Current Trends in the Epidemiology and Outcomes of *Clostridium difficile* Infection

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*Clostridium difficile* is the most frequently identified cause of nosocomial diarrhea and has been associated with epidemics of diarrhea in hospitals and long-term care facilities. The continued increase in *C. difficile* infection (CDI) suggests that it has surpassed other pathogens in causing healthcare-associated infections. The Centers for Disease Control and Prevention recently identified CDI as an “urgent threat” in its recent report on antibiotic resistance threats in the United States, highlighting the need for urgent and aggressive action to prevent this infection. The impact of antibiotics as a risk factor for new-onset CDI is well established; however, recognizing classes of antibiotics with the highest risks and reducing unnecessary antibiotic use are important strategies for prevention of CDI and subsequent recurrence. In addition, the recognition of the community as an important setting for onset of CDI presents a challenge and is an area for future research.

**Keywords.** *Clostridium difficile*; epidemiology; costs.

*Clostridium difficile* is a spore-forming gram-positive anaerobic bacillus that causes gastrointestinal infections in humans, ranging in severity from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, colonic perforation, and death [1]. It is the most frequently identified cause of nosocomial diarrhea, has been associated with epidemics of diarrheal disease in hospitals and long-term care facilities [1–5], and is associated with increased healthcare utilization, morbidity, and mortality [6, 7]. The Centers for Disease Control and Prevention (CDC) reports that CDI is associated with 14,000 deaths in the United States each year and more than $1 billion in excess medical costs [7]. Despite the availability of clinical practice guidelines for the prevention, diagnosis, and treatment of *C. difficile* infection (CDI), the rate of CDI continues to rise in the United States [5]. In addition, recent epidemiologic data suggest that *C. difficile* is becoming an important pathogen in the community, with a number of reports identifying a significant proportion of CDI symptoms developing outside the healthcare setting [8, 9]. This review describes the current epidemiology of CDI and its impact on morbidity, mortality, and costs. An overview of the key findings on rates, risk factors, and outcomes provided in this review is shown in Tables 1–3.

**BURDEN OF CDI AND EPIDEMIOLOGIC ONSET**

The prevalence of *C. difficile* has been on the rise in the United States, and in fact the CDC identified CDI as one of the highest threats in its recent report on antibiotic resistance in the United States. This designation as an “urgent threat” highlights the need for immediate and aggressive action to prevent this infection [7]. In fact, CDI has been reported as the most commonly reported pathogen causing healthcare-associated infections (HAIs). A point prevalence survey of 183 hospitals in 10 states found that *C. difficile* comprised 12.1% of HAIs, surpassing *Staphylococcus aureus* infections [37]. Other studies have shown similar findings [11,
Table 1. *Clostridium difficile* Burden and Findings

<table>
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<th>Measures</th>
<th>Findings and References</th>
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<tr>
<td>CDI burden</td>
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<tr>
<td>CDI hospitalizations</td>
<td>• 336,600 hospitalizations and 1% of all stays [6]</td>
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<tr>
<td></td>
<td>• CDI discharges for 2012 and 2013 projected to continue to increase [10]</td>
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<tr>
<td>HO-HCFA CDI rates</td>
<td>• 2.8–9.3 per 10,000 patient-days [11–17]</td>
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<tr>
<td>CO-HCFA CDI rates</td>
<td>• 1.3–2.7 per 10,000 patient-days [11, 17, 18]</td>
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<td></td>
<td>• 11.1 per 10,000 patient-days [14]</td>
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<tr>
<td>CA-CDI rates</td>
<td>• &gt;20% of CDI cases [18, 19]</td>
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<tr>
<td></td>
<td>• Increasing over time [18]</td>
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<td></td>
<td>• 20–30 per 100,000 population [9]</td>
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Abbreviations: CA, community-associated; CDI, *Clostridium difficile* infection; CO, community-onset; HCFA, healthcare facility-associated; HO, healthcare facility-onset.

Data from the Agency for Healthcare Research and Quality’s Healthcare Cost and Utilization Project (HCUP) suggest that in 2009, there were 336,600 adult hospitalizations with any diagnosis of CDI—nearly 1% of all hospital stays [6]. Although the rates of CDI hospitalizations leveled off between 2008 and 2009, more recent data from HCUP show that rates continued to increase from 2010 to 2011 [6, 10]. Overall, the national rate of hospitalizations with *C. difficile* listed as any diagnosis nearly tripled, from 5.6 per 1000 discharges in 2001 to 12.7 per 1000 discharges in 2011 [10]. As HCUP data have a lag in reporting, 2012 and 2013 rates are projected to continue to increase (Figure 1) [10]. Regional variation is also seen across the United States, where New England and the Middle Atlantic regions had the highest rates of *C. difficile* hospitalizations in 2011 of 14.6 and 14.5 per 1000 discharges, respectively, whereas the lowest rates were seen in the West South Central (10.1 per 1000 discharges) and East South Central regions (9.3 per 1000 discharges) [10]. The increases in incidence and regional variations, particularly in the Northeast, have been largely attributed to the emergence of a more virulent strain, BI/NAP1/027 [40, 41]. The NAP1 strain was found to be the most prevalent strain in a sample of CDI cases from the CDC Emerging Infections Program and was associated with severe disease, severe outcome, and death [41].

The burden of CDI by epidemiologic onset varies (Table 1). The rate of HO-HCFA CDI ranges from as low as 2.8 per 10,000 patient-days to 9.3 per 10,000 patient-days [11–17]. Much of the reporting of CDI is focused on incidents associated with healthcare facilities, as most CDI cases have been reported to be healthcare related [17]. However, emerging epidemiologic studies have demonstrated increases in community-associated CDI (CA-CDI) as well as in the recognition that a large proportion of CDI cases and, in some cases, the majority are community-onset, healthcare facility-associated (CO-HCFA) [17]. In one recent study in the Kaiser Permanente Southern California healthcare system, the rate of CO-HCFA CDI was nearly twice as high as the rate of HO-HCFA CDI (11.1 per 10,000 inpatient-days vs 6.8 per 10,000 inpatient-days, respectively) [14]. Other studies have shown rates of CO-HCFA ranging from 1.3 to 2.7 per 10,000 patient-days [11, 17, 18]. In addition, multiple studies have found >20% of CDI cases to be associated with the community [18, 19]. A recent review reported rates of CA-CDI of 20–30 per 100,000 population [9]. Some findings also suggest that CA-CDI cases may be increasing [18]. A population-based study found that 41% of CDI cases were community-acquired and that the age- and sex-adjusted incidence for CA-CDI increased from 2.8 per 100,000 person-years in 1991–1993 to 14.9 per 100,000 person-years in 2003–2005 [18]. Continued research is needed in identifying unrecognized community reservoirs for cases to direct prevention efforts.

Table 2. Reported Risk Factors for *Clostridium difficile* Infection

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<th>Measures</th>
<th>Findings and References</th>
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<tr>
<td>Reported risk factors</td>
<td>• Hospitalization or length of stay [17]</td>
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<tr>
<td></td>
<td>• Antimicrobial use [17, 20–29], although some CA-CDI cases found to have no recent antibiotic exposure [8, 18, 19]</td>
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<td></td>
<td>• Older age [3, 6, 12, 14, 18]</td>
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<tr>
<td></td>
<td>• CA-CDI cases younger than HO-HCFA CDI cases [9, 18]</td>
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<tr>
<td></td>
<td>• Comorbidity [14]</td>
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<td></td>
<td>• PPIs and H2 antagonists [30–32]</td>
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Abbreviations: CA, community-associated; CDI, *Clostridium difficile* infection; HCFA, healthcare facility-associated; HO, healthcare facility-onset; PPI, proton pump inhibitor.

Table 3. *Clostridium difficile* Infection Outcomes

<table>
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<th>Measures</th>
<th>Findings and References</th>
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<tr>
<td>CDI outcomes</td>
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<tr>
<td>Recurrence</td>
<td>• 20%–30% [33]</td>
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<tr>
<td>Colectomy</td>
<td>• 8.7 per 1000 CDI cases [34]</td>
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<tr>
<td>Mortality</td>
<td>• 14,000 deaths per year [35]</td>
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<td>• 90% of CDI deaths in elderly [35]</td>
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<tr>
<td>Costs</td>
<td>• $2,454–$29,000 per episode [36]</td>
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<td></td>
<td>• $4.8 billion in excess costs to US acute care facilities [44]</td>
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<tr>
<td>Length of stay</td>
<td>• 2.7–21.3 d [36]</td>
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Abbreviation: CDI, *Clostridium difficile* infection.
RISK FACTORS

A number of major risk factors have been found to be associated with CDI (Table 2). Hospitalization or prolonged length of stay in the hospital has been shown to be a significant risk factor for development of CDI. The CDC’s Emerging Infections Program data showed that 94% of all CDI cases were associated with healthcare exposure [17]. Exposure to antimicrobial agents, including clindamycin, cephalosporins, and fluoroquinolones, is a well-established major risk factor for developing CDI [17, 20–23]. In addition, continued use of antibiotics during and after CDI treatment can result in poor outcomes including recurrence of CDI [24–27]. A recent study found that 77% of patients with CDI received at least 1 dose of an unnecessary antimicrobial and 26% received exclusively unnecessary antibiotics, with the definition of “unnecessary” based on indication [27]. Recurrence of CDI was higher in those who received any unnecessary antibiotics compared to no unnecessary antibiotics, although this was not statistically significant. The risk of CA-CDI with antibiotic exposure has also been reported and varies with antibiotic class. Two meta-analyses assessed antibiotic exposure and risk of CA-CDI and found the highest risks were seen with clindamycin, fluoroquinolones, and cephalosporins [28, 29]. Although antibiotics have been shown to be associated with CA-CDI, there are still reports of a significant proportion of these patients not having recent antibiotic exposure [8, 18, 19]. However, prevention efforts should continue to reduce the use and adverse effects of antibiotics.

Older age and underlying conditions or comorbidity are also well-recognized risk factors for CDI. The average age of those with CDI hospitalizations was nearly 20 years older than the average age of those with hospitalizations for other reasons [6]. CDI rates have been shown to be several-fold higher in persons aged ≥65 years than in younger age groups [3, 6, 12, 14, 18]. Although CA-CDI rates have also been shown to increase with older age, patients with CA-CDI are reported to be younger than those with hospital-acquired CDI [9, 18]. Recent data from Kaiser Permanente found that nearly every comorbidity assessed was associated with higher incidence rates of CDI vs patients without these conditions. Many of these conditions (ie, dementia, peripheral vascular disease) are also associated with older age and may be the reason for the high rates [14].

The use of acid suppression therapy and, in particular, proton pump inhibitors (PPIs) as a risk factor for new-onset or recurrent CDI is still controversial. However, 2 meta-analyses suggest increased risk of CDI with PPI use [30, 31]. Despite significant heterogeneity in effects, Janarthanan et al found that PPI use was associated with a 65% increased risk of CDI, and findings were consistent across study design type [30]. Another meta-analysis with a longer time period and larger number of included studies had similar findings, but also identified increased risk of CDI recurrence with PPI use, and concomitant use of PPI and antibiotic conferred a greater risk than that of PPI alone [31]. Histamine 2 receptor (H2) antagonists were also found to be associated with CDI in this study as well as a more recent meta-analysis and systematic review, but as not as high a risk as PPIs [31, 32]. These data suggest that prevention efforts should not only focus on curbing use of antibiotics, but also monitor patients taking PPIs or H2 antagonists for adverse effects.

MORBIDITY AND MORTALITY

The morbidity, mortality, and medical care costs of CDIs have reached historic highs [37] (Table 3). Recurrent disease is a
particularly troublesome aspect of CDI, with recurrence rates ranging from 20% to 30% after an initial episode, which often requires additional antibiotic therapy with its attendant costs and side effects [33]. As the incidence and severity of CDI have increased, the number of patients requiring intensive care unit care or colectomy for treatment of CDI might be expected to rise, although there are few data outside of outbreak situations to address this question. Overall rates of colectomy have ranged from 1% to 3% of CDI cases, and some studies have found a rising rate over time [42]. However, the experience of a single center or an outbreak situation may not be widely generalizable. Kasper et al undertook a multicenter study to examine colectomy rates using International Classification of Diseases, Ninth Revision codes for CDI and colectomy in patients with CDI. The investigators found that the overall colectomy rate was 8.7 per 1000 CDI cases and was higher for CA-CDI (16.5 per 1000 CDI cases) than HO CDI (4.3 per 1000 CDI cases) with no increase noted over time, which is encouraging [34].

The mortality associated with CDI is high, particularly in older adults with comorbid conditions, severe disease, and illness caused by the NAP1 strain of C. difficile [41]. The estimated number of deaths attributed to CDI, based on multiple cause-of-death mortality data, increased from 3000 deaths per year during 1999–2000 to 14,000 during 2006–2007. Nearly 90% of CDI deaths occurred in patients aged ≥65 years [35]. In HCUP data, approximately 9.1% of CDI hospitalizations ended in death vs 1.9% in all other stays [6].

Most studies of CDI, particularly clinical trials, have focused on outcomes such as cure, defined as resolution of diarrhea (≤3 unformed stools per day for 2 consecutive days), recurrence, and mortality. Although these outcomes are clearly important, additional patient-centered outcomes should also be examined. These include quality of life following CDI, fecal incontinence, functional impairment (particularly mobility), appetite and weight changes, and hydration. For patients developing CDI in a healthcare facility, these factors may be associated with increased risk of readmissions to the healthcare system. Some of these readmissions may be prevented if information on these outcomes is elicited before discharge to address them adequately. A recent study reported findings of semistructured interviews with 12 US and 12 French patients who had experienced CDI and found that CDI was associated with a marked social cost to patients, who reported experiencing emotional distress, humiliation, and embarrassment, resulting in curtailment of usual social activities. Despite continuing improvement, patients reported fear and worry of recurrent episodes [43]. Further studies on patient-centered outcomes for CDI are clearly needed, and patient input into choice of outcomes and definitions should be sought for future work in this area.

COSTS OF CDI

CDI is a costly condition for individuals and for the healthcare system (Table 1). Dubberke et al undertook a critical analysis of studies that evaluated the economic burden of CDI and found that most studies were undertaken in acute care facilities and that, using 2008 data, CDI may have resulted in $4.8 billion in excess costs in US acute care facilities [44]. A recent systematic review of 24 studies found a wide variation in the excess costs associated with CDI ranging from $6774 to $10,212 for CDI requiring admission, $2992 to $29,000 for hospital-acquired CDI, and $2454 to $12,850 where no categorization of hospital-acquired vs community-acquired illness was made. The ranges for length-of-stay values were 5–13.6, 2.7–21.3, and 2.8–17.9 days, respectively [36]. Studies of costs related to CDI are challenging to compare because of differences in the perspective that is taken (hospital or healthcare institution vs society), choice of which costs to include, type of healthcare system from which data are extracted, and how costs are considered clearly “attributable to CDI” given that CDI occurs mainly in older individuals with comorbid illnesses. These limitations notwithstanding, it is likely that the costs of CDI are underestimated, and these are projected to increase given the rising incidence and severity of CDI. There is a lack of data on the costs of recurrent CDI, and this area deserves attention. Additional large studies that carefully categorize CDI, evaluate multiple healthcare settings, and take into account all costs associated with CDI beyond just the healthcare system with robust sensitivity analyses are needed to obtain an accurate representation of the economic toll that CDI exerts on society.

CONCLUSIONS

CDI remains a significant and increasing HAI, with antibiotic exposure being a well-established risk factor for CDI and recurrence. However, the role of CDI in the community should be further evaluated. Increased CDI-related morbidity, mortality, and costs due to CDI suggest that continued efforts are needed for both primary and secondary prevention of CDI, including curbing unnecessary use of antibiotics, providing alternative prevention strategies for those at risk due to necessary antibiotic exposure, and monitoring use of PPIs and H2 antagonists. Finally, recognizing patient-centered outcomes as a needed area of study will further efforts in identifying prevention strategies to reduce the incidence and severity of CDI.

Notes

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