Concomitant Medical Conditions and Therapies Preclude Accurate Classification of Children With Severe or Severe Complicated Clostridium difficile Infection

Larry K. Kociolek,1,2 Sameer J. Patel,1,2 Stanford T. Shulman,1,2 and Dale N. Gerding3,4
1Department of Pediatrics, Division of Infectious Diseases, Ann & Robert H. Lurie Children’s Hospital of Chicago, Illinois; 2Northwestern University Feinberg School of Medicine, Chicago, Illinois; 3Department of Medicine, Edward Hines, Jr. VA Hospital, Hines, Illinois; and 4Loyola University Chicago Stritch School of Medicine, Maywood, Illinois

Corresponding Author: Larry K. Kociolek, MD, 225 E. Chicago Ave, Box 20, Chicago, IL 60611. E-mail: larry-kociolek@northwestern.edu.

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Severe and severe complicated Clostridium difficile infections (SCDI/SCCDI) were retrospectively assessed in a pediatric cohort. Underlying medical conditions and concomitant medical therapy preclude accurate classification of children with SCDI/SCCDI, using current CDI severity definitions. Revised CDI definitions in children should focus on more objective, age-appropriate, and CDI-specific markers of severity.

Key words. Clostridium difficile; complicated; definition; pediatric; severe.

INTRODUCTION

The frequency of pediatric Clostridium difficile infection (CDI) is increasing [1]. Although CDI severity has increased in adults [2], severe CDI (SCDI) and severe complicated CDI (SCCDI) are relatively uncommon in children [3–5]. Although standard definitions for SCDI and SCCDI are available [6, 7], the authors of these guidelines acknowledge that they are based on expert opinion with suboptimal validation of their predictive value [6]. Consequently, SCDI and SCCDI definitions vary among pediatric studies [3, 4, 8]. The poor discriminatory value of various laboratory and clinical markers of pediatric CDI severity was reported at a single center [5]. We explored cases of SCDI and SCCDI at our institution to identify common themes leading to potential misclassification of CDI severity in children.

METHODS

In conjunction with a molecular epidemiologic survey and retrospective cohort study of CDI at Ann & Robert H. Lurie Children’s Hospital of Chicago, we evaluated severity of pediatric CDI diagnosed between December 9, 2012 and December 8, 2013. The Institutional Review Board waived informed consent. Patients ≥12 months old who had an unformed stool that tested positive by C. difficile toxin B gene polymerase chain reaction were identified through an electronic infection surveillance tool. Clinical and demographic data were manually extracted from the electronic medical record. Patients were included if they had diarrhea or ileus, CDI documented by their healthcare providers or hospital infection control personnel, and/or received CDI treatment. Saved stool specimens from CDI cases underwent anaerobic culture [9], and C. difficile isolates were typed by restriction endonuclease analysis (REA) [10].

In accordance with published guidelines [6], patients with SCDI had one of the following: (1) peripheral white blood cell (WBC) count >15 000 cells/µL or (2) serum creatinine ≥1.5 times premorbid level. The definition for SCCDI was derived from Khanna et al [3], whose criteria were consolidated from 2 publications endorsed by the Infectious Diseases Society of America (IDSA) [6] or the Society for Healthcare Epidemiology of America (SHEA) [6, 7]. Patients had SCCDI if their infection was associated with one of the following: (1) sepsis; (2) hypotension (requiring vasopressor support); (3) ileus (radiographic or clinical diagnosis); (4) toxic megacolon; (5) perforation; (6) need for...
intensive care unit (ICU) transfer or admission; (7) surgery for CDI-related complication (eg, megacolon, perforation, refractory colitis); or (8) death. Rates of SCDI and SCCDI were calculated as the proportion of total CDI cases [7].

RESULTS

Between December 9, 2012 and December 8, 2013, 189 CDI cases meeting inclusion criteria occurred in 145 patients. Of those, 17 (9%) SCDIs occurred among 16 patients; 16 SCDI cases had WBC > 15 000 cells/µL (median, 19 000; range, 15 100–34 000); and 1 had elevated creatinine. Five (31%) of the 16 SCDI patients with leukocytosis likely had an alternate etiology for WBC elevation (Table 1; concomitant receipt of corticosteroids [n = 3]; concomitantly diagnosed with spontaneous bacterial peritonitis [n = 1]; and a 1-year-old patient with WBC 16 000 cells/µL [normal for age; n = 1]). Of the 172 cases that did not meet SCDI criteria, 24 (14%) were neutropenic related to their underlying medical condition (chemotherapy-related [n = 22]; immunosuppressive medication-related [n = 1]; and primary immunodeficiency [n = 1]). Of these 24 neutropenic patients, 1 (4%) met criteria for SCCDI. Initial treatment for SCDIs included metronidazole alone (n = 13), vancomycin alone (n = 2), and both metronidazole and vancomycin (n = 2). One patient receiving metronidazole did not respond to therapy and was switched to vancomycin, to which there was also no improvement.

Among the 189 CDI cases, 8 (4%) SCCDIs occurred among 8 patients. One patient with SCCDI had leukocytosis and also met the SCDI definition. Four (50%) SCCDI cases had radiographic evidence of ileus, and 5 (63%) were admitted to the pediatric ICU (PICU). All patients with SCCDI had an underlying medical condition potentially causing ileus or the need for PICU admission (Tables 1 and 2). Initial treatment for SCCDIs included metronidazole alone (n = 5), vancomycin alone (n = 2), and none (n = 1). All patients responded to therapy.

Stool was available for culture in 12 of 17 (71%) and 7 of 8 (88%) SCDI and SCCDI cases, respectively. Clostridium difficile was isolated from stool from 10 (83%) SCDI cases, and REA groups were as follows: A (n = 2), AH (n = 1), AL (n = 1), DH (n = 3), and nonspecific (3). Clostridium difficile was isolated from stool from 6 of 8 (86%) SCCDI cases whose REA groups are listed in Table 2.

DISCUSSION

Our findings suggest that underlying medical conditions and concomitant medical therapies preclude accurate classification of children with SCDI and SCCDI using current CDI severity definitions. Although this study is limited by its relatively small sample size and retrospective design, we provide further evidence for the need for pediatric-specific

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<th>Table 1. Proportions of Patients with SCDI/SCCDI with Concomitant Medical Conditions and Therapies That Likely Resulted in Mischaracterization of CDI Severity</th>
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Abbreviations: CDI, Clostridium difficile infection; SCCDI, severe complicated CDI; SCDI, severe CDI.

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<th>Table 2. Summary of All Cases of Pediatric SCCDI Over a 1-Year Period</th>
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<td>SCCDI Criteria</td>
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Abbreviations: CDI, Clostridium difficile infection; Metro, metronidazole; N/A, stool not available for culture; PICU, pediatric intensive care unit; SCCDI, severe complicated CDI; Vanc, vancomycin; y/o, year-old; +, culture positive.
CDI severity definitions to guide clinical management of children with CDI. More reliable definitions for CDI severity are also needed to guide investigation of the clinical and molecular epidemiology of SCDI and SCCDI in children.

The frequency of SCDI and SCCDI in our cohort was 9% and 4%, respectively, which is very similar to other multicenter [3,4] and single-center [5] and pediatric studies using similar definitions for SCDI [3, 4] and SCCDI [3, 5]. Kim et al [8], who used a different SCDI definition, reported a substantially greater proportion of SCDI in their children's hospital (59%). The prevalence of C dif ficile strain BI/NAP1/027 was 11%–35% in other pediatric studies [4, 8]. BI/NAP1/027, which is associated with increased CDI severity in adults [2], was isolated from only 1 patient in our entire 145-patient cohort, and this patient did not meet criteria for SCDI or SCCDI. Similar to that reported by Tschudin-Sutter et al [5], SCDI and SCCDI were nearly completely mutually exclusive in our cohort. Only 1 patient with SCCDI also met criteria for SCDI, and that 6-year-old patient, whose WBC was only 15 100 cells/µL, had ileus likely associated with concomitant receipt of narcotics.

The current SHEA/IDSA definition for SCDI in both children and adults only uses laboratory findings [6]. However, young children normally have WBC counts that exceed 15 000 cells/µL. In particular, the 95% confidence interval of mean normal WBC includes 15 000 cells/µL in children younger than 5 years old [11]. In the present study, approximately one third of patients with SCDI had another potential reason for leukocytosis, such as concomitant corticosteroid use or coexisting bacterial infection. In addition, children with neutropenia, who comprised a significant proportion of our cohort, cannot be evaluated reliably for SCDI based on a change in their WBC count. This result is similar to that previously reported in adult patients with hematologic malignancy [12].

Similar to SCDI, children with SCCDI often had concomitant medical problems that likely contributed to their SCCDI classification. For example, all patients with ileus had an underlying medical condition or were receiving a medication that likely contributed to ileus. Among children with SCCDI in this study, none had particularly significant or objective complications attributable to CDI, such as toxic megacolon, perforation, sepsis, need for surgery, or death. Instead, most patients with SCCDI were classified as such because of admission to the PICU at the time of CDI diagnosis. In 3 of these 5 patients, PICU admission occurred because of the patient's underlying medical condition that was unrelated to CDI (heart failure, hypoxia, or mental status changes) but concomitant with a new CDI diagnosis. The underlying medical conditions of the other 2 patients admitted to the PICU with SCCDI likely contributed to their gastrointestinal complaint (gastrointestinal bleed in the patient with chronic hepatic failure) or medical complexity (dehydration and electrolyte changes in a medically complex 1-year-old child with multiple congenital anomalies).

Only 12% of patients with SCDI received vancomycin monotherapy as recommended in the SHEA/IDSA guidelines [6]. One patient with SCDI receiving metronidazole did not respond to therapy and was switched to vancomycin, to which there was also no improvement. This finding likely suggests colonization with C dif ficile along with another cause of diarrhea, particularly because this 1-year-old patient was never hospitalized and did not develop a CDI-related complication. Likewise, no patients with SCCDI received combined oral vancomycin and intravenous metronidazole therapy as recommended [6]. The reasons for deviation from treatment guidelines are unknown, but clinicians may not be aware of these guidelines or believe they apply only to adult patients. Alternatively, current classification of SCDI and SCCDI likely overestimate severity of illness in children. Sammons et al [13] report opportunities to improve consistency in the management of CDI in children, and our findings support this observation.

CONCLUSIONS

In conclusion, SCDI and SCCDI are uncommon in children, and current SCDI and SCCDI definitions, which lack prospective validation, have particularly poor predictive value in children. Our findings suggest that the classification of a pediatric patient as having SCDI or SCCDI using current definitions most often reflects the child's underlying medical complexity rather than severity of CDI specifically. Optimizing the definitions of CDI severity is essential to better understand the relationship between C dif ficile strain type and disease severity, as well as to guide comparative effectiveness studies of therapies for SCDI and SCCDI in children. Revised CDI definitions in children should focus on more objective and CDI-specific markers of severity. Strategies for improving the definitions for CDI severity in children may include pediatric-specific laboratory criteria; incorporation of symptom-based criteria for SCDI, particularly for neutropenic patients; and guidance for accurately attributing specific symptoms, laboratory findings, and need for ICU admission to CDI.

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L.K.K. reports having received laboratory assays from Alere. D.N.G. reports being a board member for Sanofi Pasteur, Actelion, Merck, and Rebiotix and having consulted for Summit and Viropharma. D.N.G. holds patents licensed to Viropharma/Shire.

References