CLOSTRIDIUM DIFFICILE

The importance of toxin A is re-established in *Clostridium difficile* infection

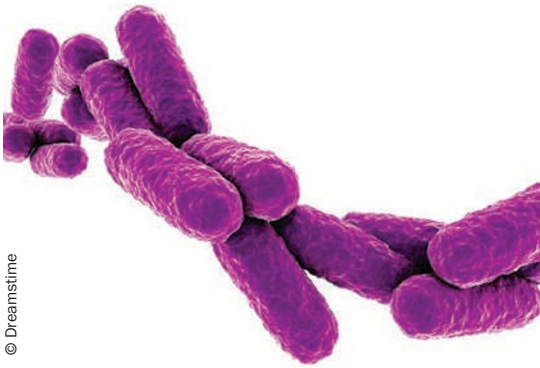
In a hamster model of *Clostridium difficile*, infection with *C. difficile* strains producing either toxin A or toxin B caused fulminant disease, according to a research team from the University of Nottingham, UK.

Following the identification of the two toxins of *C. difficile*, there has been uncertainty regarding their relative roles in the development of *C. difficile* infection. Initial studies suggested that purified toxin A alone was lethal and that toxin B was unable to initiate the symptoms of *C. difficile* infection unless it was mixed with toxin A. Later studies using unstable, isogenic mutants indicated that the converse was true; mutants that produced only toxin A were avirulent and those that produced toxin B alone caused disease. "What was really needed was a perfectly controlled experiment, in which a strain that produced both toxins was permanently mutated such that stable variants were made that produced one or other of the toxins, or neither," explains Nigel P. Minton, corresponding author.

The researchers used a gene knockout system (ClosTron) to create three stable mutant strains: A^+B^-, A^-B^+ and A^-B^-. The relative virulence of all three mutants was then compared to the parent strain (A^+B^+).

The A^-B^- mutant strain was avirulent. Hamsters infected with the A^-B^+ mutant succumbed extremely rapidly to the disease, suggesting that toxin B is the most virulent toxin. However, in contrast to a previous study that used the same model and similar mutants, hamsters infected with the A^+B^- also developed the infection. This finding suggests that toxin A could also be important in *C. difficile* infection.

"There are subtle differences between the strains used," says Minton, "that have affected the virulence of the A^+B^- mutant strains used in these two studies." The investigators are now planning to resequence the strains to identify the cause of the differences in virulence.



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Toxins from different strains of *C. difficile* have inherent variability, so these results must be interpreted with caution. However, "these findings re-establish the importance of toxin A in the disease," concludes Minton. When developing diagnostic tests and preventive measures for *C. difficile* it is, therefore, important to consider both toxin A and toxin B.

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