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RESEARCH BRIEFS

Using Clinical Scenarios to Understand Preventability of *Clostridium difficile* Infections by Inpatient Antibiotic Stewardship Programs

Clostridium difficile infections (CDIs) pose an urgent threat to public health.¹ Both the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend 2 approaches to combat CDI: (1) infection prevention interventions to limit transmission of *C. difficile* from infected patients and (2) antimicrobial stewardship to limit unnecessary antimicrobial use. Antibiotic stewardship programs (ASPs) have been shown to effectively reduce CDI, but ASPs cannot directly address non-antimicrobial factors that contribute to CDI, including chemotherapy, immunosuppressant medications, surgery, gastrostomy or jejunostomy tubes, gastric acid suppression, and consumption of processed meats.^{2,3}

Thus, we designed a 2-phase study (1) to define the types of CDI that clinicians consider unlikely preventable by inpatient ASPs and (2) to estimate the relative proportion of inpatient CDI cases at a tertiary-care hospital that belongs to this category of “nonpreventable” CDI.

This study was conducted at Duke University Hospital (DUH), a 924-bed, quaternary-care, academic medical center. First, study investigators presented 11 hypothetical clinical scenarios with various CDI onset locations (ie, hospital onset [HO] vs community onset [CO]), preceding antibiotic exposure, and stewardship interventions (eg, change of antibiotic). We queried 29 infectious diseases physicians using a 2-step Delphi survey to determine the perceived preventability of CDI.⁴ Each respondent was asked to use a 5-point Likert scale to indicate whether they agreed that the CDI scenario would be preventable by an inpatient ASP. In round 2, participants were provided the average responses from round 1 and were asked to repeat the survey. Consensus was defined a priori as >80% of respondents indicating “strongly agreed” and/or “agreed” or “strongly disagreed” and/or “disagreed.” In round 1, 22 individuals responded, and 10 responded in round 2. Answers from round 2 were used to determine consensus except when participants failed to respond in round 2, in which case the responses from round 1 were used.

Second, we performed a retrospective cohort study of CDI cases among inpatients at DUH from January to December 2014. CDI cases were extracted from the infection control database. CDI cases were defined using National Healthcare Safety Network (NHSN) surveillance definitions and were categorized as hospital onset (HO CDI), community onset (CO CDI), or community-onset healthcare-associated (CO-HCFA CDI).⁵ Patient records were reviewed to determine

whether antibiotics had been administered during the current hospitalization prior to CDI diagnosis. Additionally, records from 5% of the cohort patients were reviewed to validate CDI cases and probable location of acquisition. The DUH Institutional Review Board approved the study.

Survey respondents agreed that 4 CDI scenarios were unlikely to be prevented by inpatient ASP efforts: CO CDI, CO-HCFA CDI, HO CDI in the absence of preceding antibiotics, and relapse of HO CDI (Table 1).

A total of 432 CDI cases were detected during the study period; 183 cases (42%) belonged to 1 of the 4 previously mentioned scenarios deemed to be unlikely to be prevented by inpatient ASP according to the Delphi survey results (Table 1). Of these 183 cases, 123 cases (67%) were CO CDI, 36 cases (20%) occurred in HO-CDI patients without recorded antibiotic exposure within 90 days, 20 cases (11%) were CO HCFA, and 4 (2%) were relapsed HO CDI. In addition, in 19 HO-CDI cases, patients received a single dose of antibiotics, either for surgical prophylaxis or empirical therapy, prior to developing CDI.

We found that nearly half of all CDI cases at our hospital were unlikely to be prevented by activities of an inpatient ASP. While numerous studies show the benefits of ASPs, our study is the first to describe the proportion of CDI cases unlikely to be prevented by inpatient ASPs. In our cohort study, most “nonpreventable” cases were CO CDI cases (67%). CO CDI cases made up 28% of all CDIs detected during the study period. Because other studies found that approximately 50% of hospitalized CDI cases are CO,⁶ an even greater proportion of CDI cases at other hospitals may not be prevented by activities of their local inpatient ASPs.

While inpatient ASPs may not be able to affect the development of CO CDI, interventions implemented by outpatient ASPs could have a big impact because most antibiotics are prescribed in the outpatient setting, where overuse is common. Moreover, 2 prior systematic reviews have concluded that outpatient ASPs can reduce inappropriate use and/or selection of antibiotics.^{7,8} Indeed, the Centers for Medicare and Medicaid Services (CMS) has commenced discussions on policies relating to ASP interventions in ambulatory clinics and in long-term-care facilities outside acute-care hospitals.⁹ Our data support the need for more comprehensive outpatient ASP interventions.

This study had several limitations. First, the study was performed at a single academic center and the results may not be applicable to all hospitals. Second, the 11 clinical scenarios used in the survey were not representative of all possible CDI cases. Finally, there was a low response rate in round 2 of the survey.

In conclusion, a subset of hospitalized CDI cases, including community-onset cases and cases arising in patients without preceding inpatient antimicrobial exposure, are unlikely to be

TABLE 1. Results of a Delphi Survey of Preventability of *Clostridium difficile* Infection by an Inpatient Antimicrobial Stewardship Program and the Proportion of "Nonpreventable" Cases at Duke University Hospital, 2014

Variable	Delphi Survey Results, N = 22		
	Round 1 Agreement, No. (%)	Round 2 Agreement, No. (%)	DUH Cases, No. (%) (N = 432)
"Nonpreventable" Based on Survey Consensus			
Community onset CDI	21 (95)	21 (95)	123 (28)
Community onset healthcare-associated CDI	19 (86)	19 (86)	20 (5)
Hospital onset, absence of antibiotic exposure	17 (77)	18 (82)	36 (9)
Hospital onset, relapsed CDI	18 (82)	18 (82)	4 (1)
Total			183 (42)
Indeterminate Preventability Based on Survey Consensus			
	Round 1 Agreement, No. (%)	Round 2 Agreement, No. (%)	
Hospital onset, recurrent CDI	14 (64)	14 (64)	...
Hospital onset, antibiotics deemed appropriate by ASP review	17 (77)	16 (72)	...
Hospital onset, inpatient ASP changed antibiotics but CDI occurred within 24 h of change	17 (77)	15 (68)	...
Hospital onset, inpatient ASP changed antibiotics to another broad-spectrum agent	11 (50)	11 (50)	...
Hospital onset, inpatient ASP changed antibiotics to decrease risk of CDI	14 (64)	14 (64)	...
Hospital onset, inpatient ASP considered antibiotics appropriate but decreased duration	14 (64)	15 (68)	...
Hospital onset, patient did not qualify for inpatient ASP review	14 (64)	14 (64)	...

NOTE. DUH, Duke University Hospital; ASP, antimicrobial stewardship program, CDI, *Clostridium difficile* infection.

prevented by an inpatient ASP. These findings suggest that key stakeholders must (1) expand outpatient antimicrobial stewardship programs to address unnecessary antimicrobial use outside of hospital settings and (2) devise new strategies to prevent CDIs that occur in the absence of antimicrobial exposure or following appropriate antimicrobial exposure. Such strategies include selective use of vaccines and new technologies to assess and manipulate the microbiome in high-risk patients.

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Neonatal Outbreak of Methicillin-Resistant *Staphylococcus aureus* Clone Geraldine: A Bundle of Measures to Halt Transmission

Methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks are frequent in neonatal intensive care units (ICUs).¹ Toxic-shock-syndrome toxin 1 (TSST-1)–producing MRSA Geraldine clone represented 6.3% of invasive MRSA isolates in France in 2006 and 2007,² and has been implicated in one outbreak among newborns.³ We describe here a neonatal MRSA Geraldine clone outbreak.

On March 31, 2014, a TSST-1–positive MRSA was isolated in bronchial aspirates from 2 ICU neonates (case patients 3 and 4) (Figure 1). Our subsequent investigation identified 2 prior cases of TSST-1 MRSA carriage, the index case 1 by umbilical swab in November 2013 and case 2 by bronchial aspirate in December 2013. A case was defined as a positive culture for an MRSA strain expressing TSST-1 and/or specific antibiotic susceptibility in a patient hospitalized in the neonatal ICU or general neonatal ward. In total, we identified 8 cases (7 cases of carriage and 1 skin infection) over a 9-month period (Figure 1). All case patients were premature (26–30 weeks gestation; mean birth weight, 975.2 g) and were hospitalized in the neonatal ICU. Among them, the mean interval of MRSA carriage detection was 25.1 hospitalization days, and mean length of ICU stay was 33.1 days. During the outbreak, case surveillance consisted of weekly nasal *S. aureus* carriage screening of the neonates of both wards; this procedure remained in place for 5 months after the last case was discovered. All MRSA isolates expressed resistance to penicillin G, methicillin, kanamycin, tobramycin, and fucidic acid according to guidelines of the French Antibiogram Committee. All of the isolates were typed by the National Reference

Center for staphylococci (*S. aureus* Genotyping Identibac, Alere, Waltham, MA) and were identified as the Geraldine clone, which is characterized by the following criteria: (1) sequence type ST5, *agr2*, (2) positivity for TSST-1, enterotoxins SEC, SED, SEJ, SEL, and SER as well as the *egc* locus, and (3) negativity for Pantone-Valentine leukocidin.⁴ All case isolates underwent molecular analysis except strains from cases 1 and 2, as these strains had not been stored.

Immediately after the alert, we implemented contact precautions (ie, glove and gown usage) for HCP in contact with infected and colonized neonates. We also held information meetings for healthcare personnel (HCP) and audited HCP practices. The audit revealed a lack of consistency in standard precaution application and hygiene practices. The control measures implemented consisted of team support for multidrug-resistant bacteria management, standard precautions, and hand-hygiene reinforcement. We focused on the use of hydroalcoholic solutions, lack of hand jewelry verifications, and daily changes of work outfits. We assessed the effectiveness of these measures using indicators such as bedsores prevalence, cleaning activities records, environmental samples, and compliance with hand hygiene procedures, which was assessed by hydroalcoholic solutions consumption according to French guidelines.⁵ Compliance to the minimum hydroalcoholic consumption, calculated according to clinical activity, increased from 57.4% 6 months before the outbreak to 84.4% during the outbreak to 102.9% 6 months after the outbreak.

We sought environmental links between cases. In total, 60 environmental swabs and 20 surface samples from patient rooms, drug preparation area, transfrontanelar ultrasound apparatus, and x-ray devices were tested between May 3 and June 25, 2014. No medical devices or environmental sources were found to be involved in transmission.

Despite the control measures, transmission continued. Some carrier neonates were hospitalized in neighboring rooms (Figure 1), suggesting possible cross transmission via HCP hands, especially because HCP compliance to the measures was not consistent at the beginning of the outbreak. In addition, *S. aureus* may have been spread by airborne transmission by HCP.⁶ The long interval between the first 2 and subsequent 6 cases also pointed to HCP carriage. HCP are often involved in horizontal MRSA transmission to neonates,^{6,8} and HCP decolonization is a proven outbreak control measure.^{3,7,8} We opted for universal decolonization of all HCP, both permanent and rotating staff (including students, radiology technicians, radiologist physiotherapist, psychologist, milk-bank technicians, cleaning staff, social workers, laboratory couriers, and secretaries), regardless of their screening results, in order to cover the risk of false negatives due to intermittent carriage. We sampled both the noses and throats of the HCWs to improve sensitivity.⁹ Decolonization consisted of a 5-day course based on twice-daily mupirocin nasal ointment and daily showering with chlorhexidine soap,¹⁰ which were dispensed to each HCP during screening interviews to promote adherence. HCP voluntarily participated in decolonization; no