

# Cephamycins: Treatment Option for Recurrent *Clostridioides difficile* Infection

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Bacteria are known to withstand adverse conditions by differentiating vegetative cells into spores as a means of survival. Spore-forming bacteria are ubiquitous in nature ranging from natural food contaminants (*Bacillus cereus*), bioterrorism agents (*B. anthracis*) to specific representatives of *Clostridium* sp. as animal pathogens. *Clostridium difficile*, a toxin-producing spore bearer now known as *Clostridioides difficile* is one of the human pathogens found to be associated with antibiotic-associated diarrhea and pseudomembranous colitis.<sup>1</sup> Literature suggests that around 35% of patients experience *C. difficile* infection relapse once the treatment with first-line of antibiotics (metronidazole and vancomycin) is stopped and even multiple relapses were observed in 40–60% of these patients.<sup>2,3</sup> The major cause of initiation, dissemination, and reinfection of *C. difficile* disease is the formation of spores since metronidazole and vancomycin merely act upon the vegetative cells and do not possess sporicidal activity.<sup>3</sup> Other than these, the Food and Drug Administration-approved fidaxomicin is also currently in use, but its affordability is already an ongoing debate.<sup>4</sup> So in the present scenario when there is no *C. difficile* vaccine, it calls for an urgent need to devise economical therapeutic strategies that can control the cycle of *C. difficile* reinfection by acting not only on the vegetative cells but also on the spores.

In a recent study published in *Nature Microbiology*, August 2019, Srikhanta et al.<sup>3</sup> from Monash University tested the sporicidal efficacy of cephamycins (cefoxitin, cefotetan, and cefmetazole) in bacterial pathogens. In a mouse disease model, authors used transmission electron microscopy imaging to visualize the effect of subinhibitory concentration of cephamycins on *C. difficile* sporulation at different days and compared them with the untreated control cultures. In cephamycin-treated cells, the absence of spores was evident, which suggested that cephamycins affect *C. difficile* sporulation negatively. A significant reduction in spores was seen in other representatives of the *C. difficile* ribotype 027 (RT027) clade 2 epidemic lineage, together with R20291 (UK), M7404 (Canada), DLL3109 (Australia), and the historical, nonepidemic RT027 strain CD196. Similar results were noticed in human isolates of other *C. difficile* clades. Also the antispore-forming properties of the cephamycins were evident in other spore-forming pathogens such as *Bacillus subtilis* and *B. cereus* validating its broad-spectrum activity. But no significant reduction was seen in the number of vegetative cells at any time point. Among the three tested cephamycins, cefotetan represented with the strongest antispore-forming activity. Antispore-forming capability of cephamycins were then compared with three different cephalosporins (cefactor, cefuroxime, and cefotaxime), and it was found that cephalosporins showed 50–80-fold reduction in spores as compared to 10<sup>3</sup>–10<sup>4</sup>-fold reduction in the presence of cephamycins. Authors have also tested the antispore-forming activity of first-line antibiotic such as vancomycin which was found to have no effect on sporulation.<sup>3</sup>

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Subsequently to identify the target molecules of cephamycins, the team used fluorescently labeled penicillin-derivative bocillin-FL (Boc-FL) as a competitive inhibitor of cephamycin. Membrane proteins of cephamycin-treated and untreated cells were isolated and later exposed to Boc-FL. Since Boc-FL is a competitive inhibitor of cephamycin, it competed for the same  $\beta$ -lactam-binding site to which cephamycin was bound. Hence when visualized, membrane proteins of cephamycin-treated cells showed reduced Boc-FL-binding sites and three proteins were exclusively found absent in treated cells but were present in untreated cells. These three proteins (*CdspovD*, *Cdpgt*, and *CddacF*) were identified as a subset of penicillin-binding proteins by mass spectrometry that had earlier been implicated in *C. difficile* sporulation. To phenotypically confirm their importance in sporulation, authors carried out gene transfer experiments by TargeTron mutagenesis. It was observed that the *CdspovD* gene knockout completely affected the spore-forming capability of *CdspovD* mutant and impaired the expression of other two genes (*Cdpgt* and *CddacF*) as well. In *Cdpgt* mutant, the antispore-forming activity was not completely impaired but sporulation was reduced between 21- and 123-fold, whereas *CddacF* mutation had no effect on sporulation. This clearly stated that *CdspovD* was the prime antispore-forming target of the cephamycins, which in future could be exploited as a target for drug development.<sup>3</sup>

Till now it was seen that vancomycin is the primary standard of care and does not have any effect on sporulation, whereas cephamycins do not act against vegetative cells. Therefore, in another set of experiment, authors coadministered vancomycin with different concentrations of cephamycin (cefotetan) to check the activity against *Clostridioides difficile* infection (CDI) relapse and it was noticed that cotreatment with vancomycin and cefotetan (50  $\mu$ g/mL) prevented CDI relapse remarkably. Therefore, the combination of drugs demonstrated in this study appears to be a promising therapeutic for CDI relapse and while *C. difficile* vegetative cells show resistance to cephamycins, other spore-bearing pathogens may have different set of penicillin-binding proteins sensitive to cephamycins where the drug alone can be used as an effective antispore-forming agent.

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