presentation/visit/encounter included any interaction with Alberta's health care system, including a primary care physician, emergency department (ED), walk-in clinic, or Health Link (Alberta's 24 hour/day, 7 days/week, nurse advice and general health information phone system).[21] Time of sample submission for enteric bacterial culture was defined as the time of stool sample receipt at the laboratory. Time of positive culture was the time the presumptive or final culture result was reported, as recorded on the microbiology laboratory report. A case of HUS required all the following criteria: (1) hematocrit <30% with smear evidence of hemolysis; (2) platelet count <150 000/mm^3; and (3) serum creatinine greater than the upper limit of normal for age.[7] Symptom onset date was defined as the day of the first episode of bloody or nonbloody diarrhea. Blood test monitoring was defined by time periods with baseline tests being those performed within 3 days (plus/minus) of the positive STEC culture and follow-up testing being performed 3-7 days after the positive culture result (ie, the window of clinical deterioration).[22]

Our patient population included children <19 years of age in the province of Alberta, Canada, who had a stool specimen test positive for an STEC pathogen between June 1, 2014, and October 31, 2014. This time frame was defined by the reported symptom onset dates of the first and last cases included in our series from the summer of 2014. A list of children infected with STEC from the study time period was obtained from the Provincial Laboratory for Public Health (ProvLab), which operates as the reference laboratory in the province. All STEC isolates identified by regional laboratories in the province are sent to ProvLab for molecular typing by pulse-field gel electrophoresis via the use of standardized PulseNet protocol[23] for epidemiologic surveillance. ProvLab also provides testing for outbreak investigations through collaborations with provincial public health partners. Verotoxin testing was performed at several local diagnostic laboratories before specimen submission to ProvLab on stool that was incubated in selective broth that used either the Immuno*Card* STAT! EHEC (Meridian Bioscience, Inc, Cincinnati, Ohio) or the Shiga toxin Quik Chek (Techlab, Blacksburg, Virginia).[24] All culture-positive *E coli* O157 specimens that tested negative for the presence of toxin when the Immuno*Card* STAT! EHEC was used were retested with the Shiga toxin Quik Chek. Although of suboptimal sensitivity[25] as stand-alone tests, these toxin tests can be positive when cultures are negative, particularly when the pathogen is a non-O157 STEC.[25]

Data Collection and Extraction

Data were extracted from multiple administrative health data sources held by the Ministry of Health, which captures resource use for all provincial residents with public health care insurance. All residents of Alberta are eligible for public health care insurance, and more than 99% of residents participate in this government-sponsored plan. Each person registered with the plan receives a personal health number (PHN), which is a unique lifetime identifier. The PHN, which is linked to information such as date of birth, sex, and address, is captured in each administrative health data source, allowing for deterministic linkage. Public health care insurance covers the cost of all medically necessary physician visits, hospitalizations, investigations, and procedures. Alberta's fee-for-service physicians submit claims to the provincial health care insurance program for payment. Even though various reimbursement models exist, regardless of payment model (ie, fee-for-service, alternative payment program), all physicians submit claims outlining the services provided based on a set of established billing codes and the Canadian Classification of Procedures. Consequently, Alberta's billing databases capture complete and valid information on inpatient and outpatient physician services.[26]

The data sources accessed included: (1) the ProvLab Alberta microbiology database; (2) the Health Link database,[21] which provided data related to call date and time, advice protocol, disposition recommendation (eg, to ED or physician within 4 hours, physician within 24 hours, self-care at home, information sharing only), chief complaint, questions, priority symptoms; (3) medical charts for all children who presented to the Alberta Children's Hospital (Calgary; N = 29) and the Stollery Children's Hospital (Edmonton; N = 16); (4) ambulatory and inpatient records, including *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, Canadian Adaptation codes and length of stay; and (5) the Alberta Pharmaceutical Information Network (PIN); all