

## CLOSTRIDIUM DIFFICILE

Restoring the balance—microbes for the management of *Clostridium difficile* infection?

The available evidence suggests that some probiotics are safe and effective for the prevention of *Clostridium difficile*-associated diarrhoea (CDAD) after antibiotic use, report the authors of a new analysis published in the *Cochrane Database of Systematic Reviews*. The findings raise the question of whether we are moving towards an era in which microbes are pitted against one another to prevent and treat infection?

*Clostridium difficile* infection (CDI) has dramatically increased in the past few decades—it is now one of the leading causes of health-care-associated infection and diarrhoea—and is typically linked with antibiotic use. Management of this infection is difficult, with patients often experiencing recurrent disease, trapped in a vicious cycle of antibiotic treatment that perpetuates the problem.

Goldenberg *et al.* performed an extensive search of the literature for research detailing randomized controlled trials (RCTs) of probiotics for the prevention of CDAD or CDI. A total of 1,871 studies were identified, with 31 (totalling 4,492 study participants) matching their eligibility criteria.

“We conducted a systematic review and meta-analysis of randomized trials, published our protocol *a priori*, and applied standard and emerging meta-analytic methods, including methods for assessing the credibility of our subgroup analyses, assessing the risk of bias associated with missing participant data and rating the confidence in the estimates of effect,” explains author Bradley Johnston.

Of the 23 trials ( $n=4,213$ ) in which participants completed the study (inpatients and outpatients), the evidence indicates that probiotics substantially reduce the risk of CDAD (64% relative risk reduction) in individuals taking antibiotics. However, taking probiotics in combination with antibiotics did not affect the incidence of CDI.

In line with requirements from the Cochrane Collaboration, the study authors will repeat their analysis in 2 years. Moreover, Johnston calls for head-to-head RCTs of competing probiotics to determine the best strains and dosages to use, as well as studies for the safety of probiotics in immunocompromised individuals.

Christina Surawicz, an expert in CDI who was not involved in this study, agrees with this call for further RCTs. “The problem with meta-analyses of probiotics to date is that they combine several different probiotics when ideally each one should be studied individually using specific strains with standard doses, confirmed viability, and studied for specific indications” she notes. “We need to know which probiotics work, who is at high risk and needs them, and who should not take them because of safety risks.”

Another example of microbial manipulation to manage CDI that has been gaining momentum in the past few years is faecal microbiota transplantation (FMT), which has so far proven to be an effective treatment for recurrent CDI

in case series and an RCT. However, the recent ruling by the FDA that when FMT is used to prevent, treat or cure any disease or condition it is considered a biological product or ‘drug’—thus requiring an investigational new drug application for use (*American Gastroenterological Association*, 6 May 2013)—could stall its popularity.

The subject garnered a lively debate in a session at Digestive Disease Week 2013, as well as in social media, and demonstrates the change in attitudes towards using microbes and their products as potential therapies or for prevention. “I think physicians are slowly starting to appreciate that microbes are not all bad, and use of antibiotics is not without adverse consequences,” says independent commentator Alexander Khoruts, who notes that this attitude is slowly being adopted by patients too.

Crucially, the exact mechanisms for how probiotics and FMT work in the context of CDI are unknown, as are the long-term effects, and further study should help to clarify these issues. For now, current guidelines from the American College of Gastroenterology, which were published before the new findings from Goldenberg *et al.*, take a cautious approach, noting the following: insufficient evidence that probiotics prevent CDI; limited evidence for the use of adjunct probiotics to decrease recurrences in patients with recurrent CDI; and only a ‘conditional recommendation’ to consider FMT after failed vancomycin treatment.

Katrina Ray

**Original article** Goldenberg, J. Z. *et al.* Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD004549. doi:10.1002/14651858.CD006095.pub3.

**Further reading** Surawicz, C. M. *et al.* Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am. J. Gastroenterol.* **108**, 478–498 (2013)

