Taking Control of C. difficile

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Clostridium difficile (*C. difficile*) is a gram positive, anaerobic, spore-forming bacterium that inhabits the human intestine. Strains that carry genes which express enterotoxins and/or cytotoxins can cause human illness, ranging from diarrhea to pseudomembranous colitis, which, if it progresses, can lead to sepsis-like outcomes. If not treated effectively, or early enough, complications can include:

- gut hemorrhage,
- toxic megacolon,
- shock and
- death.

This article will focus on *C. difficile* and efforts to control the *C. difficile*-associated diseases (CDAD), for which host factors provide an important role.

Trends in CDAD epidemiology include increasing numbers of cases and rates of disease in health-care facilities and institutional outbreaks of disease, often with more severe sequelae than had previously been noted.

Host factors

The majority of those who become clinically ill from *C. difficile* are individuals > 65 years of age. Those who become ill usually have a disruption of normal colonic flora, either through preceding chemotherapy or antibiotic use, or through antacid medications.[1] Illness from *C. difficile* has also been shown to result from an insufficient production of neutralizing antitoxin antibody in the serum after colonization with the organism.[2] This immune response may be reduced by elderly age, chronic diseases, or medications and may contribute to the vulnerability of these individuals to CDAD, after colonization by *C. difficile*.

Trends in CDAD

Trends in CDAD epidemiology include increasing numbers of cases and rates of disease in health-care facilities and institutional outbreaks of disease, often with more severe sequelae than had previously been noted.[3] *C. difficile* is also emerging as an important cause of GI illness in the community. Recent changes in virulence factor production by some *C. difficile* strains contribute to these observations and are of particular relevance in efforts to control CDAD.

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Virulence factors of C. Difficile

C. difficile toxins

Strains of *C. difficile* are found widely dispersed in nature, but strains that do not produce toxins are not pathogenic. The pathogenicity of toxin production is encoded in the pathogenicity locus of five genes that the virulent strains possess.[4] The gene of toxin A expresses an enterotoxin and that of toxin B expresses a cytotoxin. Strains with mutations in one or both of these genes are able to produce human disease. Deletion mutations in repressor gene C (tcdC) that lead to upregulation of toxin A and toxin B (resulting in 16 and 23 fold increases in these toxin products respectively), have been observed from recent outbreak isolates in Quebec.[5] This enhanced toxin expression contributes to the enhanced morbidity and mortality observed to be associated with these strains. The presence of an additional toxin, binary toxin CDT, in some of these more virulent strains is of undetermined clinical significance and requires further study.

Antibiotic resistance genes and antibiotic susceptibilities

Comparison of recent strains from outbreaks associated with more severe outcomes, to historical isolates, have shown similar binary toxin genes and 18-bp deletions in the tcdC gene, but these historical isolates were not resistant to fluoroquinolone antibiotics. Consequently, Gerding has analyzed the nosocomial CDAD situation as an antibiotic resistance-driven outcome, where it is shown that the *C. difficile* strains are resistant to the antibiotic.[6] Where gut flora is disrupted by means other than antibiotics, *C. difficile* resistance is not required to produce illness. Upon disruption of the bowel flora by antibiotic use, susceptibility to colonization by virulent *C. difficile* strains may last for a variable amount of time. Clindamycin has the longest window of susceptibility, lasting over a month post-administration. Not all antibiotics pose a uniform risk of CDAD. The lowest risk has been observed following:

- penicillin,
- aminoglycosides and
- trimethoprim-sulfamethoxazole.

The highest rates have been observed for third generation cephalosporins to which *C. difficile* strains are inherently resistant and to quinolones and clindamycin.[7]

Sporulation

Vegetative *C. difficile* bacilli can transform into hardy spores and can survive for months in natural and institutional environments.

The rate of sporulation and percentage of cells forming spores varies by strain and the environmental conditions. Wilcox and Fawley have shown that in the presence of some hospital disinfectants, the proportion of sporulating *C. difficile* cells can increase significantly above non-exposed control levels.[8] The choice of cleaning agents can influence the extent of environmental contamination with spores. Oxidizing microbicides containing free chlorine or hydrogen peroxide at appropriate concentrations are effective at producing 6 log10 reduction in spores, within < 10 minutes of contact.

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Take-home message

1. *Clostridium difficile* is an emerging infectious agent with new virulence factors resulting in increased toxin production and resistance to fluoroquinolones. These new virulent clones have been associated with substantial increases in the incidence of *C. difficile* difficile-associated diseases (CDAD) and an increased severity of illness
2. Control efforts to reduce CDAD rates require a combined approach, emphasizing:
   - the prevention of horizontal transmission (especially through gloves and hand-washing),
   - control of spores in the environment and
   - antibiotic stewardship.

Factors in nosocomial control of C. difficile

Gut colonization of patients with virulent strains of *C. difficile* from the environment can occur rapidly and increases proportionately to the length of stay in the facility.

The hands of individuals working in facilities are often colonized with *C. difficile* and within facilities this increases proportionately with higher percentages of environmental sites contaminated with *C. difficile*. Horizontal spread of *C. difficile* has been proven to be reduced by:

- glove use,
- disinfection of patient rooms and
- by the avoidance of rectal thermometer sharing.

Handwashing with chlorhexidine solutions or soap and water are equally effective at preventing horizontal spread by killing vegetative cells and diluting vegetative cells and spores. Alcohol gels do not kill vegetative cells or spores. Control measures for outbreaks or in facilities with ongoing transmission include the use of cleaning solutions containing hypochlorite.

Antibiotic restriction can also minimize CDAD incidence as clindamycin and gatifloxacin restriction policies and practices have interrupted *C. difficile* outbreaks. Prudent and appropriate use of antimicrobials is essential and this can be facilitated by audits of antimicrobial prescriptions and the development of policies and practices to minimize unnecessary and inappropriate antibiotic use.[9,10]

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