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HOUSE FLY AS A MECHANICAL VECTOR OF NOSOCOMIAL CLOSTRIDIOIDES DIFFICILE AND INFECTION CONTROL

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Abstract

Prevention and control of *Clostridium difficile* associated diarrhea (CDAD) in the healthcare settings requires careful attention to hand hygiene, contact precautions, and environmental cleaning. Antibiotic restriction can reduce *C. difficile* rates; strategies for antibiotic use should be tailored to health care delivery in particular institutions. There is insufficient data for routine use of probiotics, treatment of asymptomatic carriers, or vaccination.

Key words: House flies, *Clostridium difficile*, Nosocomial, Infection control, Review.

Introduction

Clostridioides difficile (formerly *Clostridium difficile*) is a Gram-positive, anaerobe, spore-forming bacterium, causes infectious diarrhea in man (Czepiel *et al,* 2019) and livestock (Moono *et al,* 2016) making *C. difficile* infection (CDI) a one health problem that encompasses at least five CDI-associated clades and three different so called cryptic clades (Knight *et al,* 2021). Both incidence and severity of *C. difficile*-associated diarrhea (CDAD) are increasing in the health care facilities (Dubberke *et al*, 2008). Mitchell *et al.* (2022) in Ireland reported that *C. difficile* infection causes pseudomembranous colitis, rapid fluid loss, and death, as a sole nosocomial pathogen, isolated from patients on antimicrobial therapy especially elderly ones. *C. difficile* in USA caused about half a million infections annually, and 1/11 people over age 65 died within a month, and about 1/6 patients get infection again in subsequent of 2-8 weeks (CDC, 2023).

Again, houseflies (*Musca domestica*) are associated with all humans' activities and female lays many eggs in animal waste, garbage, and other decaying matter, and developed into larvae, pupae, and adults in 7 to 10 days (Abdel Ha-lim and Morsy, 2006). They prefer warm weather for optimal development, and hence they thrive in summer more than in winter (Atta, 2014). The adults have a close association with microorganisms and their environments, especially at a crucial moment in each developmental stage (Nayduch and Burrus, 2017). The internal bacterial community of houseflies from different sites was similar and relatively stable, but external ones were affected by geography and habitat (Park *et al,* 2019). Laziz *et al.* (2021) in Iraq from 300 *M. domestica* isolated many species of Gram-positive & Gram-negative bacteria on body (45.2%), right wing (35.7%), and left one (19.1%).

Review and Discussion

C difficile is ubiquitous bacteria colonizing the intestines of 3% to 5% of healthy individuals without any diseases (Ghose, 2013). Nowadays, *C. difficile* infection became a significant healthcare-associated infection globally causing fever, abdominal pain, diarrhea and severe pseudo-membranous colitis (Aronsson *et al*, 1985). Severe complications may lead to toxic megacolon and fatal intestinal perforation (Elgendy *et al,* 2020). Al-Tawfiq and Abed (2010) in Saudi Arabia reported that patients who become colonized were at risk for developing CDAD, primarily after treatment with antibiotics. Dinleyici and Vandenplas (2019) in Belgium reported that prevention of recurrent *C. difficile* infection by measures such as hand washing and isolation of patients is very important. But, these preventive measures were sometimes often overlooked in clinical practice.

The prevention and control of *C. difficile* requires a variety of interventions. This was shown in *C. difficile* hyper-virulent strain's

outbreak in an 834bed hospital that was successfully controlled by using good, tiered interventions with guidance of ongoing studies (Muto *et al*, 2007).

Contact precautions: Patients with suspected or proven *C. difficile* infection must be added to contact precautions. Modi *et al.* (2011) in Scandinavia reported *C. difficile* is one of the commonest causal agents of nosocomial enteric infections in hospitals, and that exotoxins A and B (TcdA & TcdB) are major virulence factors associated with *C. difficile* infection. Rodriguez *et al.* (2012) in Belgium found that *C. difficile* was widely recognized as the etiologic agent of enteritis in piglets. The incidence and severity of *C. difficile* infection was significantly increased globally during the last 20 years (Rodrig uez-Palaciosm *et al,* 2013). Martin *et al.* (2016) reported *C. difficile* is a gram-positive, anaerobic, spore-forming bacillus colonizes the gastrointestinal tract of man and animals. Davies *et al.* (2017) in the UK reported that *C. difficile* spores were acquired and internalized by house fly larvae during feeding, retained through moulting to adults, and disseminating infection in the hospital environment. Kachrimanidou *et al.* (2019) in Greece reported that *C. difficile* must be considered as a zoonotic pathogen, with interspecies transmission from animals to humans and also existence of a common contamination source is possible with animals' reservoir for human. Marshall *et al.* (2023) reported that globally *C. difficile* causes the anti-biotic-associated diarrhea, is a genetically diverse species which can metabolise a number of nutrient sources upon colonizing a dysbiotic gut environment. They added that Trehalose, a disaccharide sugar of two glucose molecules bonded by α 1, 1-glycosidic bond hypothetically involved in emergence of *C. difficile* hypervirulence due to its increased utilization by the RT027 and RT078 strains

Isolation precautions: In addition to the standard precautions, there are three isolation categories that reflect the major modes of microorganism transmission in nosocomial settings: contact, droplet, and airborne spread (Garner, 1985). The rooms of patients requiring contact precautions must be clearly marked with instructions regarding the type of precautions that must be observed. Ample supplies should be readily available outside the patient room to facilitate adherence, and hospital policies must be enforced (Muto *et al*, 2003). Data suggested that *C. difficile* contaminated skin may persist after resolution of diarrhea, and reasonable to continue contact precautions for a longer time period, although more studies clarify infection control risk associated with *C. difficile* spores persist after diarrhea resolution (Bobulsky *et al*, 2008). Burt *et al.* (2012) in the Netherland found that vermin (house mice, drain flies, lesser house-flies, and yellow mealworms) played a role in spreading of *C. difficile* types 078 & 045 were within pig farms and other locations. Krijger *et al.* (2019) reported that wild rodent and insectivore in farms were a risk for *C. difficile* zoonotic transmission. Neumann-Schaal *et al.* (2019) in Germany reported that *C. difficile* exhibited vast metabolic flexibility that utilized a range of nutrient sources to sustain its strict anaerobic lifestyle. Marcos *et al.* (2023) in Ireland reported that ribotype 078, a hypervirulent strain commonly associated with *C. difficile* infection (CDI) was the most frequent ribotype along the food chain; resistance to clinically important antibiotics was common in *C. difficile* food chain isolates, but without relationship between ribotype and antibiotic resistance profile.

Hand hygiene: Hand hygiene refers to either hand-washing with soap and water or the use of alcohol-based gels or foams that do not require the use of water. It is the single most important measure to reduce microorganisms' transmission from one person to another or one site to another on the same patient (Pittet *et al*, 2006). Alcohol-containing hand disinfection products are recommended over soap and water in controlling most organisms of epidemiologic importance (Siegel *et al*, 2007). Washing with soap

and water: 15 **vs.** 20 seconds, wash hands for more than 15 seconds, not exactly 15 seconds. Time it takes is less important than making sure you clean all areas of your hands, and alcohol-based hand sanitizers are the preferred way to clean the hands in healthcare facilities (CDC, 2024). However, alcohol didn't eradicate *C. difficile* spores (Boyce and Pittet, 2002). Because proper handwashing with soap and water involves vigorous mechanical scrubbing and rinsing, it may be more effective than other hand hygiene products in physically removing bacterial spores from hands. There was wide spread use of alcohol-based hand sanitizers that played a role in *C. difficile* outbreaks (McMichael, 2019). Beside, because soap and water hand hygiene requires more time than ethanol-based hand hygiene and avoidance of this hand hygiene may decrease overall hand hygiene compliance. These concerns remain unproven; overall CDAD rates have tended to decrease or remain after wide use of ethanol-based sanitizers as primary mode of hand hygiene (Boyce e*t al*, 2006).

Nonetheless, the CDC recommends soap and water hand hygiene when caring for patients with CDAD. If a facility is experiencing a *C. difficile* outbreak, it is prudent to emphasize that health care workers must wash hands with soap and water and ethanol-based hand sanitizer (McDonald, 2005).

Hospital environmental cleaning: As *C. difficile* spores can survive on dry surfaces for several months, environmental cleaning in a patient care setting for CDAD needs special attention (CDC, 2007). Few studied the use of cleaning agents for *C. difficile* spores inactivation, but without well-controlled trials to determine efficacy of surface disinfection and its impact on associated diarrhea (.

Hypochlorite solutions were more effective than at least some other solutions. This was given in a study of environmental cleaning solutions in which a 1:10 hypochlorite was substituted for quaternary ammonium in three hospital units. CDAD rate decreased significantly on bone marrow transplant unit, from 8.6 to 3.3 cases/1000 patient-days. After being back to quaternary ammonium, rate was 8.1/1000 patient-days, but without significant changes in the two other units with lower baseline rates of 1.3 to 3.0 cases/1000 patient-days (Wilcox *et al*, 2003).

Products that appear to reliably kill *C. difficile* spores contain at least 5000 parts per million of sodium hypochlorite and can cause caustic damage to the surfaces of hospital equipment. Nonetheless, use of such a solution should be considered for environmental cleaning of rooms and bathrooms used by patients with CDAD, particularly in the setting of an outbreak. Based upon the available evidence, the CDC recommends use of a hypochlorite-based solution in the CDAD setting (Valiquette *et al*, 2007). Symptoms often begin within 5 to 10 days after antibiotic, but can occur as soon as the 1st day or up to 3 months later. The most common symptoms of mild to moderate infection are: 1- Watery diarrhea three or more times a day for more than one day, & 2-Mild belly cramping and tenderness. Severe infection caused patients to lose too much body fluid, and must be hospitalized for dehydration. *C. difficile* infection can cause colon inflammation or sometimes can form patches of raw tissue that can bleed or make pus. Symptoms of severe infection include: 1- Watery diarrhea as 10 to 15 times a day, 2- Belly cramping and pain, sometimes severe, 3- Fast heart rate, 4- Loss of fluids (dehydration), 5- Fever, 6- Nausea, 7- More WBC, 8- Kidney failure, 9- Appetite loss, 10- Swollen belly, 11- Weight loss, and 12- Blood and/or pus in stool (Mayo Clinic, 2023). Diagnosis: Infection is by stool culture or testing for bacteria's DNA or toxins A positive test person without symptoms, it was *C. difficile* colonization rather than an infection (CDC, 2012). Differential diagnosis must be from 1- Crohn's disease, 2- Diverticulitis, 3- Irritable bowel syndrome, 4- Malabsorption, 5- Peritonitis, 6- Salmonellosis, 7- Shigellosis, 8- Ulcerative colitis, 9- Vibrio infections, and 10-Viral gastroenteritis.

Antibiotic restriction: Implementation of antimicrobial stewardship program during Quebec outbreak led to decrease in nosocomial CDAD incidence by 60%, but, no formal restrictions were applied; targeted antibiotics included cephalosporins, ciprofloxacin, clindamycin, and macrolides (Johnson *et al*, 1999). Antimicrobial therapy plays a central role in pathogenesis of *Clostridium difficile* infection, presumably through disruption of indigenous intestinal microflora, thereby allowed *C. difficile* to grow and produce toxin (Owens *et al,* 2008). Possible, recommendations were avoidance of clindamycin and aminoglycosides or trimethoprim-sulfamethoxazole used rather than fluoroquinolones, antibiotics duration was limited as appropriate (Niode *et al,* 2022)

Clindamycin: In several *C. difficile* outbreaks in the 1990s, clindamycin restrictions were followed by rapid reductions in CDAD cases. This was evident in controlling outbreaks caused by highly clindamycin-resistant J strain, by infectious disease physician approval for clindamycin use caused a significant and sustained reduction CDAD from 11.5 to 3.3 cases/ month (Biller *et al*, 2007).

Fluoroquinolones: Fluoroquinolone appears to be a class effect in outbreaks caused by hyper-virulent NAP1/BI/027strain, since the fluoroquinolones rates in two studies were similar, and restriction or reduced use of all fluoroquinolones may be required for effective control (Labbe *et al*, 2008).

Cephalosporins: Restriction of third generation cephalosporins has been successful in reducing CDAD rates. The risk of CDAD was significantly lower after empiric treatment with the piperacillin-tazobactam rather than ceftriaxone. Formulary restrictions reduced CDAD rates by minimizing inappropriate cephalosporin use and by limiting antibiotics to penicillin, trimethoprim-sulfamethoxazole, and aminoglycosides in an outbreak setting (Dendukuri *et al*, 2005).

Home hygiene: *C. difficile* can be spread to household contacts, although it was rare for healthy individuals to become sick with symptomatic *C. difficile* infection, without antibiotics. To prevent spread to household contacts, *C. difficile* patients should wash hands frequently with soap and water, especially after using bathroom and before food preparation. Patients with diarrhea must avoid using the same toilet as other family members. Besides, bathroom and kitchen areas (including toilet seats, toilet bowl, flush handle, sink faucet handles and countertops) may be cleaned with bleach and water to prevent *C. difficile* spread (Warny *et al*, 1994).

Use of probiotics: Many probiotics were evaluated in treating and preventing antibiotic-associated diarrhea, which focused specifically on CDAD are inconclusive regarding a benefit of treatment or prevention, but routine use was not indicated (Aronsson *et al*, 1985).

Vaccination: Several studies showed that the humoral immune response of the host to *C. difficile* toxins A & B influences the clinical course of CDAD as well as the risk of relapse. Thus, vaccination with a partially purified preparation of inactivated toxins A and B may be a viable strategy for active immunization (Kotloff *et al*, 2001). A vaccine containing toxoids A & B induced adequate antibody responses in healthy volunteers. The efficacy of this vaccine was subsequently evaluated in an open-label study in three patients with recurrent *C. difficile* colitis. After four intramuscular inoculations over an eight week period, the three patients discontinued antibiotic treatment without recurrence for a six-month follow-up. These supported active vaccination feasibility but must be validated in larger, randomized, controlled trials (Aboudola *et al*, 2003).

Treatment: Many antibiotics used for *C. difficile* gave more or less equally effective (Drekonja *et al,* 2011). Data on asymptomatic carriers' treatment are limited regarding whether their treatment might minimize nosocomial *C. difficile*. Thirty asymptomatic *C. difficile* carriers were randomly assigned to one of three treated groups: oral vancomycin 125mg 4 times daily; metronidazole 500

mg orally twice daily; or placebo. Patients 9/10 given vancomycin were culture-negative during and immediately post treatment, compared to 3/10 on metronidazole and 2/10 on placebo, but decolonization was transient, as most patients became recolonized in few weeks (Johnson *et al*, 1992). Cholestyramine, an ion-exchange resin, is effective in binding both toxin A & B, slowed bowel motility, and prevents dehydration (Stroehlein, 2004). Loperamide® slowed to stop diarrhea post treatment initiation (Kelly *et al,* 2021). Metronidazole was not effective in treating asymptomatic carriers. Vancomycin may be useful for transient elimination of carrier state, but routine treatment was not indicated. In the setting of a hospital outbreak in which temporary elimination of the organism is felt necessary to reduce horizontal transmiss ion, vancomycin may be a useful tool, but further studied (Sougioultzis *et al*, 2005). Vancomycin or fidaxomicin orally were indicated for children and adults infections (McDonald *et al,* 2018).

In Egypt, few dealt with nosocomial *C. difficile*, Brooks *et al*. (1985) studied eleven diarrheal stool specimens and ten control stool specimens from Cairo, by frequency-pulsed electron capture gas-liquid chromatography (FPEC-GLC). Four patients involved *Shigella sonnei*, three cases involved *S. boydii*, and four cases involved *S. flexneri*. The aqueous stools were centrifuged, extracted with organic solvents, and derivative to form specific electron-capturing derivatives of carboxylic acids, alcohols, hydroxy acids, and amines. Analyses were performed on high-resolution glass columns with an instrument equipped with an extremely sensitive electron capture detector that is specific for the detection of electron-capturing compounds. Diarrheal stools showed specific FPEC-GLC profiles and metabolic markers that readily distinguished between the *Shigella* spp. and *Escherichia coli* producing heat-stable or heat-labile enterotoxins. *S. sonnei* stools contained hexanoic acid, 2-hydroxy-4-methylmethiobutyric acid, and some unidentified alcohols distinguished organism from other enteric pathogens. *S. boydii* produced an acid that was unique for this species, and *S. flexneri* produced alcohols that distinguished between it and other enteric organisms. The FPEC-GLC profiles were also very different from those reported earlier for *C. difficile* & rotavirus. Haberberger *et al*. (1991) studied travelers' diarrhea in a United States Military population deployed in Cairo from July to August 1987 found that acute diarrhea required treatment in 183/4.500 (4%) of them. A possible agent identified in 49% of all diarrhea cases was enteric pathogens associated with diarrhea included: *E. coli* (17% ST-producers, 13% LT-producers, and 3% LT/ST-producers); *Shigella* (9%), *Campylobacter* spp. (2%), *Salmonella* (2%) and vibrio cholerae non-01 serogroup (2%). Other enteric pathogens isolated from one episode each of diarrhea included *Aeromonas hydrophila* group, *Plesiomonas shigelloides*, *Bacillus cereus*, *Yersinia enterocolitica*, enteroinvasive *E. coli*, intoxications by *C. perfringens,* and *C. difficile* with no parasite. They added that acute gastroenteritis was the main cause of substantial morbidity. El-Sharif *et al.* (2012) gave a complete microbial spectrum of anaerobes in various infection sites in hospitalized cancer patients, the most common infection was respiratory tracts (55.8%), mainly in leukemic ones, followed by skin infection (18%), only in solid-tumor patients, GI tract infections (9.7%), bloodstream infections (9.4%), and urinary tract (7.1%). *Fusobacterium necrophorum* (32.7%) and *Eubacterium lentum* (23.8%) were mostly recovered from solid-tumor patients, followed by *C. perfringens* (11.9%), *C. difficile* (10.9%), *E. limosum* (5.9%), and *Veillonella parvula* (5%). Nosocomial infections cause significant morbidity and mortality among them due to debilitated immune system that was risky for anaerobes colonization. Abdel-Glil *et al.* (2018) identified strains related to RT 001 that cause man infection in birds, which is one of the *C. difficile* potential reservoirs.

Conclusion

To achieve the main goal of preventing or reducing the risk of hospital-acquired infections, a hospital epidemiology program must have the following oversight functions and responsibilities: Surveillance, either hospital-wide or targeted, education about prevention of infections (proper hand disinfection), outbreak investigations cleaning, disinfection, and sterilization of equipment and safety disposal of infectious materials.

Hospital health workers post exposure to blood-borne or respiratory pathogen must be given a suitable prophylactic antibiotic dose.

Recommendations

Infection control policies must be developed. One must avoid not indicated antibiotics. Vacuum or sweep up insects and commensal pests' eradication by safe measures.

Simple educational illustrated programs are indicated for nursing staff and inpatients.

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