Mechanistic Modeling of the Fidaxomicin Effects on Clostridium Difficile Infection

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Objectives: Clostridium difficile infection (CDI) is the leading cause of hospital-associated infection in the elderly and a major burden on healthcare facilities in Europe and North America. Options of treatments are often limited to antibiotic therapy and commonly associated with high rates of recurrence. Fidaxomicin is a narrow spectrum macrocyclic antibiotic drug approved in Europe and Americas for treatment of CDI. Based on observations from an \textit{in vitro} gut model [1], a mechanistic model was developed to study effects of fidaxomicin on CDI and subsequent changes in colon that lead to diarrhea and other more severe medical complications.

Methods: A mechanistic model involving \textit{Clostridium difficile} \textit{(C. difficile)} cytotoxin, spores and vegetative cell counts, clindamycin as the experimental trigger of CDI after \textit{C. difficile} inoculation, and fidaxomicin as the antibiotic treatment was developed in SAAM II. The model was calibrated to observations from the published \textit{in vitro} gut model data, which simulated the bacterial activities and composition in different areas of human colon during CDI and following 200mg/L fidaxomicin twice-daily dosing.

Results: The fitted model has well characterized the development of CDI in terms of time profiles of active \textit{C. difficile} cells (vegetative), inactive \textit{C. difficile} cells (spore), and cytotoxin released from active \textit{C. difficile} cells. The model was used to test hypotheses on interaction of \textit{C. difficile} cells and antibiotic therapies.

Conclusions: This is the first comprehensive mechanistic model that characterizes development of CDI, the subsequent cytotoxic release and effects of antibiotic treatment on these processes. It serves as a useful tool to facilitate the understanding of CDI and its intervention.