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Evolving Insights Into the Epidemiology and Control of *Clostridium difficile* in Hospitals

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Typing studies suggest that most cases of hospital-onset *Clostridium difficile* infection (CDI) are unrelated to other cases of active disease in the hospital. New cases may instead be due to transmissions from asymptomatic carriers or progression of latent *C. difficile* present on admission to active infection. Direct exposure to antibiotics remains the primary risk factor for CDI but ward-level antibiotic use, antibiotic exposure of the prior room occupant, and *C. difficile* status of the prior room occupant increase risk for *C. difficile* acquisition while antibiotic exposure, gastric acid suppression, and immunosuppression increase risk for progression to infection. These insights suggest possible new approaches to prevent CDI, including screening to identify and isolate carriers, universal gloving, greater use of sporicidal cleaning methods, enhancing antibiotic and possibly proton pump inhibitor stewardship, and prescribing prophylactic vancomycin and/or probiotics to colonized patients to prevent progression from colonization to infection. We review current evidence and questions related to these interventions.

Keywords. *Clostridium difficile*; infection control; screening and isolation; environmental cleaning; antibiotic stewardship.

Current practices to prevent *Clostridium difficile* infection (CDI) have reduced hospital-onset CDI, but new cases remain common [1–3]. A growing number of studies challenge the long-standing theory that most new cases of hospital-onset CDI are attributable to organisms and spores from symptomatic patients. Typing studies find that only 10%–30% of hospital-onset CDI can be linked to concurrent or prior inpatients with symptomatic CDI [4–9]. This suggests that many cases may instead be due to activation of latent *C. difficile* present on admission or transmission from asymptomatic carriers in the hospital. We will review recent data on the epidemiology of *C. difficile* transmission, activation, and prevention, and consider their implications for hospital-based infection control programs.

NEWER INSIGHTS INTO THE EPIDEMIOLOGY OF *CLOSTRIDIUM DIFFICILE*

Sequencing Studies

In 2013, Eyre and colleagues used whole-genome sequencing to evaluate *C. difficile* transmission within a network of hospitals with robust infection control programs [9]. Among 957 specimens from incident symptomatic CDI cases over a 3.6-year period, only 333 (35%) were closely genetically related to a previous case. Of those, only 181 could be linked to a concurrent or prior CDI case that received care in the same hospital. All told, only 181 of 957 (19%) CDI patients were infected with strains traceable to current or prior inpatients with CDI. Other investigators have made similar observations [4–8].

Discontinuing Contact Precautions for *Clostridium difficile* Infection Patients

Widmer and colleagues reasoned that if most cases of hospital-onset CDI are not attributable to contact with concurrently hospitalized CDI patients, then routine contact precautions for all CDI patients might not be necessary [10]. They discontinued contact precautions for all CDI patients in their hospital except for those with hypervirulent ribotypes or stool incontinence. They then assessed for transmissions between CDI patients and same-room occupants using ribotyping. Toxigenic *C. difficile* was acquired in 27 of 451 (6.0%) roommates exposed to 279 CDI patients. The index patient's and same-room occupant's *C. difficile* isolates had matching ribotypes in only 6 of the 27 cases, for a net transmission rate of 6 of 451 (1.3%). The investigators did not assess for delayed transmission to subsequent room or ward admissions (they evaluated concurrent room occupants alone), so the study may have underestimated transmissions. In addition, the investigators noted a significant increase in overall *C. difficile* rates during the study, suggesting that discontinuing precautions for patients with known CDI may increase transmission risk. Nonetheless, this study supports the contention that known CDI cases account for only a small number of new CDI cases.

If the majority of hospital-onset CDI is not attributable to symptomatic inpatients, then where does hospital-onset CDI come from? Possible explanations include transmission from

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asymptomatic carriers via healthcare workers and/or the environment, activation of latent endogenous *C. difficile* present on admission, or acquisition of latent spores present in the hospital environment from patients admitted years prior (Eyre and colleagues' study included almost 4 years worth of surveillance [9], so the latency period would have to be very long indeed).

Clostridium difficile in Asymptomatic Carriers

Screening studies suggest that toxigenic *C. difficile* is present on admission in 4.1%–15% of asymptomatic adult inpatients (Table 1) [11–17]. A recent meta-analysis suggested the rate of colonization present on admission may be increasing over time and currently stands at 10.0% (95% confidence interval [CI], 7.1%–13.4%) in North America [18]. These patients constitute a substantial reservoir of *C. difficile* that may play an important role in hospital-onset CDI and nosocomial transmission.

Risk of Progression From Asymptomatic Colonization to Clinical Infection

Older series suggested that the risk of progression from asymptomatic colonization to clinical infection is low and that *C. difficile* colonization may be protective against infection [19]. These studies did not consistently differentiate between colonization with toxin producing vs nonproducing strains and sometimes assessed for colonization some time after admission. More recent series suggest the risk of progression from colonization to infection is about 10%–15% (Table 1) [20–22]. Asymptomatic carriers are about 6 times more likely to develop CDI compared to noncarriers [18]. Noncarriers who acquire CDI after admission still account for more cases overall given that the risk of active infection is particularly high immediately after *C. difficile* acquisition and that there are many more noncarriers than carriers in the general hospital population [23]. Nonetheless, colonized patients' high risk for CDI makes them an attractive target for directed interventions.

Risk Factors for Progression From Colonization to Infection

Risk factors for progression from colonization to infection have not been well characterized. Loo and colleagues demonstrated that risk factors for colonization and infection differ [24]; the same may be true of risk factors for progression from colonization to infection. Recent hospitalizations, chemotherapy, gastric acid suppressants, and antibiotics have been associated with colonization [17, 18, 24–26]. Older age, antibiotics, and proton pump inhibitors (PPIs) have been associated with infection [18, 24]. The data on the association between antibiotics and colonization are mixed, as are the data on the association between gastric acid suppressants and both colonization and infection [13, 17, 18, 21, 24–29]. Two small studies in colonized patients specifically sought risk factors for progression from colonization to active infection. Both identified antibiotics as risk factors; 1 also found identified PPIs as a risk factor [25, 30].

These analyses imply that enhanced antibiotic stewardship and possibly PPI stewardship programs could help protect colonized patients from progression to infection. Audits indicate that 30%–64% of antibiotics and 33%–47% of gastric acid

Table 1. Selected Studies of Asymptomatic Toxigenic *Clostridium difficile* Colonization in Hospitalized Adults

Study, First Author	Setting	Timing of Testing	*Clostridium difficile* Assay	Sample Size and Colonization Rate	Progression to Active Infection
McFarland, 1989 [11]	Academic hospital, Seattle	At hospital admission	Culture	29/428 (6.8%)	4/29 (13.8%)[a]
Kyne, 2000 [15]	Academic hospital, Boston	At hospital admission, patients on antimicrobials expected to stay >2 d	Cytotoxicity assay + culture	18/271 (6.6%)	NR
Curry, 2013 [12]	Academic hospital, Pittsburgh	Patients undergoing VRE screening on admission and weekly for selected high-risk populations	Cytotoxicity assay + culture	314/3006 (10.4%)	NR
Leekha, 2013 [16]	Academic hospital, Rochester, Minnesota	At hospital admission	PCR	31/320 (9.7%)	NR
Alasmari, 2014 [13]	Academic hospital, St. Louis	Within 48 h of hospital admission	Culture	40/259 (15.4%)	NR
Kong, 2015 [17]	6 academic hospitals, Quebec and Ontario	At hospital admission	Culture	212/5232 (4.1%)	NR
Lin, 2015 [30]	District hospital, Taiwan	During hospitalization	PCR	86/483 (17.8%)	14/86 (16.3%)
Longtin, 2016 [14]	Tertiary hospital, Québec City	At hospital admission	PCR	368/7599 (4.8%)	NR
Tschudin-Sutter, 2015 [22]	Academic hospital, Baltimore	At intensive care unit admission	PCR then toxigenic culture	17/542 (3.1%)	2/17 (11.8%)
Truong, 2017 [21]	Academic hospital, Stanford	At hospital admission	PCR	43/365 (11.8%)	5/43 (11.6%)
Blixt, 2017 [20]	2 academic hospitals, Copenhagen	At hospital admission	PCR then culture	193/3141 (6.1%)	23/225 (10.2%)[b]

Abbreviations: NR, not reported; PCR, polymerase chain reaction; VRE, vancomycin-resistant *Enterococcus*.

[a]Includes patients with nonspecific colitis (n = 3) and pseudomembranous colitis (n = 1).

[b]Includes multiple admissions for some patients.

suppressants administered to hospitalized patients may be inappropriate [28, 31–35].

Clostridium difficile Transmission by Asymptomatic Carriers

Asymptomatic carriers of *C. difficile* can spread spores to healthcare workers' hands and clothing, fomites, the environment, and other patients. In a prospective study of long-term-care residents during a CDI outbreak, *C. difficile* could be recovered from the skin and environment of almost two-thirds of asymptomatic carriers [36]. Skin and environmental isolates matched patients' rectal specimens in the majority of cases. Asymptomatic carriers contaminated their skin and the environment at similar rates regardless of whether they were continent or incontinent of stool. Other investigators have also found high rates of environmental contamination in the rooms of asymptomatic carriers [11, 12, 37].

Clostridium difficile transmission from asymptomatic carriers is well documented [12, 20, 38–40]. One of the first studies to demonstrate this was conducted almost 30 years ago [40]. Investigators obtained weekly stool samples from 634 inpatients and classified *C. difficile* strains by restriction endonuclease analysis. They identified 19 nosocomial transmissions. In 15 of 19 (79%) cases, the source patient was asymptomatic. This study included both toxigenic and nontoxigenic *C. difficile* strains, however, which might have led them to overestimate the contribution of asymptomatic carriers to CDI.

More recently, Curry and colleagues used vancomycin-resistant *Enterococcus* perirectal swabs to screen for asymptomatic *C. difficile* carriers and multilocus variable number of tandem repeats analysis (MLVA) to evaluate genetic relatedness between isolates [12]. Based on MLVA, 17 of 56 (30%) hospital-onset CDI cases were acquired from patients with symptomatic CDI and 16 of 56 (29%) were acquired from asymptomatic carriers.

Blixt and colleagues prospectively screened all patients admitted to 2 Danish hospitals over a 4-month period [20]. Patients admitted to wards with 1 or more asymptomatic carriers were almost twice as likely to develop CDI as patients admitted to wards without carriers (CDI rate, 4.6% vs 2.6%; odds ratio [OR], 1.79 [95% CI, 1.16–2.76]). Findings were similar when restricted to roommates of asymptomatic carriers. The investigators were able to confirm transmission from an asymptomatic carrier in 20% of new CDI cases. The low confirmation rate may have been because investigators only looked for transmissions between concurrent ward contacts; some transmissions may have been due to residual environmental contamination from more remote cases or transmission via healthcare workers and fomites from other parts of the hospital. In addition, the investigators were unable to culture and type 22% of carriers' samples.

Two additional studies provide indirect evidence of transmission from asymptomatic carriers and bespeak the importance of antibiotic pressure as a risk factor for *C. difficile* transmission. Investigators from Toronto reviewed patients admitted to a large academic hospital over a 46-month period [41]. Among 34 298 inpatients without previous CDI, 255 developed infection. The relative risk of CDI increased by 34% (relative risk [RR], 1.34 [95% CI, 1.16–1.57]) for every 10% increase in ward-level patient-days of antibiotic therapy. The increase in CDI due to ward-level prescribing was similar in patients who did and did not receive antibiotics themselves. In the second study, investigators assessed CDI risk as a function of the prior room occupant's antibiotic exposures [42]. Among 288 patients that developed hospital-acquired CDI, prior occupant antibiotic exposure increased CDI risk by about 20% (hazard ratio, 1.22 [95% CI, 1.02–1.45]).

POTENTIAL NEW APPROACHES TO PREVENTING *CLOSTRIDIUM DIFFICILE* INFECTION

The emerging picture from these studies is that a large fraction of hospital-onset CDI may be due to transmission from asymptomatic carriers or progression from asymptomatic colonization present on admission to symptomatic CDI. These insights suggest potential new strategies to decrease hospital-onset CDI.

Preventing Transmission From Asymptomatic Carriers

Strategies that might decrease transmission from asymptomatic carriers include (1) enhanced environmental cleaning for carriers or for all patients; (2) universal gloving to care for all patients; (3) active case finding to identify asymptomatic carriers; and (4) stronger antibiotic and possibly PPI stewardship programs. These pathways are not mutually exclusive and may be synergistic. For example, one might target carriers identified through screening for enhanced environmental cleaning and more stringent stewardship efforts.

Enhanced Environmental Cleaning

The potential value of enhanced environmental cleaning follows from observations that both symptomatic and asymptomatic patients shed *C. difficile* into the environment, and that patients in rooms previously occupied by CDI patients or by patients on antibiotics are at increased risk of CDI [37, 42–44].

One way to augment environmental cleaning would be to use sporicidal agents to clean all inpatient rooms regardless of CDI status either daily or upon discharge. Many hospitals currently use sodium hypochlorite (bleach) for terminal cleaning of CDI rooms as it is sporicidal [45, 46]. Some hospitals, however, have extended this practice to include daily cleaning of all inpatient rooms, particularly during outbreaks.

Barnes Jewish Hospital in St Louis, for example, introduced a CDI prevention bundle to combat high CDI rates in their medical intensive care and bone marrow transplant units [47]. The bundle included staff education, contact precautions, hand washing signs, and daily bleach-based cleaning of all inpatient rooms. Following introduction of the bundle, CDI rates dropped by 48%–64%. Similarly, Mayo Clinic reported an 85% drop in

CDI rates in high-incidence wards following the introduction of daily bleach-based room cleaning for all patients [48].

Daily cleaning with sporicidal agents in all patient rooms has not yet been widely adopted. Barriers include odor, staff and patients' chemical sensitivities to bleach and other sporicidal agents (such as hydrogen peroxide plus peracetic acid), and corrosion of hospital equipment and the environment [49]. Developing better-tolerated sporicidal agents could help make routine cleaning with sporicidal agents more feasible.

Another option is hydrogen peroxide vapor or ultraviolet (UV) light decontamination after discharge cleaning. A number of observational studies have reported lower CDI rates [50–54]. These studies were limited, however, by before–after design and small sample sizes. Two higher-quality studies were recently published. Investigators from Duke University conducted a cluster-randomized crossover trial of UV disinfection for terminal room cleaning in 9 hospitals. The rooms of all patients with *C. difficile* were cleaned with bleach with or without UV light following discharge. The addition of UV did not change CDI rates in subsequent room occupants compared to terminal cleaning with bleach alone (RR, 1.0 [95% CI, .57–1.75]) [55]. The investigators did not report on the impact of UV disinfection on *C. difficile* rates in subsequent occupants of non-CDI rooms, however, leaving unanswered whether broader utilization of UV could decrease transmission from occult, asymptomatic carriers of *C. difficile.* In the second study, investigators from the University of Pennsylvania added UV light to terminal cleaning with bleach for patients with CDI and patients on contact precautions for other antibiotic-resistant pathogens [56]. CDI rates dropped by 25% on intervention units and rose by 16% on nonintervention units (incidence rate ratio, 0.49 [95% CI, .26–.94]). The study design did not allow the investigators to disentangle whether lower CDI rates were primarily due to enhanced disinfection of the rooms occupied by patients with known CDI, enhanced disinfection of the rooms occupied by patients with contact precautions for other reasons, or both.

Universal Gloving

Healthcare workers caring for patients with *C. difficile* frequently contaminate their hands with *C. difficile* [57]. Staff caring for occult *C. difficile* carriers may thus unwittingly transfer *C. difficile* between patients. Alcohol-based hand rub has a minimal effect on spores [58–60]. Washing with soap and water is more effective but does not completely eliminate spores and is difficult to encourage as it is inconvenient, time consuming, and apt to cause dry skin [61, 62]. Wearing gloves, however, is associated with lower hand contamination rates and clinical *C. difficile* rates and may be more acceptable to staff than requiring hand hygiene with soap and water after all patient contacts [63, 64]. Johnson and colleagues observed a significant decrease in both symptomatic CDI and asymptomatic *C. difficile* carriage rates in wards assigned to universal glove use compared to their preglove rates and concurrent control wards' rates [64].

Screening to Identify Asymptomatic Carriers

Another strategy to prevent transmission from asymptomatic carriers is active screening to identify occult *C. difficile* carriers followed by implementation of contact precautions. One hospital in Québec reported on screening all inpatient admissions for *C. difficile* using rectal swabs and polymerase chain reaction [14]. Carriers were placed on a limited version of contact precautions until discharge (gloves, no gown, room sharing permitted). CDI rates decreased from 6.9 to 3.0 cases per 10 000 patient-days. Rates in other Québec hospitals without screening, by contrast, were stable during this period. Universal screening is controversial, however, because of the large effort involved, discomfort for patients, potential negative impact on bed flow, and the cost of materials to screen, test, and isolate. It is also unclear whether screening in Québec reduced CDI rates through isolation, modified medical management of known carriers, or other concurrent efforts to prevent CDI and other infections.

Focused screening of high-risk patients may be a way to streamline this program and increase acceptability. For example, restricting screening to patients with prior admissions, prior CDI, and/or recent antibiotic use could identify the majority of *C. difficile* carriers [16, 18, 65]. Modeling studies predict that screening and isolation of asymptomatic carriers could reduce hospital-onset CDI by 10%–25% and hospital-onset colonization by 40%–50% [66, 67].

Antimicrobial Stewardship

The observations that ward-level antibiotic prescribing and prior room occupant antibiotic exposures increase CDI risk in antibiotic unexposed patients hint that population-level antimicrobial stewardship might prevent transmission from asymptomatic carriers. Multiple investigators have documented that implementing hospital and community antibiotic stewardship programs are associated with significant decreases in CDI rates [68, 69]. To our knowledge, however, no study has directly assessed the extent to which antimicrobial stewardship can prevent transmission from asymptomatic carriers in particular.

Preventing Progression From Asymptomatic Colonization to Clinical Infection

If asymptomatic carriers are common in the hospital population and these patients are at high risk for progression from colonization to clinical infection, then preventing progression could reduce hospital-onset CDI rates. The primary modifiable risk factors for developing CDI are antibiotics and PPIs. Potential strategies to prevent CDI therefore could include enhanced antimicrobial stewardship, PPI stewardship, and prophylaxis with antibiotics and/or probiotics.

Antimicrobial Stewardship

Ample data suggest that antimicrobial stewardship programs can lower CDI rates [68]. To our knowledge, however, no studies have specifically evaluated the impact of antimicrobial stewardship targeted toward known carriers. Targeting known carriers for extra stewardship interventions such as pharmacist review or infectious disease consultation is appealing: Providers may be more willing to follow stewardship advice if they know their patient is colonized, and targeting high-risk patients could help make stewardship programs more efficient. This strategy is contingent, however, on knowing patients' colonization status and thus needs to be balanced against the complexity and cost of screening.

Proton Pump Inhibitor Stewardship

There are very few data available on the impact of PPI stewardship on CDI rates. One quasi-experimental study of a computerized order entry alert targeting dual use of antibiotics and PPIs showed a significant reduction in coadministration of these agents but no change in adjusted monthly CDI rates [70]. This strategy requires further evaluation.

Antibiotic Prophylaxis and Decolonization

A few studies have assessed whether prophylactic antibiotics can prevent CDI in colonized patients. Johnson and colleagues randomized asymptomatic carriers to metronidazole vs vancomycin vs placebo. *Clostridium difficile* colonization persisted in most patients randomized to metronidazole and placebo; patients randomized to vancomycin had transient negative stool cultures for *C. difficile*, but most developed positive cultures again within 2 months [71]. Rodriguez and colleagues retrospectively evaluated whether oral metronidazole given for non–*C. difficile* indications prevented CDI in patients receiving ciprofloxacin or piperacillin-tazobactam; patients who received oral metronidazole had significantly lower CDI rates (OR, 0.21 [95% CI, .11–.38]) [72]. Likewise, Van Hise and colleagues compared recurrent CDI rates in patients who received oral vancomycin along with broad-spectrum antibiotics vs those receiving broad-spectrum antibiotics alone. CDI recurred in 4.2% of patients who received oral vancomycin prophylaxis vs 26.6% of patients who did not (OR, 0.12 [95% CI, .04–.4]) [73]. Although these studies are promising, their retrospective design leaves open the possibility of residual confounding. Fecal microbiota transplantation is gaining in popularity, and may one day represent a unique option for targeted *C. difficile* decolonization or normal bowel repopulation among high-risk asymptomatic carriers.

Probiotic Prophylaxis

Probiotics may also help prevent CDI in high-risk patients [74–76]. A recent meta-analysis of 26 randomized controlled trials with almost 8000 participants reported a 60% reduction in CDI (RR, 0.40 [95% CI, .29–.53]; $I^2 = 0\%$) [74]. Some of the early studies included in the meta-analysis reported very high CDI rates (up to 25%), likely indicating they were biased toward sicker patients. More recent, larger and more robust trials have reported much lower rates (0.8%–3.0%), which may in turn explain why they failed to detect a benefit to probiotics (underpowered) [77]. Targeting higher-risk patients, such as those known to harbor *C. difficile*, may make this intervention more impactful. Note that probiotics are not appropriate for highly immunocompromised patients given reports of probiotic-associated bacteremia and fungemia [78–80].

CONCLUSIONS

A growing body of literature is enhancing our understanding of *C. difficile* transmission and the transition from asymptomatic *C. difficile* carriage to clinical infection. There is increasing recognition of the importance of asymptomatic carriers as sources of *C. difficile* transmission and infection, the direct and indirect impact of antibiotic and PPI exposure on CDI risk, and the potential value of prophylactic antibiotics and/or probiotics to diminish risk. These insights present the possibility of new strategies to reduce the risks of *C. difficile* acquisition and infection in healthcare settings, such as screening and isolating asymptomatic carriers, universal gloving, greater use of sporicidal methods for environmental cleaning, ward-level and targeted antibiotic stewardship, PPI stewardship, and use of prophylactic antibiotics and/or probiotics to prevent CDI in known carriers. These approaches all require further study, however, as significant questions remain. These include characterizing the relative importance of transmission from symptomatic patients vs transmission from asymptomatic patients vs endogenous progression from asymptomatic colonization to active infection; the burden vs benefit of universal vs targeted vs no screening for carriers; and whether targeting known carriers for enhanced environmental cleaning, augmented antibiotic stewardship, PPI stewardship, antibiotic prophylaxis, and/or probiotic prophylaxis can increase the efficiency and net benefit of these interventions. Cost–benefit evaluations should take into account feasibility, resources, staff tolerance, patient acceptability, and impact on bed flow in addition to *C. difficile* rates. Despite the success of standard prevention measures, *C. difficile* infection rates remain unacceptably high. Innovative approaches are needed.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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