REVIEW

Important clinical advances in the understanding of *Clostridium difficile* infection

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Purpose of review

Clostridium difficile remains an important cause of infectious colitis, particularly in healthcare facilities. This review summarizes recent advances in the epidemiology, diagnosis, and treatment of this endemic pathogen.

Recent findings

C. difficile infection (CDI) hospitalizations and mortality rates have increased over the last decade. The BI/NAP1/027 strain has been responsible for epidemics with increased severity and mortality and is now endemic in many settings, particularly North America. Concurrent antibiotics have now been shown to decrease the cure rates for anti-*C. difficile* therapy and increase the risk of recurrence. Although studies implicate proton pump inhibitors as a risk for CDI, the magnitude of and the biological basis for that risk remain unclear. Molecular diagnostic techniques are rapid and sensitive but highlight the importance of using appropriate clinical testing criteria. Fidaxomicin is a promising new therapy associated with decreased recurrence; infections due to BI strains, however, are associated with inferior outcomes regardless of the treatment agent. Fecal transplantation continues to have impressive success rates for patients with recurrent CDI, and a new colon-sparing surgical procedure presents an intriguing suggested alternative to total colectomy in severe, complicated cases.

Summary

Elucidating CDI risk factors, identifying rapid, accurate diagnostic tools, and validating new treatment approaches remains an urgent priority.

Keywords

acid suppression therapy, *Clostridium difficile*, fecal microbiota transplantation, fidaxomicin, molecular diagnostics

INTRODUCTION

Clostridium difficile is the most important cause of infectious colitis among patients in healthcare settings and is frequently seen in patients outside of the hospital as well. Many important advances in understanding the epidemiology, diagnosis, and treatment of *C. difficile* infection (CDI) have occurred in the last year. In addition, recent advances in the genetic manipulation of *C. difficile* have provided insight into the molecular pathogenesis of CDI, including support for an independent role of toxin B [1], as well as confirming the importance of toxin A [2], the two main virulence determinants of this pathogen. The epidemic BI/NAP1/027 strain has become endemic in many North American healthcare settings [3▪,4▪,5▪▪] and over the past decade has had enormous impact on the epidemiology and management of CDI. This strain, often referred to as 'hypervirulent' has an additional toxin, *C. difficile* transferase (CDT), the role of which has remained unclear. New data, however, suggest that CDT may act by inducing microtubule-based protrusions on the surface of epithelial cells, which facilitate adherence of *C. difficile* [6]; a possible receptor for this toxin has also recently been identified [7▪]. We anticipate a surge of data over the next several years highlighting new insights into the pathogenesis of CDI using these new molecular

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continues to play an important role in susceptibility to both incident and recurrent CDI, but the role of acid-suppression therapy remains less clear. Our ability to accurately predict severe complicated disease and mortality remains inadequate. NAAT testing is improving diagnostic sensitivity, including for epidemic strains, but requires consideration of the clinical context for interpretation. Fidaxomicin shows promise in decreasing overall CDI recurrence, whereas fecal transplantation continues to show encouraging results for those with recurrent or refractory CDI. We anticipate more data in the near future on new treatment and prevention strategies, including additional narrow spectrum antibiotics [46], monoclonal antibodies [47], more effective probiotics [48] and biotherapeutics [49], and vaccines. One *C. difficile* toxoid vaccine (using inactivated whole toxins) was shown to be well tolerated and immunogenic in a phase I dose-finding trial [50▪] and other vaccines are in preclinical development phases [51▪]. Hopefully, with these and other advances, we can start to significantly impact the rates of this persistent pathogen.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
▪ of special interest
▪▪ of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 99–100).

1. Lyras D, O'Connor JR, Howarth PM, *et al.* Toxin B is essential for virulence of *Clostridium difficile*. Nature 2009; 458:1176–1181.
2. Kuehne SA, Cartman ST, Heap JT, *et al.* The role of toxin A and toxin B in *Clostridium difficile* infection. Nature 2010; 467:711–713.
3. ▪ Loo VG, Bourgault A-M, Poirier L, *et al.* Host and pathogen factors for *Clostridium difficile* infection and colonization. N Engl J Med 2011; 365: 1693–1703.

Risk factors for healthcare-associated CDI and healthcare-associated *C. difficile* colonization were evaluated and strain typing by pulsed field gel electrophoresis was performed in a 15-month prospective study of 4143 patients in six Canadian hospitals. Rates of infection and colonization were similar, but the prevalence of NAP1 (aka, BI/027) among those infected (62.7%) was twice that of those that were colonized (36.1%), supporting increased virulence for this strain.

4. ▪ Black SR, Weaver KN, Jones RC, *et al.* *Clostridium difficile* outbreak strain BI is highly endemic in Chicago area hospitals. Infect Control Hosp Epidemiol 2011; 32:897–902.

The authors prospectively evaluated CDI cases in 25 hospitals in Chicago in February 2009 and described rates of incident CDI, rates of related complications, and results of genotyping showing endemicity of the BI strain.

5. ▪▪ Petrella LA, Sambol SP, Cheknis A, *et al.* Decreased cure and increased recurrence rates for *Clostridium difficile* infection caused by the epidemic *C. difficile* BI strain. Clin Infect Dis 2012; 55:351–357.

C. difficile isolates from phase III clinical trials evaluating fidaxomicin were typed using restriction endonuclease analysis; multivariate analysis demonstrated the BI strain to be a risk factor for decreased clinical cure and increased recurrence including patients treated with fidaxomicin.

6. Schwan C, Stecher B, Tzivelekidis T, *et al.* *Clostridium difficile* toxin CDT induces formation of microtubule-based protrusions and increases adherence of bacteria. PLoS Pathog 2009; 5:e1000626.
7. ▪ Papatheodorou P, Carette JE, Bell GW, *et al.* Lipolysis-stimulated lipoprotein receptor (LSR) is the host receptor for the binary toxin *Clostridium difficile* transferase (CDT). Proc Natl Acad Sci U S A 2011; 108:16422–16427.

The lipolysis-stimulated lipoprotein receptor has been identified as a likely receptor for the binary actin-ADP-ribosylating toxin of *C. difficile*. This finding helps elucidate the mechanism of action of the binary toxin produced in some strains of *C. difficile*, including the epidemic BI/NAP1/027 strain.

8. ▪ Lucado J, Gould C, Elixhauser A. *Clostridium difficile* infections (CDI) in hospital stays, 2009. HCUP Statistical Brief #124. January 2012. Rockville, MD: Agency for Healthcare Research and Quality. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf.

This update from the Agency for Healthcare Research and Quality reports data from the Healthcare Cost and Utilization Project on rates of *C. difficile* hospitalization, associated conditions, and mortality through 2009.

9. United Kingdom. Department of Health. The health and social care act 2008: code of practice on the prevention and control of infections and related guidance. December 2010. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_123923.pdf. [Accessed 1 August 2012]
10. Ontario, Canada. Ministry of Health and Long-term Care. Public Hospitals Act. Hospital Management, RRO 1990, Reg 965. July 2012. http://canlii.ca/t/51v7k. [Accessed 1 August 2012]
11. ▪▪ McDonald LC, Lessa F, Sievert D, *et al.* Vital signs: preventing *Clostridium difficile* infections. MMWR Morb Mortal Wkly Rep 2012; 61:1–6.

The Centers for Disease Control and Prevention report epidemiological data for US CDIs obtained from Emerging Infections Program active surveillance in eight areas, National Healthcare Safety Network reporting, and three state-led healthcare-associated infection reduction programs. The majority of infections from this population-based study were noted to be related to healthcare exposure.

12. ▪ Kasper AM, Nyazee HA, Yokoe DS, *et al.* A multicenter study of *Clostridium difficile* infection-related colectomy, 2000–2006. Infect Control Hosp Epidemiol 2012; 33:470–476.

Colectomy rates for *C. difficile* at five academic US medical centers did not increase over the period; community onset of disease was identified as an independent risk factor for colectomy.

13. ▪ Hall AJ, Curns AT, McDonald LC, *et al.* The roles of *Clostridium difficile* and Norovirus among gastroenteritis-associated deaths in the United States, 1999–2007. Clin Infect Dis 2012; 55:216–223.

Gastroenteritis mortality was reviewed between 1999 and 2007 and estimates of the proportion related to *C. difficile* and Norovirus discussed; *C. difficile* was the predominant infectious contributor to increasing mortality.

14. ▪ Alonso CD, Treadway SB, Hanna DB, *et al.* Epidemiology and outcomes of *Clostridium difficile* infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2012; 54:1053–1063.

The 1-year incidence of CDIs was described for a cohort of 999 hematopoietic stem cell transplant patients and risk factors for disease in allogeneic transplants were evaluated; an association with gastrointestinal GVHD was noted.

15. Hun Kim J, Toy D, Muder RR. *Clostridium difficile* infection in a long-term care facility: hospital-associated illness compared with long-term care-associated illness. Infect Control Hosp Epidemiol 2011; 32:656–660.
16. Guerrero DM, Nerandzic MM, Jury LA, *et al.* *Clostridium difficile* infection in a Department of Veterans Affairs long-term care facility. Infect Control Hosp Epidemiol 2011; 32:513–515.
17. ▪▪ Mullane KM, Miller MA, Weiss K, *et al.* Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis 2011; 53:440–447.

Outcomes of cure rate and recurrence in patients with CDI with and without concurrent antibiotic use were evaluated in two phase III trials comparing fidaxomicin and vancomycin. Patients who took concurrent antibiotics had inferior outcomes for both cure and recurrence (the latter did not reach statistical significance) compared with those who did not receive additional non-*C. difficile* antibiotics.

18. ▪ Drekonja DM, Amundson WH, DeCarolis DD, *et al.* Antimicrobial use and risk for recurrent *Clostridium difficile* infection. Am J Med 2011; 124:1081.e1–1081.e7.

Patients with CDI were assessed for risk of infection recurrence based on whether they were given non-*C. difficile* antimicrobials after completion of therapy for CDI; antimicrobials given after infection were associated with a three-fold increased risk.

19. Morrison RH, Hall NS, Said M, *et al.* Risk factors associated with complications and mortality in patients with *Clostridium difficile* infection. Clin Infect Dis 2011; 53:1173–1178.

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