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
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 *Clostridium 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).

4. 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/NAP1/027) among those infected (62.7%) was twice that of those that were colonized (26.1%), supporting increased virulence for this strain.
6. 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.
8. Additional clinical trials evaluating fidaxomicin were typied 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.
11. The lipoprotein-stimulated lipoprotein receptor has been identified as a likely receptor for the binary actin-ADPribosylating 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.
13. The Centers for Disease Control and Prevention reported epidemiological data for USA infections obtained from Emerging Infections Program active surveillance in eight areas, National Healthcare Safety Network reporting, and state-led healthcare-associated infection reduction programs. The majority of infections from this population-based study were noted to be related to healthcare exposure.
15. 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.
17. Gastronenteritis 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.
19. 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.
23. Outcomes of cure rate and recurrences in patients with CDI with and without concurrent antibiotic use were evaluated in two phase III trials comparing fidaxomycin and vancomycin. Patients with toxic 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-CDI antibiotics.
25. Patients with CDI were assessed for risk of infection recurrence based on whether they were given non-CDI antibiotics after completion of therapy for CDI; antimicrobials given after infection were associated with a three-fold increased risk.