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Concise Communication

Transmission of *Clostridioides difficile* infection (CDI) from patients less than 3 years of age in a pediatric oncology setting

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Abstract

Clostridioides difficile infection (CDI) is prevalent in pediatric oncology patients, but the transmission risk to peers is unknown. In 224 children with CDI, multilocus sequence typing (MLST) identified only 7 alleged transmission events (18%) originating from children <3 years old. None of these events were corroborated by WGS.

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The epidemiology of *Clostridioides difficile* infection (CDI) in pediatric patients is less well reported than that of adults, particularly with respect to age-related transmission risk.[1] Up to one-third of infants harbor toxigenic strains of *C. difficile* as part of their normal gut flora, yet the incidence of CDI is lowest in the pediatric population.[2] Pediatric cases account for <4% of all hospital discharges with CDI, and the overall incidence of disease is 24 per 100,000 persons (age group, 1–17 years) compared to 14-fold higher rates in elderly patients.[3,4] Furthermore, the risk of CDI is nonexistent in infancy due to a lack of toxin receptors.[5] Based on the most recent guidelines, testing and surveillance of hospital-onset CDI (HO-CDI) is discouraged in infants and children <2 years old. Unnecessary clinical testing in this age group is a valid concern; it could lead to overrepresentation of disease burden in a population with high colonization prevalence and frequent occurrence of loose stools (strong recommendation with a moderate level of evidence).[6,7]

The basis of current Infectious Disease Society of America (IDSA) recommendations originate from single-center research studies in general pediatric populations.[5,8] Although the need for treatment in patients <3 years old who test positive for toxigenic *CD* may not be routinely necessary, the question remains: Do these patients represent an unappreciated source of transmission to others who represent a target for prevention efforts? This is especially relevant for specific groups of pediatric patients, including (1) older hospitalized children for whom CDI is now a common nosocomial threat and (2) pediatric oncology patients.[9]

The aim of this study was to evaluate the risk of *C. difficile* transmission from pediatric oncology cases <3 years old to their unit-based contacts using whole-genome sequencing (WGS).

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Methods

Study setting

Memorial Sloan Kettering (MSK) is a 475-bed hospital with 1 inpatient 33-bed pediatric unit and an adjoining 5-bed pediatric intensive care unit. These inpatient units are directly connected to the outpatient pediatric day hospital and urgent care unit through a single hallway. The pediatric service manages >1,200 admissions accounting for >10,000 patient days annually. The mean length of stay (LOS) for the inpatient unit is 8.1 days. The annual number of stool tests for CDI diagnosis on the pediatric service averages 415 test (range, 319–571). Pediatric patients identified with CDI based on positive stool polymerase chain reaction (PCR) testing are placed in private rooms with contact isolation precautions, including restriction from common play areas. Enhanced bleach-based cleaning is performed daily and at discharge.

Study design

To assess potential transmission events from oncology patients <3 years old to ward contacts, we retrospectively reviewed a cohort of pediatric *C. difficile* PCR–positive patients. So-called "donors" (D) were those patients <3 years old who plausibly could have spread CDI to other pediatric oncology patients (≤18 years old), who were defined as "recipients" (R). R cases had direct or indirect contact with D cases, defined as follows: direct contact included as an overlapping donor–recipient (D–R) stay on the study unit while, indirect contact was defined by a subsequent R admission within 12 weeks of D discharge. R cases with CDI diagnosis within 12 weeks of discharge from the unit, irrespective of CDI onset location (hospital vs community), were included in the analysis.

Any pediatric patient who tested positive for CDI based on positive PCR test from October 1, 2014, through December 31, 2017, from inpatient or outpatient pediatric treatment areas at MSK was eligible to be included in the study.

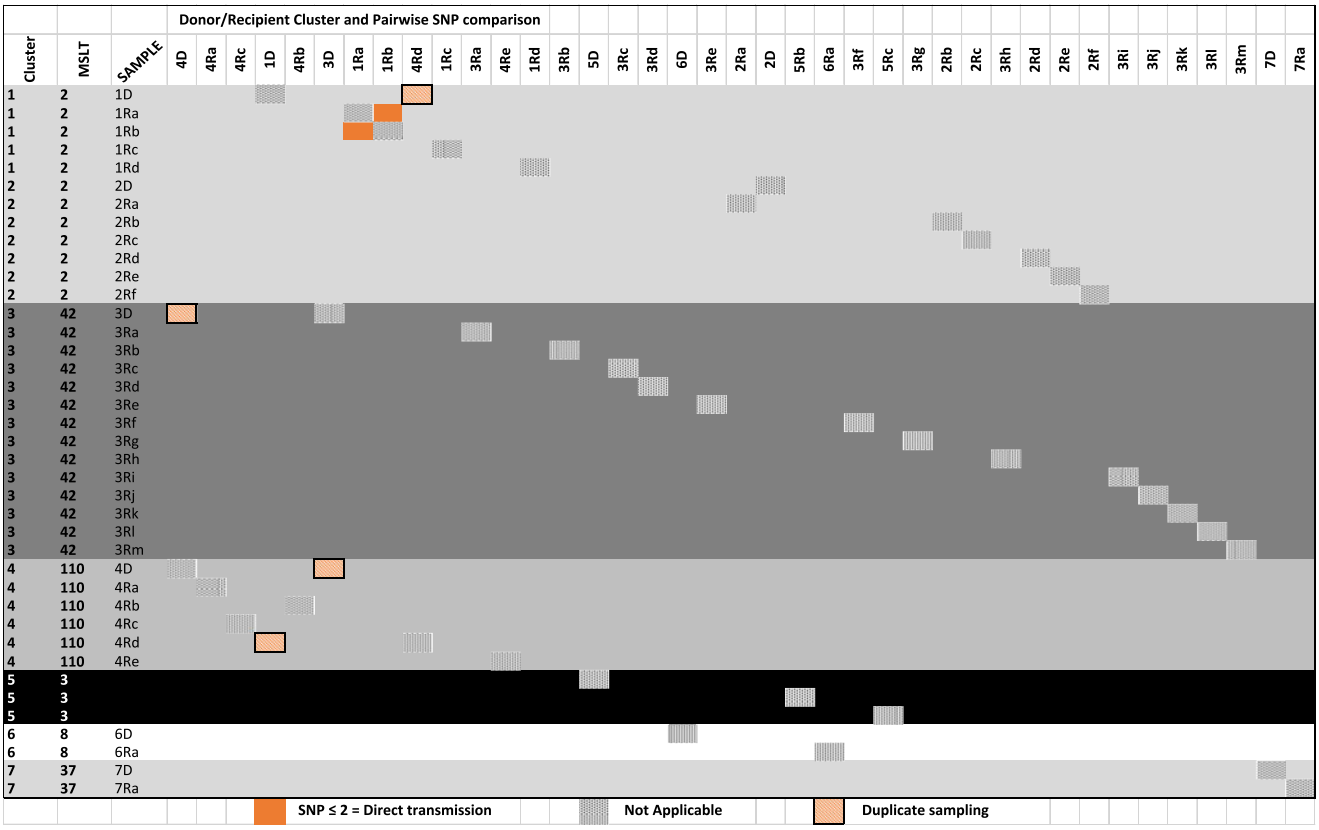

Fig. 1. Pairwise SNP difference from WGS core by MLST cluster.

Fingerprinting with multilocus sequence typing (MLST) is routinely performed on all CDI cases as part of infection control surveillance at MSK using standard methods.[10] The following criteria were used to establish putative D–R pairs: (1) concordance of D–R-infecting strains by MLST and (2) overlapping direct or indirect hospital ward contact as defined in the previous text. Potential donors were restricted to CDI cases in patients <3 years old in keeping with the aim of the study. Finally, D–R pairwise comparison of MLST concordant cases was performed using WGS to establish whether a D case was indeed the source of transmission. A cutoff of ≤2 single-nucleotide polymorphisms (SNPs) indicating direct transmission was used to assess relatedness of WGS core pairwise comparisons derived from >3,000 genes compared to the standard 7 housekeeping genes of MLST.

Laboratory methods for the diagnosis of CDI

Clinical diagnostic testing for CDI is performed using a 1-step testing platform and a single positive test result from our standard assay (Xpert C. difficile Epi assay Xpert, Cepheid, Sunnyvale, CA) defines a clinical CDI case. A rejection policy for CDI testing based on stool consistency has been in effect since October 3, 2016, and stool consistency of cohort patients is reported in the supplementary material.[11] Genetic fingerprinting of CDI positive specimens by MLST was successfully performed on 307 of 377 pediatric specimens (81%) collected during the study period. Cryopreserved stool specimens from our routine banking of *C. difficile*–positive specimens were retrieved for further analysis. Standard methods for MLST and WGS were used (see Supplementary Methods online). The MSK Institutional Review Board approved this study.

Results

During the study period, CDI was diagnosed in 224 unique pediatric patients, including 39 (17%) children <3 years old. Among these 224 patients, specimens from 194 (83%) were successfully genotyped by MLST with identification of a single sequence type (ST) type in 179 (80%), including all 39 patients <3 years old. The median age of CDI diagnosis for the entire cohort was 7 years old, and 35% of all cases were HO-CDI. The overall frequency of dominant MLST types matched the distribution among our adult patient population, with represented strains accounting for >60% of all recovered strains at the study institution (Supplementary Fig. 1 online). Hypervirulent or epidemic strains were notably absent among patients <3 years old.

We defined transmission events originating from children ≤3 years old using WGS. Overall, 39 cases of CDI in children <3 years old were identified during the study period, and 7 of these were defined as potential donors based on MLST concordance with direct and indirect unit contacts. Overall, 41 R cases were linked with the 7 D cases. The remaining 32 CDI patients ≤3 years old (82%) could not be linked to other pediatric cases with direct and indirect contact within 12 weeks and were excluded from further WGS analysis. For the 48 MLST-concordant D–R samples in 7 clusters, 39 (81%) could be retrieved for WGS phylogenetic analysis: 7 D and 32 R.

In addition, 3 donors had documented diarrheal stools during index hospitalization based on chart review. Of the 7 donors, 4 (57%) received chemotherapy and all had antimicrobial exposure in the 30 days preceding CDI diagnosis (Supplementary Table 1 online).

We detected concordance between WGS for all alleles used to determine MLST types. The pairwise comparison of WGS core data revealed 3 pairs with ≤ 2 SNP differences in our cohort (Fig. 1).

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Two of these pairs represent duplicate sampling of the same patients who were implicated as an R in one network and as a D in a subsequent network due to recovery of different MLST on separate admissions separated by >8 weeks and who may have been harboring multiple *C. difficile* strains. The third pair represented a true transmission event between patients in adjoining rooms during an overlapping admission and with CDI diagnosis 7 days apart. Neither patient in this pair was <3 years old at the time of *C. difficile* diagnosis; therefore, both were identified as recipients in the same D–R cluster. Nevertheless, this pair confirms a transmission episode based on WGS evaluation of this cohort.

Discussion

In this study, we examined direct and short-term indirect transmission of *C. difficile* originating from children <3 year old. The WGS interrogation of epidemiologically and MSLT-linked cases did not confirm any credible source of transmission from children <3 years old who tested positive for CDI. No clonal outbreaks originating from donor patients in our cohort were uncovered with the application of WGS. The contribution of common environmental reservoirs of *C. difficile* toward hospital-based transmission within the hospital environment deserves further exploration, especially among immunocompromised hosts. Previous assessments in pediatric healthcare settings including children of all ages have also found limited evidence of transmission from symptomatic children.[12,13] Most pediatric CDI cases are healthcare-associated and occur in older hospitalized children (>5 years old) with serious comorbid conditions, among which cancer is the most common.[14] In recent years CDI is increasingly been diagnosed among children <3 years old in oncology settings, largely due to the widespread use of highly sensitive molecular diagnostic methods.[6,15] Differentiating true disease from colonization can be especially challenging in younger children, particularly if adult criteria are used to define disease severity in pediatric cases.[16] The high frequency of symptomatic or asymptomatic *C. difficile* carriage in the very young posits a unique nosocomial threat to older susceptible children admitted to the same pediatric unit. Although cautious testing is advised for children <2 years old and treatment is often not indicated, control measures are almost universally instituted for *C. difficile*–positive cases. Our study sheds light on the possible transmission dynamics of *C. difficile* from patients <3 years old with likely route of cross infection to others through shared environment reservoir rather than direct patient to patient spread of a clonal strain.

Our data, although compelling for a lack of direct *C. difficile* transmission from the youngest oncology patients to other pediatric oncology patients, have some limitations. First, not all the pediatric patients identified as *C. difficile*–positive had stool retrievable for typing and subsequent sequencing, which could have led to an underestimation of overall transmission events. However, with >80% coverage of both community-acquired and healthcare-associated cases, the likelihood of missed transmission events is minimal. Our study was not designed to examine the indirect transmission potential arising from an environmental reservoir in the community or hospital setting. Finally, our WGS analysis was performed from a single colony, and a broader analysis would enable evaluation of mixed strain infections which are known to occur in up to 9%–15% of all CDI cases. Transmission from undetected coinfecting strains would be missed in our analysis, although such events may occur infrequently. Unfortunately, no benchmarks balancing cost and sensitivity exist for the number of colonies per isolate to sequence in WGS epidemiologic investigations evaluating transmission.[17,18]

In summary, the findings from our study do not indicate that CDI patients <3 years old pose a substantial immediate transmission risk to other hospitalized patients. Routine *C. difficile* testing, which often begets CDI treatment, should be balanced with downstream consequences, including potential for alterations of gut microbiome.[19] Transmission-based precautions are unlikely to further reduce CDI rates in this age group based on the dynamics revealed here, and larger epidemiologic studies are needed to identify appropriate scalable CDI prevention efforts.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.360

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Conflicts of Interest. All authors report no conflicts of interest relevant to this article.

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