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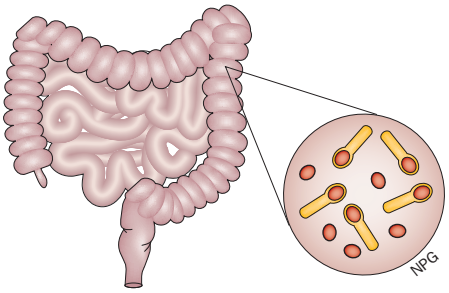
INFECTION

# Bacteriotherapy for recurrent *C. difficile* infection—spores to the rescue?

Administration of spores of nontoxigenic *Clostridium difficile* was found to be a safe and effective treatment to reduce recurrence of *C. difficile* infection (CDI), according to a study published in *JAMA*. This new approach is a twist on traditional bacteriotherapy—the treatment of disease by using bacteria or their products—that in recent years has led to the emergence and increase in popularity of faecal microbiota transplantation as a treatment for CDI.

CDI is one of the most common health-care-associated infections and a major public health issue. Symptoms can include severe diarrhoea, abdominal pain and fever, with toxins causing intestinal inflammation and cell death. In severe cases, patients can develop pseudomembranous colitis. Arguably, CDI is a disease governed by antibiotics. Typically, the infection is acquired after antibiotic treatment and ingestion of environmental *C. difficile* spores, which germinate and lead to growth of *C. difficile* in the gut and production of toxins that result in diarrhea symptoms. Currently, standard treatment for CDI relies on use of antibiotics such as metronidazole or vancomycin, but this approach can often exacerbate the problem: once a patient finishes the course of antibiotics, recurrence can occur, leading to repeated cycles of infection.

In their phase II, randomized, double-blind, placebo-controlled clinical trial, Gerding and colleagues investigated the safety and optimal dosing for spores of nontoxigenic *C. difficile* strain M3 (NTCD-M3) as treatment for CDI. They also examined whether administration of these spores led to colonization of nontoxigenic *C. difficile* in the gastrointestinal tract and reduced recurrence rates for CDI.




The researchers recruited 173 patients who were diagnosed as having CDI (first episode or first recurrence) and had been treated successfully with either metronidazole, vancomycin or both. Patients were randomly assigned to one of four regimens: oral liquid dose of NTCD-M3 spores at $1 \times 10^4$ spores per day for 7 days ($n = 43$), $1 \times 10^7$ spores per day for 7 days ($n = 44$) or $1 \times 10^7$ spores per day for 14 days ($n = 42$) or placebo for 14 days (liquid formulation with no spores, $n = 44$). 157 study participants completed treatment, and outcomes were monitored during the course of treatment and over the 6-week period thereafter.

Colonization with NTCD-M3 was reported in 69% of patients (71% of those receiving $1 \times 10^7$ spores and 63% of those receiving $1 \times 10^4$ spores per day). Crucially, recurrence rates for CDI were markedly reduced in those receiving NTCD-M3 spore treatment (11% versus 30% in those receiving placebo). Moreover, those with successful colonization with NTCD-M3 had much lower rates of recurrence (2%) than those who received NTCD-M3 spores but did not have successful colonization (31%). Clinical interventions for CDI recurrence were also reduced by spore treatment, with use of antibiotics for recurrent CDI in 33% of the placebo group and 14% in the NTCD-M3 groups. NTCD-M3 spores seemed to be well tolerated and safe, with incidence of treatment-emergent adverse events (such as diarrhoea) similar to, and in some cases fewer than, for placebo.

How NTCD-M3 prevents recurrent CDI is currently unknown. "The most likely hypothesized mechanism of action of NTCD-M3 is that it occupies the same metabolic and adherence niche in the gastrointestinal tract as does toxigenic *C. difficile* and, once established, is able to outcompete resident or newly ingested toxigenic strains," write the authors. Further trials are awaited.

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**Original article** Gerding, D. N. *et al.* Administration of spores of nontoxigenic *Clostridium difficile* strain M3 for prevention of recurrent *C. difficile* infection. *JAMA* **313**, 1719–1727 (2015)