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Diagnosis and Treatment of *Clostridioides* (*Clostridium*) *difficile* Infection in Adults in 2020

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***Clostridioides* (formerly *Clostridium*) *difficile* infection** (CDI) remains a major public health problem and accounted for an estimated 450 000 cases and 35 000 deaths in the US in 2015.[1] Since publication of a review of the diagnosis and management of CDI in adults,[2] new clinical tests and therapies have become available and clinical practice guidelines were updated. New evidence supports fecal microbiota transplant (FMT).[3] While overall rates of CDI have stopped increasing, rates of recurrent CDI (rCDI), defined as 2 or more recurrences after an initial CDI, have increased from 1.07 to 3.09 cases per 100 000 person-years between 2001 and 2012.[4] Because rCDI is associated with adverse outcomes, such as hospitalization, the increased incidence deserves attention. This update summarizes current evidence regarding diagnosis and management of CDI in adults, emphasizing management of rCDI.

CDI Diagnosis

The diagnosis of CDI requires documentation of the presence of toxigenic *C difficile* in stool along with a compatible clinical syndrome, which typically includes diarrhea (defined as ≥3 unformed stools in 24 h).[2] Dysbiosis of the gut microbiome (loss of normal bowel microorganisms) leads to asymptomatic carriage of *C difficile*. This may initially provide protection against CDI, but management of asymptomatic C *difficile* colonization can worsen dysbiosis while increasing risk of continued or subsequent colonization, increasing the risk of symptomatic infection. Therefore, managing asymptomatic colonization is not recommended, and it remains important to distinguish asymptomatic colonization from symptomatic disease.

Most US laboratories use single-step (1 test), highly sensitive nucleic acid amplification tests (NAATs). Enzyme immunoassay testing for toxins and/or multistep testing for *C difficile* bacterial products and/or genes are now less common.[5] Single-step testing has increased concerns of the potential harms of false-positive test results, which could result in inappropriate treatment of patients who are colonized with *C difficile* but do not have symptomatic infection. The addition of CDI to the Centers for Medicare & Medicaid Services' safety domain measures, which affects reimbursement through the agency's Hospital Value-Based Purchasing Program, has led to increased scrutiny of CDI testing practices. For these reasons, the new Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America guidelines recommend measures to improve test specificity for symptomatic disease over asymptomatic colonization, including laboratory rejection of formed stool specimens submitted for testing and electronic health record alerts for scenarios in which diarrhea is common, such as after receipt of water-soluble oral contrast (**Table**). The guidelines also recommend multistep testing over single-step NAATs to improve specificity when ordering and sample submission restrictions (such as laboratory rejection of formed stool specimens) are not in place.

Table. Highlights From Updated Clinical Practice Guidelines for the Diagnosis and Management of *Clostridioides difficile* Infection (CDI)

Guideline topic	2020 Update
Diagnosis	
Policy regarding submission of formed specimens for *C difficile* testing	Laboratory-based rejection of formed stool specimens should be performed
Implementing institutional criteria for ordering *C difficile* tests	Institutions should limit testing to certain patients (eg, those receiving laxatives)
Multistep testing for *C difficile*	Multistep testing recommended rather than single-step NAAT-based testing when rejection of formed specimens and/or other institutional sample submission restrictions are not implemented
Treatment	
Initial episode of mild/moderate CDI	125 mg of vancomycin 4 times per day or 200 mg of fidaxomicin twice per day for 10 days 500 mg of metronidazole 3 times per day for 10 days if vancomycin and fidaxomicin are unavailable or not appropriate (eg, because of an allergy)
Initial episode of severe CDI[a]	125 mg of vancomycin 4 times per day or 200 mg of fidaxomicin twice per day for 10 days
Initial episode of complicated/fulminant CDI[b]	No change
First recurrence of CDI	125 mg of vancomycin 4 times per day for 10 days if metronidazole was used for the initial episode, prolonged vancomycin taper/pulse,[c] or 200 mg of fidaxomicin twice day for 10 days if vancomycin was used for the initial episode
Second or subsequent recurrence of CDI	Prolonged vancomycin taper/pulse,[c] 125 mg of vancomycin 4 times per day for 10 days followed by rifaximin 400 mg 3 times per day for 20 days, 200 mg of fidaxomicin twice per day for 10 days, or fecal microbiota transplant

Abbreviation: NAAT, nucleic acid amplification test.

[a] Serum white blood cell count >15 000/μL and/or serum creatinine with >1.5-fold elevation above baseline.

[b] Hypotension or shock, ileus, or megacolon.

[c] Example taper/pulse: 125 mg of vancomycin 4 times per day for 10 to 14 days, twice per day for 1 week, and then every 2 to 3 days for 2 to 8 weeks.

CDI Treatment

Recent recommendations focus on reducing the risk of rCDI. Guidelines recommend discontinuing the inciting antibiotic as soon as possible, because continued exposure increases the risk of rCDI.[2] Based on data demonstrating worse rates of initial clinical cure (resolution of diarrhea at the end of 10 days of treatment) and sustained cure (clinical cure and no CDI recurrence 1 month after treatment), the new guidelines no longer recommend metronidazole as first-line therapy. For both mild and severe CDI, either vancomycin or fidaxomicin are preferred,[3] and metronidazole is only recommended if allergy, intolerance, or financial considerations preclude prescription of vancomycin or fidaxomicin (Table).

The treatment recommendations for complicated and fulminant CDI have not changed.

For rCDI, in addition to the previously recommended vancomycin taper/pulse regimen, 2017 IDSA guidelines recommend other treatment options, including 10 days of vancomycin followed by 20 days of rifaximin. Alternatively, a case series suggested that fidaxomicin could be prescribed for 20 days instead of rifaximin.[3] Guidelines also recommend FMT as an option when there are 2 or more CDI recurrences, based on recent randomized clinical trials demonstrating safety and efficacy of FMT. However, FMT remains experimental and the US Food and Drug Administration (FDA) only permits its clinical and noninvestigational use for refractory CDI or rCDI. In a 2019 meta-analysis of a randomized clinical trial, FMT was associated with a cure rate of only 76.1%.[6] Many unanswered questions about FMT remain, including the optimal timing, preparation, and route of delivery and which patients would benefit most. Accordingly, the IDSA guideline recommends treatment with antibiotics for at least 2 recurrences (ie, 3 CDI episodes) before prescribing FMT.

New and Emerging Options in Diagnosis and Treatment of CDI

Diagnosis

The first ultrasensitive toxin detection assay obtained UFDA approval in 2019 (Clarity C. diff toxins A/B, Singulex, Inc). Similar to existing tests, these assays are rapid, but, unlike an enzyme immunoassay for toxins, they have better analytic sensitivity (ie, picograms per mL), which is up to 3 orders of magnitude more sensitive than enzyme immunoassay tests and comparable to the reference-standard, time-consuming cell cytotoxicity assay. It is unknown whether these tests are more specific for CDI vs asymptomatic colonization, but a 2019 study using one of the ultrasensitive toxin tests could not differentiate between these 2 states.[7] Multiplex NAAT panels that simultaneously test for a number of gastrointestinal organisms are also available and include *C difficile* along with at least 12 other targets in 1 test (FilmArray Gastrointestinal Panel, BioFire Diagnostics). Although these tests are convenient in patients in whom multiple other diagnoses are suspected, there are some disadvantages. First, they are costly ($463 per test). Second, they require sample collection in media, precluding laboratory-based rejection of formed specimens. Third, the use of a DNA purification step in addition to DNA extraction increases sensitivity for toxin genes and, thus, could increase detection of colonization and lower specificity for symptomatic CDI.

Treatment

Several primary and adjunctive treatments are currently being studied for individuals with CDI, including new agents such as ridinilazole, a nonabsorbable, small-molecule antibiotic, and immune treatments, live biotherapeutics/probiotics, and treatment with bacteriophages with activity against specific *C difficile* strains.[8] Of these, only the antitoxin B monoclonal antibody, bezlotoxumab, has FDA approval, and it reduces the risk of rCDI by approximately 40% when prescribed during an initial episode.[9] The high cost of bezlotoxumab has limited its availability for patients, although a recent analysis suggested treatment was cost-effective.[10]

Conclusions

Differentiating CDI from asymptomatic carriage remains challenging, but new recommendations regarding testing can improve specificity. Current evidence supports fidaxomicin for management of CDI. Finishing treatment with rifaximin after the initial vancomycin course and FMT shows benefit in reducing rCDI and are now recommended by IDSA guidelines. New diagnostic (eg, ultrasensitive rapid toxin assays) and therapeutic (eg, novel antibiotics with lower rCDI risk) approaches are underway in clinical trials and may yield new options for the management of CDI in the near future.

ARTICLE INFORMATION

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