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Changing epidemiological pattern of hospital and community borne *Clostridium difficile* infections: A cause for public health concern

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ABSTRACT

The bacteria *Clostridium difficile* (*C. difficile*) is one of the significant nosocomial pathogens frequently implicated with antibiotic associated diarrhea. Infection with *C. difficile* can result in asymptomatic colonization to spectrum of complications collectively known as *C. difficile* associated diseases. Since the dawn of its discovery, the *C. difficile* has been a subject of research with respect to its virulence characteristics and epidemiology. Once thought to be a normal flora of human, it was later identified as an enterotoxigenic bacteria. Subsequently, this bacteria emerged to be an important nosocomial agent affecting patients of old age. Recent reports indicate dramatic shift in the epidemiology of *C. difficile*. Some of the notable changes are increasing incidences of community acquired infections, development of resistance to wide spectrum of antibiotics, frequent recurrences, infections among young individuals without any exposure to common risk factors, *etc*. This paper reviews the literatures of past 25 years that enlighten the alarming raise and changing epidemiological features of this agent, so as to necessitate in-depth studies towards its prevention and control.

1. *Clostridium difficile* (*C. difficile*): characteristics

C. difficile is a bacillary Gram positive, anaerobic and spore-forming bacteria. This bacteria was detected in 1935 as fecal flora of healthy infants[1] and initially considered as nonpathogenic. *C. difficile* was once thought to be a commensal of human, but over the years it has emerged as an enteric pathogen. Bartlett *et al*.[2] firstly detected *C. difficile* cytotoxin from the stools of patients with pseudomembranous colitis, thereby demonstrating its pathogenic potential. *C. difficile* is generally recognized as the principal cause of nosocomial infectious diarrhea. This bacteria is frequently transmitted in health care settings where more exposure to antibiotics and air contaminated with *C. difficile* spores are common[3].

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2. Diseases and complications caused by *C. difficile*

The infection due to *C. difficile* (CDI) usually occurs when the spores prevailing in the environment or on the hands of health care personnel contacting previously infected patients are ingested[4]. One of the important factors favoring the invasion and colonization of *C. difficile* in human host is the exposure to antimicrobials. Indiscriminate use of antimicrobial agent is presumed to cause the disruption of normal intestinal microflora, especially anaerobes, of the host[5]. The organism is non-invasive and the precise mechanism which enables *C. difficile* to cause symptomatic infection is still unclear. Pathogenesis involves the production of toxin and disruption and inflammation of intestinal epithelia via damage of microtubules and cellular junctions along with the release of IL-8[6].

The *C. difficile* related infections are diagnosed as principal diagnosis if CDI associated symptoms (*e.g.*, diarrhea) or conditions (*e.g*., intestinal ailment) are observed and the secondary diagnosis refers to sole CDI. As an outcome of severe diarrhea the CDI can cause incontinence in all age groups. In the case of elderly patients, owing to urgency and frequent bowel movements, the incontinence occurs. Another complication associated with CDI is

the increase in pressure ulcers. The *C. difficile* associated diseases (CDAD) could be asymptomatic or fatal including fulminant colitis, pseudomembranous colitis and toxic megacolon[7].

The pathogenicity of *C. difficile* is attributed to its two important virulence factors namely, toxins A and B that are encoded by the genes *tcdA* and *tcdB* respectively[8]. These genes are present on a 19.6-kb so-called pathogenicity locus. Molecular and pathological investigations have revealed that the toxin B is more potent than its counterpart[9]. Since 1987 a third toxin, binary toxin called *C. difficile* toxin (CDT), unrelated to the earlier toxins, has been identified to be produced by some *C. difficile* strains. Researches conducted in recent years on the outbreaks of *C. difficile* have reported the occurrence of PCR ribotype 027 North American PFGE type 1 epidemic strains (also referred to as 027/NAP1/BI strains) and their ability to produce binary toxin. The association of PCR ribotype 027 strains with more severe disease, extraordinary resistance to fluoroquinolone antibiotics, higher relapse rates and mortality is believed to be influenced by this binary toxin[10].

3. Epidemiology of *C. difficile* infections

First report on *C. difficile* as the major infectious cause of antibiotic-associated diarrhea was published in 1978. Toxigenic *C. difficile* is recognized as the principal cause of infectious pseudomembranous colitis and the primary cause of hospital acquired infectious diarrhea[2]. For epidemiological studies, various molecular techniques such as pulse field gel electrophoresis (PFGE), PCR ribotyping, restriction endonuclease analysis, *etc*. are employed for typing of *C. difficile* strains[11].

C. difficile has been recognized to be the etiologic agent of nearly 25% of antibiotic-associated diarrhea reported worldwide[5]. Studies on CDI indicate increasing rates of incidence, severity and recurrences in recent years[12,13]. Multi-centric studies have reported a noticeable increase in incidences of CDI and mortality across the United States, Canada, Europe and Australia during the recent decade[14]. Researchers have recorded an increasing incidence of CDI to an extent of 2 to 2.5 fold from the late 1990s to the early 2000s. The rate had been even higher in the elderly individuals. A recent U.S. study involving 11 751 patients consulting a clinic between January 2010 and May 2013 reported the incidence of CDI as 21/1000 admissions and 2.1% of all-cause hospitalizations. CDI has been identified to be a significant cause of heavy health care burden as it is responsible for long hospital stay (4.5% of inpatient stays) and high rate of mortality (21.9%)[15].

Among 348 950 cases of CDI discharged in the United States during 2012, 340 401 patients were in the age group of ⩾18 years, and 113 956 cases were principally diagnosed to have CDI[7]. In the following year 453 000 cases of incident CDI, with one fourth of them community acquired, caused 29 300 deaths, and owing to this, costs of health care increased from $3427 to $9 960/patient[14]. Recurrence rate of CDI has also been noted to be on the upswing trend in recent years as evidenced by 50%–75% of first recurrences needing readmission to the hospital. About 15% of patients diagnosed with CDI require readmission subsequent to recurrent infection 30–60 days after the initial incidence[7].

C. difficile associated infections have been a cause of significant health care burden in recent decades. Although few reports have defined the cost of CDI on the healthcare system, the estimation of overall burden still needs comprehensive analysis. Recent reports infer that nosocomial cause of CDI further escalates cost of hospitalizations, thus increasing the expenditures in the United States to an extent of $1.5 billion annually[14,16,17].

4. Hospital *vs*. community acquired *C. difficile* infections and risk factors

CDI constitutes the major agent of nosocomial diarrhea in industrialized countries and contributes to increasing number of cases of diarrhea in the community[18]. Hospital acquired CDI (HA-CDI) is confirmed if the secondary diagnosis of CDI, in the absence of primary diagnosis of a CDI-related symptom, is recorded. The nosocomial acquisition of *C. difficile* may indicate inadequate infection control practices. The rate of carriage of *C. difficile* in asymptomatic and otherwise healthy adult stool has been estimated to be < 5%[19], whereas, it varies significantly and may reach up to 25% in hospitalized patients[3].

Epidemiological studies of recent years portray *C. difficile* as a leading agent of nosocomial infections. The study of Khanna and Pardi[13] conducted during the period between 1993 and 2004 has documented substantial increase in severe cases (especially among elderly individuals by 2.7 fold), as well as colectomies and mortalities (2.5 to 5 fold) among the patients with HA-CDI. A recent study investigating 15 461 cases of CDI from 10 geographic areas of US identified that 65.8% of CDI were hospital acquired while only 24.2% had the onset during hospital stay[14]. Warny *et al*.[12] based on their study on the epidemic CDI caused by the strain NAP1/027 has postulated that spread of spores in the hospital environment could be due to the severe diarrhea experienced by incontinent patients. This study has also noted that advancing age increases the risk of HA-CDI as evidenced by the increase of risk to an extent of 2% for every additional year of age after the age 18.

As outcome of many studies, an array of risk factors have been identified for HA-CDI[13,20], which are broadly grouped into three groups as shown in Table 1.

Table 1
Risk factors attributed to healthcare associated *C. difficile* infections.

S. No.	Category/mechanism	Possible risk factors
1	Host factors	Age, sex, co-morbidities
2	Factors disrupting the protective intestinal symbiotic microbes	Antibiotics, gastrointestinal surgery, gastrostomy, nasogastric tube feeding and acid-suppressing medication use *i.e*., use of proton-pump inhibitors or Histamine-2 receptor blockers
3	Higher exposure to *C. difficile* spore	Longer stay in healthcare facilities, prior admissions, infected co-patients

Exposure to antibiotics is considered critical for development of CDI. Studies show that 35% of patients who have undergone initial antibiotic therapy develop the complication of recurrent *C. difficile* infection[21]. Practically any antibiotic can predispose a patient to CDI[22]. Table 2 depicts the list of antimicrobials that have been reported to favor CDI upon their exposure[23,24]. Fluoroquinolone use (especially ciprofloxacin), as practiced in many developed countries, has emerged as the predominant risk factor for CDI as evident from the fact of emergence of the epidemic strain NAP1[12]. Besides, the frequent use of macrolides along with third-generation cephalosporins for the treatment of pneumonia has also been noted as the high risk for CDAD[25]. McDonald *et al*.[26] have demonstrated the resistance of restriction-endonuclease analysis group (BI) isolates of *C. difficile* to gatifloxacin and moxifloxacin and clindamycin. A recent study which investigated hospitalized patients infected with community acquired pneumonia reported that the duration of antibiotic therapy is a crucial risk factor for CDI and suggested that antibiotic regimens for less than 3 days would have better effect[27].

Community acquired *C. difficile* infection (CA-CDI) is defined as the onset of CDI in a person who did not have overnight stay in a hospital setting within 12 weeks before the onset. In contrast to HA-CDI, the CA-CDI occurs in patients of younger age and in those who have had no known exposure to antibiotics or other possible risk factors[24]. A study conducted at various centers of United States, Canada and Europe has recorded that nearly 20%–27% of CDI cases were community associated and occurred with an incidence rate of 20–30 per 100 000 populations[28]. The study by Lessa *et al*.[14], subsequent to testing of stool of CDI patients between 14 and 56 days of initial episode, observed that at least one recurrence of infection occurred in approximately 21% and 14% of cases of health care and community associated infections respectively.

Although hospital and community acquired *C. difficile* infections possess similar etiological patterns, studies have portrayed the contrasting features between them. A six-year study conducted between 2007 and 2012 by Saux *et al*.[23] has documented the differences in annual incidence of HA-CDI and CA-CDI. While the incidence of HA-CDI per 10 000 inpatient-days was ranging from 0.5 to 6.6, it was 0–15.6 for the CA-CDI per 10 000 admissions. This study recorded the hospitalization rates, combining health care and community associated infections, ranging from 4.8 to 49.1 per 10 000 admissions. The authors concluded that the frequency of community associated infection is higher among the children who had no comorbid conditions or any exposure to antibiotics but may experience more recurrences and complications compared to HA-CDI.

5. Changing epidemiological pattern and need for intervention

Despite intensive efforts to achieve effective prevention and treatment of *C. difficile* infection, this infection continues to be challenging in both hospital and the community settings[24]. Emergence of new epidemic strains of *C. difficile* could be attributed to its genetically facile nature and the ability to adapt to new environmental conditions. Some of the important findings in the epidemiological studies on *C. difficile* infections are presented in Table 3.

Earlier reports on the pathogenicity of *C. difficile* attributed toxins A and B as its virulence factors and it was believed that toxin B is more toxic than toxin A[9]. But, strikingly, differing from this view, recently Loo *et al*.[8] demonstrated that while usual strains of *C. difficile* colonize the asymptomatic patients, the CDI is principally caused by NAP1 strain possessing binary toxin (CDT). In order to explain the importance of CDT, Kuehne *et al*.[35] conducted experiments with wild and mutant strains of *C. difficile*. They observed that the virulence exhibited by A+B–C+ mutant was comparatively higher than that exhibited by A+B–C– mutant, and suggested the augmenting effect of CDT on the virulence of toxin B mutant strain (which could produce only toxin A). Hence, the overall

Table 2
Antimicrobials implicated with development of *C. difficile* infections.

S. No.	Category of antibiotic	Example
1	Narrow-spectrum β-lactams	Cloxacillin, ampicillin, amoxicillin, cefazolin, cephalexin, and amoxicillin-clavulanate
2	Broad-spectrum β-lactams	Ceftriaxone, ceftazidime, cefotaxime, piperacillin, meropenem and piperacillin-tazobactam
3	Other groups	Quinolones, aminoglycosides, metronidazole, vancomycin, clindamycin, trimethoprim-sulfamethoxazole

Table 3
Critical findings in the epidemiological studies on *C. difficile* infections.

Year	Finding reported	Reference
1935	Detection of *C. difficile* from fecal microflora of infants	[1]
1974	Association of *C. difficile* with pseudomembranous colitis	[29]
1978	First report on association of *C. difficile* with antibiotic associated diarrhea through detection of *C. difficile* toxin from stools of patients	[2]
1979	Characterization of toxin A (*tcdA*) and toxin B (*tcdB*)	[30]
1987	Detection of third toxin (binary toxin) of *C. difficile* (CDT)	[10]
1999	Report on clindamycin resistant *C. difficile* mediated epidemic of diarrhea	[5]
2005	Emergence of ribotype 027 e North American PFDE type 1 epidemic strain of *C. difficile* (027/NAP1/BI)	[26]
2008	Report on emergence of non-ribotype 027 epidemic strains	[11]
2008	Report on occurrence of CA-CDI without exposure to antibiotics	[31]
2013	Report on higher occurrence of CA-CDI among children	[32]
2016	Demonstration of efficacy of fidaxomicin in the control of *C. difficile* and toxin reduction	[33]
2017	Application of lyophilized encapsulated fecal microflora for control of recurrent *C. difficile*	[34]

virulence increases as a result of coordinated action of CDT with toxin A.

During the recent years there has been a changing pattern of epidemiology of *C. difficile* infections (Table 4). One of the reasons for this change is the host factor, which could play an important role in the development of CDI. This is evident from the fact that some patients, despite the exposure to antibiotics and toxigenic *C. difficile* strains, do not become symptomatic[31]. Although it is believed that toxins A and B are the chief virulence factors of *C. difficile*[19] and the patients principally develop antibodies to these toxins, nearly 67% of neonates delivered in hospitals despite the colonization by the bacteria seldom show any diarrheal symptoms. This could be due to the poor development or absence of receptors in the colon of neonates to *C. difficile* toxin, or the neutralization by maternal anti-*C. difficile* toxin A/B antibodies present in breast milk[40].

Recent epidemiological studies on CA-CDI observed that it could occur even in the absence of conventional risk factors[41]. For example, although prior use of antibiotics is a recognized risk factor for CA-CDI, some studies suggest that CA-CDI cases who have no previous exposure to antibiotics can be found in outpatient settings[31]. A population based study by Khanna *et al*.[42] noted that while the older age was more associated with hospital acquisition of CDI (60% and 39% respectively of elderly *v.s*. younger cases), the CA-CDI patients were surprisingly younger and mostly female. In addition, the CA-CDI patients have seldom or never used antibiotics (during the 90-day period prior to diagnosis) and had no co-morbidities or not on an acid-suppressing medication. A cohort study conducted by Tschudin-Sutter *et al*.[32] in U.S. demonstrated that in contrast to HA-CDI, the high incidences of CA-CDI occur with more complications and recurrences in children who have no comorbid conditions or antibiotic exposure.

In contrast to the earlier belief considering children as non-vulnerable group, data on CDI epidemics of recent years revealed higher incidences among children[43]. Lessa *et al*.[14] who investigated the pediatric CDI-related hospitalizations have reported that there had been substantial increase in the number of CDI cases among children and peripartum women from 0.724 in 1997 to 1.28 in 2006 per 1 000 hospitalizations. This study has also documented the infection rate of 78%, 19% and 3% respectively of hospital acquired, community acquired and intermediate CDI occurring among children. According to Schutze *et al*.[44], the incidence of nosocomial CDIs in the United States among hospitalized children has been on upswing since 1997. Nylund *et al*.[45] evaluated the data of pediatric CDIs (n = 21 274) at three years interval from 1997 to 2006 and demonstrated an increase in the cases from 3 565 in 1997 to 7 779 in 2006. This study concluded that the change in epidemiology of CDI in children could be attributed to the emergence in recent years of the epidemic strain of toxin-producing *C. difficile* (NAP1).

Another recent study by McFarland *et al*.[40] in U.S. recorded that the number of cases of CA-CDI was generally greater among the pediatric group (41%) compared to that of adults (30%). Significantly, among the female patients more CDIs were reported in adults (averaging 56%) compared to pediatric cases. Surprisingly, higher prevalence of hypervirulent epidemic strain of *C. difficile* NAP1/027/BI was observed in adult patients than children, which could be attributed to the limitation of fluoroquinolone use in children; whereas this drug is a risk factor for adults.

Review of other risk factors of CDI reported in recent years has brought in changing epidemiological views. For example, use of acid-suppressant medication as an independent or synergistic risk factor for CDI has been questioned[23]. In general, gastric acid suppression is believed to aid the reach of more vegetative organisms to the colon; however, the spores of *C. difficile* are acid-resistant and capable of remaining viable at the low pH gastric juice. Although some investigators have reported the increase in risk of CDI with acid suppression[28], the others have not agreed with this[37,46]. A study investigating CDI in patients aged 67 to 92 years old observed that all of these patients were non-surgical and haemodialysis and intensive care unit stay were not risk factors[39]. Wilcox *et al*.[38] from their systematic review of CDI reported that while gastrointestinal surgery was considered as a fatal risk factor during the years 2007–2009, it was not so in 2009–2010.

The shift of higher proportion of HA-CDI to CA-CDI has led to the speculation that there could be unconventional sources of infection. In U.S., 453 000 cases are reported annually, and approximately two thirds of cases are categorized as (inpatient) health care associated, but only 24% have hospital onset (23% have nursing home onset, 18% have post discharge onset). Investigations reveal that more than 8 (82%) in 10 patients with CA-CDI report recent health care exposures such as doctor or dentist visits within 12 weeks. There is increasing recognition of the role of asymptomatic carriers as a source for CDI[25]. Although fecal-oral mode is the most common

Table 4

Epidemiological concepts on *C. difficile* infections and changing views.

Epidemiological feature	Earlier report	Newer insights
Nature of bacteria	Normal fecal flora[1]	Virulent enteric pathogenic bacteria[2]
Virulence factor	Bacteria produce toxins A and B that equally contribute to virulence[2]	Toxin B is more potent than toxin A[9]
	Toxins A and B are major virulence factors[19]	Epidemic strains produce additional binary toxin (CDT) which along with toxin A (not B) contributes to higher virulence[35]
Origin of infection	Hospital borne[4]	Occur as both hospital and community borne with the later on increasing trend in recent years[28]
Susceptible group	CDIs are more common among old age group[3]	Children of > 1 year of age are also at risk of acquiring CDI[36]
Risk factors	Exposure to antibiotics[2]	CA-CDI occurs without exposure to antibiotics[31]
	Use of acid-suppressing medication[20]	CDI could occur even without prior use of such medication[37]
	Gastrointestinal surgery[20]	Not a requisite for CDI[38]
	Having comorbid conditions[20]	Not a requisite for CDI[39]
	Prior hospitalization, hemodialysis[20]	Not a requisite for CDI[39]

route of transmission of CDI, it can also be transmitted through contact with the patient and the environment contaminated by the patient. Therefore, environmental control of *C. difficile* prevailing in the health care facilities would be an appropriate method of control of CDI[44].

Contemporary epidemiological studies on CDI indicate that there has been significant decline of ribotype 027 and increasing predominance of other clones of *C. difficile* specially of the ribotypes 002, 005, 014, 015, 016, 020, 023 and 078. This change in prevalence of bacterial strains might be attributed to the successful control of cross-infection caused by the epidemic strain ribotype 027 in health care facilities, and the emergence of newer strains such as ribotype 078[11,47].

Another matter of important concern is the increase in drug resistant *C. difficile* strains in hospital environment as evidenced by the worsening response to traditionally accepted metronidazole therapy[48]. The shift of distribution and use of antibiotics over the time is speculated to be one of the causes for antibiotic associated CDI; for example, antibiotic therapy with quinolones replaces therapy with aminoglycosides[12]. Careful monitoring and administration of antimicrobial agents to treat *C. difficile* associated infections would be necessary at present. Thabit *et al*.[33] from their recent study advocated the administration of fidaxomicin as a drug of choice as it inhibits the transcription of the genes coding for toxins A and B of *C. diffcile* (*TcdA* and *TcdB*) through a macrolide based mechanism. This finding helped reveal comparatively the poorer efficacy of vancomycin than fidaxomicin in reducing the concentration of toxins that occur through the bactericidal mechanism; whereas the later has been proved to be superior in inhibiting both the bacterial cell and toxin production. Besides, encouraging results were obtained by a recent study which employed Bezlotoxumab (monoclonal antibody against toxin B) and found that there was a reduction in recurrent infection to an extent of 38% compared to that occurred with standard therapy alone[21].

It may be presumed from the literature that the actual healthcare burden caused by CDI needs to be determined through more exhaustive investigation as most of the available data are based on the reports of diagnosis and treatment of CDI carried out in acute-care hospitals[48,49]. As the available surveillance reports on CDAD are still considered preliminary[50], comprehensive study on the occurrence of CDI in community and among the patients treated in long-term care facility would help better understanding of colonization or infection caused by *C. difficile*.

6. Conclusions

C. difficile, once thought to be a normal human colonic flora, has now been identified as a precarious pathogen. Changing epidemiological patterns of CDI in recent years such as increasing incidences of community associated infections over hospital acquired infections, increasing susceptibility among younger groups, development of infections among individuals who are not exposed to antibiotics or risk factors or comorbid conditions pose new challenges. Researchers need to adopt precise surveillance measures to detect outbreaks, assess disease trends and decipher the diversity of CDI across varying ecological conditions. Eventual findings of such studies would help the public health officials and healthcare providers to offer effective clinical management of *C. difficile* associated diseases.

Conflict of interest statement

We declare that we have no conflict of interest.

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