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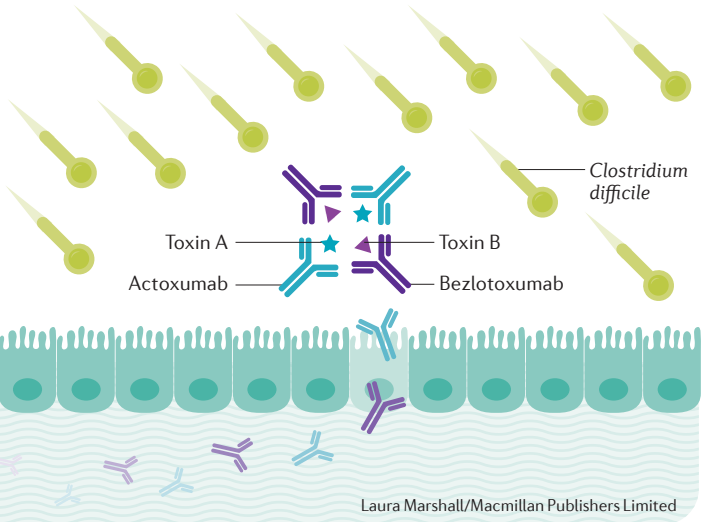
INFECTION

# Modifying recurrence of *Clostridium difficile* infection

> *Clostridium difficile* remains one of the most common causes of infectious diarrhoea in hospitalized patients…

In patients receiving antibiotics for primary or recurrent *Clostridium difficile* infection (CDI), treatment with bezlotoxumab (a monoclonal antibody against *C. difficile* toxin B) substantially reduced the rate of recurrent infection, compared with placebo. However, the addition of actoxumab (a monoclonal antibody against *C. difficile* toxin A) in a combination therapy with bezlotoxumab did not improve efficacy of this approach.

*Clostridium difficile* remains one of the most common causes of infectious diarrhoea in hospitalized patients in high-income countries. Treatment can be challenging, with repeated cycles of recurrent infection and hospitalizations. The *C. difficile* toxins A and B are considered the main virulence factors. Acting as an enterotoxin and a cytotoxin, respectively, these potent toxins damage the intestinal epithelial barrier. Crucially, *in vivo* studies indicate that passive or active immunization against the *C. difficile* toxins is protective in animals that are challenged with CDI.

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In these new phase III studies (MODIFY I and MODIFY II), in addition to standard antibiotics, the researchers investigated treatment with monoclonal antibodies that bind and neutralize the *C. difficile* toxins as a means of passive immunization. "Earlier *in vitro* and animal studies and a phase II clinical trial had established the proof of concept of using monoclonal antibodies to reduce the risk of recurrent CDI, but it remained unclear whether one antibody or both was needed and what are their relative efficacies," explains author Mark Wilcox.

MODIFY I and II were randomized, double-blind, placebo-controlled trials conducted across multiple countries worldwide, including 2,655 adults receiving standard-of-care antibiotics (metronidazole, vancomycin or fidaxomicin) for primary or recurrent CDI. Study participants received either bezlotoxumab alone (an infusion of 10 mg/kg), bezlotozumab plus actoxumab (10 mg/kg each) or placebo; patients received actoxumab alone (10 mg/kg) in MODIFY I but treatment was discontinued after a planned interim analysis. The primary end point was a new infection episode after initial cure (that is, recurrent infection) within 12 weeks after infusion.

The rate of recurrent CDI was markedly lower with bezlotoxumab alone than placebo (17% versus 28% in MODIFY I and 16% versus 26% in MODIFY II). Similar decreases in recurrence were observed with bezlotoxumab and actoxumab combination therapy — there was no added boost to protection with the addition of actoxumab. Importantly, in subgroup analyses, rates of recurrent CDI were lower in bezlotoxumab-treated groups than placebo in patients at high-risk of recurrent infection or an adverse outcome, such as those who were immunocompromised, aged ≥65 years, or had severe CDI or history of CDI. Sustained cure (initial cure without recurrent infection within 12 weeks) was highest with bezlotoxumab alone (64%) versus combination therapy (58%) and placebo (54%). The new drugs seemed to be safe, with equivalent rates of adverse events across the study groups.

"Doctors should now consider which patients could best benefit from use of bezlotoxumab," concludes Wilcox. For instance, bezlotoxumab was particularly effective in patients with risk factors for poor outcome, such as older age, immunocompromised status and severe infection. "Post-hoc analyses provided evidence that fewer recurrent episodes were associated with less chance of admission to hospital, and less future need for CDI treatment such as antibiotics or faecal microbiota transplantation," he adds.

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**ORIGINAL ARTICLE** Wilcox, M. H. *et al.* Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N. Engl. J. Med.* **376**, 305–317 (2017)
**FURTHER READING** Kociolek, L. K. & Gerding, D. N. Breakthroughs in the treatment and prevention of *Clostridium difficile* infection. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 150–160 (2016)