TRENDS-in-MEDICINE

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SUMMARY

New treatment options for *Clostridium difficile* infection are emerging that may improve outcomes. These include:

- Narrow-spectrum antimicrobials.
- Fecal microbiota transplantation.
- Monoclonal antibodies.

Treatment goals now include correcting dysbiosis, killing the organism, and helping adaptive immunity. Successful management of CDI also includes appropriate testing and disinfection practices.

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CURRENT CONCEPTS IN THE MANAGEMENT OF INITIAL AND RECURRENT *CLOSTRIDIUM DIFFICILE*
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The rate of *Clostridium difficile infection* (CDI) in hospitals is high and is *not* going down. The Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Centers for Medicare and Medicaid Services (CMS) all consider CDI a top priority. Research has provided a better understanding of the pathogenesis of CDI, including the role of intestinal dysbiosis (microbial imbalance) and host immune response on patient outcomes.

New treatment options are emerging – such as narrow-spectrum antimicrobials, fecal microbiota transplantation, and monoclonal antibodies – that hold promise to improve outcomes. Treatment goals now include correcting dysbiosis, killing the organism, and helping adaptive immunity, all of which are essential for successful treatment. Successful management of CDI also includes appropriate testing and disinfection practices.

DRUG THERAPIES

Current antimicrobial treatment options include ANI Pharmaceuticals' Vancocin (vancomycin), Pfizer's Flagyl (metronidazole), and Merck's Dificid (fidaxomicin), depending on the severity or course of the disease and the risk of a first recurrence.

Current guidelines from the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) recommend managing second CDI episodes (first recurrences) with a vancomycin taper/pulse regimen (VAN-TP). Melinda Soriano, PharmD, medical science liaison for The Medical Affairs Company, reported on a study of 47 patients managed with a VAN-TP regimen at Loyola Outpatient Care Center. Of these, 56% (26) had no further recurrent CDI episodes, with a 34-day symptom-free interval from the end of VAN-TP to recurrent CDI. Mean VAN-TP duration was 98 days.

The researchers noted that the regimens were typically longer than those suggested by guidelines. Because patients with further recurrent CDI episodes tended not to receive every third day dosing of vancomycin, they speculated that including a Q3D pulse at the end of the VAN-TP may be helpful.

PFIZER's Flagyl (metronidazole)

Metronidazole has been shown to be globally inferior to vancomycin, and there is evidence of resistance to metronidazole developing, as the minimum inhibitory concentration (MIC) has crept upward over the decades. Standard MIC susceptibility testing may fail to capture the higher MICs of metronidazole.

MERCK's Dificid (fidaxomicin)

Fidaxomicin has shown efficacy equal to vancomycin in terms of clinical cure, but fidaxomicin lessens the risk of recurrence. Fidaxomicin has a narrow spectrum of activity to preserve the host microbiota, but because of its high cost, it is often reserved for worst cases, though the wisdom of this approach is being challenged given the high costs of hospital readmission and high healthcare utilization associated with recurrence. More competition in the narrow-spectrum anti-*C. diff* world can be expected.

MERCK's bezlotoxumab (MK-6072, formerly MDX-1388)

This fully human monoclonal antibody that neutralizes *C. difficile* toxin B is currently under review by the FDA. It was granted priority review and has a PDUFA date of July 23, 2016.

A pooled analysis of two Phase III trials in CDI (MODIFY-I and MODIFY-II), with a total of 2,413 patients, showed a reduction in the rate of recurrent CDI by about one-third with the use of bezlotoxumab. The analysis, presented at the meeting by Mark Wilcox, MD, a microbiologist from Leeds Teaching Hospitals, U.K., compared a 10- to 14-day course of standard of care antibiotics (oral metronidazole, oral vancomycin ± IV metronidazole, or oral fidaxomicin ± IV metronidazole) to bezlotoxumab alone or bezlotoxumab + Merck's actoxumab (MK-3415A), an IgG1 antibody directed against *C. diff* toxin A.

The results showed that bezlotoxumab was significantly better than standard care, and the efficacy in preventing recurrence was sustained over 12 weeks of follow-up.

However, the addition of actoxumab added little, and the combination is not going forward, only bezlotoxumab.

Pooled Analysis of MODIFY-I and MODIFY-II Trials

Measurement	Bezlotoxumab (MK-6072)	Bezlotoxumab + actoxumab	Placebo
CDI recurrence	17% (p<0.0001)	15% (p<0.0001)	27%
Global cure	64% (p=0.0001)	58% (Nss)	54%

THE MICROBIOME

There is growing interest in new treatments for CDI that protect or restore the host microbiota. Among the agents directed at adjusting the microbiome are:

- **ACTELION's cadazolid (ACT-179811).** This investigational oxazolidinone inhibits *C. diff* protein synthesis, thereby suppressing toxin and spore formation. Kaiyu Wu, PhD, a postdoc from the University of Calgary, Canada, and colleagues cultured fecal samples retained during the conduct of a Phase II trial of cadazolid, measuring *C. diff* count reductions and testing the samples for quantification of major microbiota groups. They found less alteration to the fecal microbiome with cadazolid vs. vancomycin.
- **DA VOLTERRA's DAV-132.** This oral adsorbent-based product, co-administered with oral moxifloxacin, protected healthy subjects against fecal microbiome disruption without altering the plasma pharmacokinetics of moxifloxacin. DAV-132 has an activated charcoal core that adsorbs a wide range of antibiotics and a pH-dependent enteric polymer as its external coating. Jean De Gunzburg, PhD, chief scientific officer at Da Volterra, reported that DAV-132 removed free moxifloxacin from feces by >99% vs. moxifloxacin alone. In an *in vivo* human gut model and an *in vivo* hamster model of CDI, DAV-132 prevented *C. diff* overgrowth and toxin production.
- **SERES THERAPEUTICS' SER-109.** This ecology of bacterial spores enriched from the stool of healthy donors was granted both breakthrough therapy status and orphan drug status by the FDA. Mary-Jane Lombardo McKenzie, PhD, principal scientist, microbiology, at Seres, reported on an open-label trial of SER-109 for the prevention of recurrent CDI in 30 patients with ≥3 episodes of CDI in the past 12 months who had responded to standard antibiotics.

  Vancomycin-resistant *enterococcus* (VRE) colonization was diminished after SER-109 administration, with titers decreased to below the limit of detection in all eight patients with VRE at baseline. Microbiome remodeling by SER-109 was also evidenced by a shift from gut *Enterobacteriaceae* to a predominance of *Escherichia coli* and an increase in microbiome diversity via genomics analysis.

FECAL MICROBIOTA TRANSPLANTATION

CDI now recurs in up to 25% of patients and is associated with significant mortality, extended length of stay, and excess hospital costs. Fecal microbiota transplantation (FMT) is an emerging treatment for recurrent CDI.

Elizabeth Hohmann, MD, an infectious disease specialist from Massachusetts General Hospital, spoke about FMT as an option after antibiotics fail. Only ~25% of potential stool donors qualify, she said. Among the qualifications, donors must not have received antibiotic therapy within the previous six months and must not have a history of gastrointestinal disease.

Efficacy of stool infusion is 87% in total. Oral frozen fecal microbiota capsules have success equivalent to that with a naso-gastric tube for colonic delivery, she said.

The protocol used at Massachusetts General Hospital calls for administration of 15 capsules on each of 2 successive days. Patients must be NPO (nothing by mouth) for 4 hours before and 1 hour after taking the capsules. Dr. Hohmann said:

- This protocol achieved an 87% cure with one dose, improving to 94% with three doses.
- The course of recovery is generally rapid, with spontaneous relapses rare but occurring as late as 2-3 months.
- Microbiota diversity post-treatment is similar to that of donors.

REBIOTIX'S RBX-2660

Another study found a large number of outwardly healthy volunteer stool donors were unsuitable due to underlying conditions, but their suitability as a donor changes over time. Courtney Jones from Rebiotix and co-investigators screened 62 potential donors who were recruited by word of mouth. The donors were recruited for the purpose of supplying raw material to support Phase II trials of RBX-2660, a microbiota suspension under investigation for the treatment of recurrent CDI. RBX-2660 was granted breakthrough therapy status by the FDA shortly after IDWeek.

Donors were screened for an extensive list of blood and stool pathogens, with 11 (17.8%) failing the initial screening process. On subsequent testing, 22 more were excluded. Asymptomatic infection was the primary reason for screen or rescreen failure. The researchers recommended that potential stool donors should be tested each time their donation is to be used for treatment.

CO-INFECTION

Co-infection with *Candida* and *C. difficile*, although rare, is associated with substantial 30-day mortality, according to CDC data. Among patients with CDI, 0.7% developed candidemia co-infection. Their 30-day mortality was 29%. *Candida* species found in co-infected patients included *C. albicans* (37%), *C. glabrata* (28%), and *C. parapsilosis* (19%). Risk factors for CDI-candidemia co-infection were severe CDI, colectomy, and CDI treatment with vancomycin or metronidazole.

CDI is not a risk factor for subsequent bloodstream infection. A retrospective review of a cohort of medical and surgical inpatients hospitalized for >72 hours and who developed diarrhea, presented by Robert Ulrich, MD, a hospitalist from the University of Michigan, found *C. diff* was not a risk factor for subsequent bloodstream infection. Inpatients who were male, had a central line, or had a higher comorbidity score were more likely to develop a bloodstream infection.

Another study, presented by Andrea Censullo, MD, a hospitalist from Cedars-Sinai Medical Center, found that the incidence of bacteremia associated with hospital-onset CDI was 1.8% for inpatients at her tertiary care teaching hospital.

When bacteremia did develop, it was associated with worse clinical outcomes. This case-control study found significant risk factors for developing bacteremia were an elevated Charlson comorbidity score, a diagnosis of malignancy, and neutropenia. Of the patients with CDI-bacteremia, 80% had underlying malignancy, and 40% were neutropenic. Most (79%) received chemotherapy during their index hospitalization for CDI. The researchers concluded that the data do not support the use of empiric antimicrobial therapy for enteric bacterial translocation unless patients have neutropenia or malignancy.

CDI-Bacteremia and CDI Recurrence

Measurement	Control	Patients with CDI-bacteremia	p-value
Colectomy	12%	0.6%	<0.001
Hospitalization	39.5 days	24.0 days	0.02
More frequent ICU admission	44%	28%	Nss, 0.07
In-hospital mortality	20%	11%	Nss, 0.18

OVER-DIAGNOSIS OF CDI

Heightened awareness of CDI leads to frequent testing of *C. difficile* toxin. Evidence suggests that sensitive polymerase chain reaction (PCR) assays may contribute to an over-diagnosis of CDI given a significant number of asymptomatic colonized patients.

Barbara Pahud, MD, MPH, a pediatric infectious disease specialist from Children's Mercy Hospital in Kansas City, presented the findings from a four-center study in which the frequency of *C. diff* detection in healthy children <2 years

old was compared to children with acute gastroenteritis (AGE).

C. diff was detected more often in healthy control children than in those with acute gastroenteritis (28% vs. 14.4%), which is evidence that *C. diff* detection by real-time PCR alone in young children does not differentiate clinical disease from *C. diff* colonization.

Laxative use or delayed testing for *C. diff* toxin (CDT) may overestimate the true burden of hospital onset-CDT by >20%, according to data presented by Stephen Rineer, BS, from the University of Central Florida College of Medicine. *C. diff* toxin tests ordered at Florida Hospital in Orlando were compared with patients receiving laxatives for ≥24 hours. A total of 3,234 CDT tests were run on 2,543 unique patients, and 387 (12.0%) were positive, of which 149 (4.6%) were classified as hospital-onset CDT. Among cases of hospital-onset CDT, the sensitivity of enzyme immunosorbent assay (EIA) was 44%.

During this time, CDT tests were ordered for 234 patients (9.2%) who were on laxatives ≥24 hours, of which 10.3% were positive for CDT, and 7.8% were classified as hospital-onset CDT. Stool collection was delayed ≥24 hours for 203 patients (8.0%), of which 27 (13.3%) were positive, and 15 (7.4%) were classified as hospital-onset CDT.

The sensitivity of EIA testing in patients on laxatives and among those with delayed stool collection was 16% and 40%, respectively. The researchers concluded that this lower EIA sensitivity in patients on laxatives or delayed collection "suggests an overestimate of patients with true CDI. Assuming every such case represented asymptomatic colonization, this would result in an over-reporting of hospital-onset CDT cases by 23%. They suggested that processes be established, perhaps through electronic health records, to remind providers about laxative use or other alternate explanations for diarrhea when testing for CDT is ordered.

Outcomes are worse among patients with CDI detected by both EIA and PCR vs. those who are only PCR-positive, but outcomes in the latter group are significantly improved by CDI treatment. This finding suggests that patients with CDI detected by highly sensitive PCR have true CDI and not just colonization, according to data presented by Becky Smith, MD, an infectious disease specialist from NorthShore University HealthSystem, and co-investigators. They identified 127 patients at their hospital with true-positive CDI.

Of these, 56 were positive by both EIA and PCR (Group 1), and 71 were positive by PCR only (Group 2). On multivariate analysis, patients in Group 2 were less likely to have severe CDI, less likely to receive treatment, and had shorter length of stay. Group 2 patients were also significantly less likely to have recurrent CDI or a CDI-related readmission within 90 days.

NEW MODES OF DISINFECTION

Environmental surfaces play an important role in the cross-transmission of pathogens that cause CDI and other healthcare-associated infections. *C. difficile* spores are resistant to many disinfectants and may persist for long periods in the hospital. New weapons being explored to reduce cross-transmission include ultraviolet (UV) irradiation and novel surface films.

UV germicidal irradiation (UVGI)

Deployment of UVGI was studied in three adult hematology-oncology units at the Hospital of the University of Pennsylvania, as reported by David Pegues, MD, an infectious disease specialist from the Perelman School of Medicine at the University of Pennsylvania. Following room cleaning with bleach, UVGI was deployed for two 8-minute cycles on either side of the patient's bed. Over 52 weeks, UVGI was deployed for 21.1% of all patient discharges on the three study units. Compared with a 1-year baseline period before the intervention, the rates of CDI declined by 25% on the study units but increased by 16% on non-study units during the 1-year intervention period. The authors estimate that up to $191,000 in direct annual costs were averted by preventing cases of CDI on study units.

XENEX's Full Spectrum, a pulsed xenon-ultraviolet (PX-UV) disinfection system

A study found using this system in patient rooms did *not* reduce the rate of CDI when overall compliance with its use was only 60%. Kathleen McMullen, MPH, lead infection preventionist at Barnes-Jewish Hospital in St. Louis, conducted a two-phase study of this PX-UV light disinfection system in addition to routine hospital room cleaning.

- In Phase 1, PX-UV was used after the discharge of patients with a positive CDT assay.
- In Phase 2, use expanded to all rooms regardless of CDI status in the four patient care areas with high CDI rates. Each phase lasted for 4 months.
- Compliance with utilization was 70% in Phase 1 and 59% in Phase 2.
- Hospital-wide CDI rates were not statistically different between the two phases, nor were they significantly different in the four areas with expanded PX-UV use.

ENGINEERED MATERIALS' copper film

A novel copper surface film that can be applied directly to pre-existing surfaces was found to rapidly kill nosocomial gram-positive and gram-negative pathogens but had little activity against *C. difficile*. Christopher Crnich, MD, PhD, an infectious disease specialist from the University of Wisconsin, studied the effect of copper film on test surfaces inoculated with MRSA, *Acinetobacter baumannii*, and a toxigenic strain of *C. difficile* (ATCC 9689). *In vitro* testing yielded no recovery of MRSA or *A. baumannii* at all time periods up to 36 hours, with no significant activity against *C. difficile*.