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Natural history of Clostridioides difficile infection in cystic fibrosis knockout mice

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Abbreviated title: *C. difficile* infection in cystic fibrosis knockout mice

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Abstract

Background: *Clostridioides difficile* is an anaerobic bacterium that is the most common cause of antibiotic-associated diarrhea. Despite being at high risk for *C. difficile* infection (CDI) the risk for CDI in people with cystic fibrosis (PwCF) is not well understood. We hypothesized that CFTR dysfunction leads to reduced risk for development of symptomatic CDI in CF due to alterations in the intestinal microenvironment.

Methods: CF and wild-type (WT) control mice were administered cefoperazone for five days then challenged with $1x10^5$ CFU of C. difficile. Concentrations were measured in stool collected on Days 1, 3, 7, 10, and 14 post-inoculation; toxin presence was assessed with an immunoassay for toxins A/B. Signs of disease were assessed daily for 7 days. Histology was examined on days 3 and 14.

Results: WT and CF mice were successfully colonized with C. difficile, with average initial concentrations of 5.27 and 4.71 log10 CFU/g of stool, respectively (P=0.07). In comparison to WT controls, CF mice had significantly faster clearance of C. difficile over 14 days (P<0.001). 100% WT mice had detectable toxin versus only 13.3% of CF at day 10. CF mice had less signs of disease and less severe histologic scores than WT (P<0.01).

Conclusion: The results support CF mice provide a useful model for CDI in PwCF. CF mice showed faster clearance of infection, minimal signs of disease and histologic changes. Our results suggest that CFTR dysfunction influences alterations in the intestinal environment that may play a role in reduced risk of C. difficile infection

INTRODUCTION

Clostridioides difficile is a Gram-positive, spore forming, toxin-producing, anaerobic bacterium that is the most common cause of antibiotic-associated diarrhea [1]. Diagnosis of *C. difficile* infection (CDI) requires presence of symptoms such as diarrhea, abdominal pain, and fever and a positive test for a toxigenic *C. difficile* strain or toxins tcdA and/or tcdB [2]. Antibiotic therapy is the most important risk factor for CDI by disrupting colonization resistance and creating gut dysbiosis that promotes *C. difficile* proliferation and subsequent infection. The risk for developing CDI increases with 1) prolonged antibiotic courses, 2) two or more classes of antibiotics, and 3) long-term hospitalization [3].

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene that affects at least 40,000 people in the US [4]. CFTR dysfunction leads to improper movement of chloride and bicarbonate, and persistent absorption of sodium, leading to thick, viscous mucus [4]. The build of mucus in the lungs leads to chronic respiratory infections and frequent pulmonary exacerbations. CFTR dysfunction is also associated with many changes in the intestinal microenvironment including a thickened mucus layer that alters nutrient absorption, an acidic pH, gut dysbiosis, increased sodium absorption and cellular alterations including those associated with endosomal processing [5-7].

People with CF (PwCF) are frequently hospitalized for chronic pulmonary infections [8]. Treatment of pulmonary infections often includes 2-4 different classes of intravenous antibiotics with an average duration 10-21 days of in-patient therapy, which may increase their risk for CDI. Yet, it remains uncertain whether this population shows evidence of innate protection against the infection, or whether they develop CDI at the same rate as other high-risk groups. PwCF have been shown to have toxin-producing *C. difficile* present in their gut while remaining asymptomatic [9, 10]. On the contrary, PwCF have also been shown to have the same risk for CDI infection following lung transplant as other pulmonary disease recipients [11, 12]. The purpose of this work is to clarify the risk of CDI in CF.

Our overall hypothesis is that CFTR dysfunction leads to reduced risk for development of symptomatic CDI in CF due to alterations in the intestinal microenvironment. We explored if CFTR-knockout mice, or CF mice, are a viable model for investigating *C. difficile* infection. We investigated if CF mice can be successfully colonized with *C. difficile*. We hypothesized that CF mice have similar levels of *C. difficile* colonization and toxin production but diminished clinical signs of disease when compared to wildtype mice.

METHODS AND MATERIALS

Mouse *in vivo* Models

To test our hypotheses, we used two genotypes of mice: wildtype (WT) mice (*Cftr* +/+) (N=25) and *Cftr G542X* (CF) mice (*Cftr G542X/G542X*) (N=25). WT and CF mice were littermates, with 12 male mice and 13 female mice for both groups. As part of our lab's breeding protocol, young CF mice (less than 6 weeks of age) are maintained on colyte to prevent small bowel obstructions. All CF mice used in this study were 10 weeks of age or older and had successfully been transitioned off colyte for at least four weeks prior to the start of this study. Adult mice were housed in a Biosafety Level 2 animal room due to the infectious nature of *C. difficile.* All

procedures were approved by the Case Western Reserve University IACUC (approval #2024-0036). All mice were humanely euthanized by CO_2 asphyxiation at the end of the experiment. The data underlying this article will be shared on reasonable request to the corresponding author.

Antibiotic Treatment and Challenge with *C. difficile.*

Thirty mice (15 CF and 15 WT) were administered cefoperazone in drinking water for five days to induce susceptibility to *C. difficile* colonization and disease [13] and twenty (10 CF and 10 WT) were given sterile water as a control. Cefoperazone was prepared in sterile water (0.5mg/ml), refreshed every 48 hours, and administered for 5 days. Cefoperazone is a cephalosporin antibiotic that is commonly associated with CDI in humans, thus making it an excellent choice for mimicking clinical disease. Sterile water was administered for the remainder of the experiment once the antibiotic regimen completed. Mice had a 2-day recovery off antibiotics and then were gavaged with $1x10^5$ colony-forming units (CFU) of *C. difficile* spores in 100 µl PBS, deemed "Day 0". The *C. difficile* isolate was VA17, a clinical ribotype 027 strain [14]. Spores were prepared according to the Environmental Protection Agency standard operating procedures for the production of *C. difficile* spores [15]. Because mice are coprophagic, they were individually housed after inoculation with *C. difficile.*

Monitoring Mouse Weight Loss and Clinical Signs of Disease Throughout *C. difficile* Infection.

Mice were weighed daily during the 5-day cefoperazone antibiotic treatment, after the 2-day recovery period (Day 0), and then once or twice daily for the duration of the experiment. Weight measured on Day 0 was used as the initial baseline weight for comparison throughout the experiment. Mice were monitored daily (at a minimum) for signs of clinically severe CDI, including lethargy, anorexia, diarrhea, and hunched posture.

Quantification of *C. difficile*

Stool was collected from mice on Days 1, 3, 7, 10, and 14 post inoculation. *C. difficile* concentrations in stool specimen were quantified as described previously [16]**.** Stool specimens were emulsified in 10-fold (weight/volume) pre-reduced phosphate-buffered saline (PBS). Aliquots were serially diluted then anaerobically inoculated onto pre-reduced cycloserine-cefoxitin-brucella agar containing 0.1% taurocholic acid and 5 mg/mL lysozyme (CDBA) and incubated for 24-48 hours [17]. The number of CFU per gram of stool was calculated. To determine toxin production, we used a commercially available kit for detection of *C. difficile* A/B enzyme-linked immunoassay (Techlab TOX A/B ELISA) and observed by visual scoring depth of color change (0-3, higher scores indicating higher concentration of toxin).

Clinical Signs of *C. difficile* infection

Clinical signs of *C. difficile* were assessed using a scoring chart [18] every day. Five signs were assessed: activity level, posture, pelage, diarrhea, and eye/nose on a scale 0-3 and total scores 0-15, with lower numbers correlating with less clinical signs.

Histopathologic Procedure and Examination

Mice were sacrificed on Day 3 (n=10) and Day 14 (n=10) post inoculation by CO_2 asphyxiation. The tip of the cecum was cut and flayed longitudinally, contents collected, and then tissue washed with ice-cold phosphate-buffered saline before fixing in formalin. Tissue was then laid flat, and all rolls removed before fixing in formalin and rolled for a Swiss-roll histologic technique.

Histological slides were coded, randomized and scored in a blinded manner by a pathologist, one of the authors (EB). A scoring system was adopted from a previously published method [19]. Explained briefly, edema, cellular infiltration, and epithelial damage were scored on a five-point Likert scale (0-4) in cecum and colon tissue according to define criteria. Edema was scored ranging from no swelling (0) to severe (4), widespread submucosal expansion. Inflammation grading similarly progressed from no inflammatory cells (0) to extensive neutrophilic infiltration (4), including coalescing lesions or abscess formation at the highest score. Epithelial injury was assessed from normal tissue (0) to widespread ulceration (4), with intermediate scores reflecting increasing degrees of superficial epithelial damage—such as vacuolation, apoptosis, and villus tip necrosis—and the possible presence of pseudomembranous at more advanced stages.

Statistical Analysis

Data were assessed for normality and missingness. Fisher's exact, ANOVA, repeated-ANOVA and descriptive statistics were used to analyze the data as well as differences between two groups. Multilevel growth models were used to assess the rate of change in *C. difficile* colony forming units (CFU) between and within groups over 14 days. An alpha of 0.05 was considered significant. All data were analyzed using R-studio version 4.5.1.

RESULTS

***C. difficile* colonization rates in challenged mice**

All thirty mice pretreated with cefoperazone were successfully colonized with *C. difficile* and had toxin detected in their stool on Day 1 of the study. No saline-control mice (N=20) became colonized with *C. difficile.* Henceforth, the data presented is from pretreated antibiotic mice. For all mice, the average $\log_{10}$ CFU/g on Day 1 4.99. A table with statistical output from the growth model is available in Supplemental Table 1. In comparison to the WT mice, the CF mice had a lower average *C. difficile* level on Day 1 but the difference was not statistically significant (4.71 versus 5.27 $\log_{10}$ CFU/g, respectively; P=0.07). CF mice cleared the infection significantly faster ($p< 0.001$) than WT mice over 14 days (Figure 1). The predicted mean deceleration was -0.13 $\log_{10}$ CFU/g per day, holding all else constant. The CF mice were predicted to have an increased deceleration of -0.06 $\log_{10}$ CFU/g per day compared to average deceleration and WT had a predicted growth of 0.06 $\log_{10}$ CFU/g per day, holding all else constant. CF mice had significantly greater clearance per day compared to WT mice, -0.19 vs -0.7 $\log_{10}$ CFU/g per day respectively ($p<0.01$). By Day 14 CF mice averaged 2.08 $\log_{10}$ CFU/g and WT mice averaged 4.22 $\log_{10}$ CFU/g ($P <0.001$).

Toxin levels were assessed through color change (0=no color, no toxin present; 3=bright yellow, high toxin burden present) and light microscopy. Days 1-3 CF and WT mice had high toxin burden present with no significant differences seen between groups (p=0.073). By Day 10

few CF mice (13.3%) had discernable toxin present, compared to all WT (100%) still being toxin positive (fig 2) ($p<0.001$). The differences seen in toxin burden is not surprising given that the CF mice had a low burden of *C. difficile* colonization by Day 10 while the WT mice had moderate colonization.

Clinical signs of *C. difficile* disease in mice

CF mice experienced significantly reduced clinical signs of disease ($p<0.001$) than WT mice on Days 1-6. Figure 3 portrays all signs experienced by WT and CF mice per day for the first 7 days of the study infection.

Wildtype mice: Throughout the study diarrhea was the most common sign followed by decreased activity. **Day 1** WT mice had total scores ranging from 1-5, with the mean and median total score of 2.6. Twelve of the fifteen mice experienced diarrhea, and five mice experienced severe diarrhea (score= 3). Seven WT mice (46%) experienced decreased activity, five hunched posture (33%), and five pelage (33%). WT experienced the most severe signs on **Day 3**, with scores ranging from 1 to 10, median total score of 2 but an increase in the mean of total score to 3.3. Fifteen WT mice (100%) had diarrhea, with three mice experiencing severe diarrhea (score =3). Ten WT mice (66.7%) experienced decreased activity levels, seven hunched posture (46%), six pelage (40%), and two eye/nose (13%). Between Days 1 to 3 all fifteen WT mice (100%) experienced diarrhea and thirteen experienced decreased activity (86%) at least once. We humanely euthanized one WT mouse that lost 20% of its baseline bodyweight and developed severe clinical signs of CDI such as liquid diarrhea, hunched posture and shaking on Day 3. All signs were resolved by Day 7 and mice had recovered clinically.

Cystic fibrosis mice: **Day 1,** no CF mouse (0%) experienced any clinical signs, **total scores =0. On Day 3, only three CF mice (20%) had clinical signs.** Total scores ranged from 0 to 1, with a median total score of 0 and a mean score of 0.2. One CF mouse (6%) experienced pelage, one mouse experienced hunched posture (6%), and one mouse experienced decreased activity (6%). All signs were resolved by Day 4. CF mice experienced significantly less clinical signs of disease on each sign assessed and total signs of disease on Days 1-6 ($p<0.001$).

No CF mouse experienced diarrhea at any point in the study compared to all WT mice.

Histology report of *C. difficile* challenged mice

Histologic examination of the cecum provided further evidence that CF mice experience less severe CDI compared to WT mice (figure 4). Histology on Day 3 of infection showed that WT mice had mild edema, moderate neutrophil infiltration, and moderate to severe epithelial damage. Histologic scoring of the sections demonstrated evidence of inflammatory infiltrates penetrating into the muscular wall, increased apoptosis and vacuolization of the epithelium with focal epithelial erosion. Comparatively, the histologic scores on Day 3 of infection in CF mice for all three parameters were significantly lower than WT mice ($p<0.05$). Histologic scoring of CF mice showed no evidence of edema or neutrophilic inflammation, and a minor increase in apoptotic bodies in the epithelium. On Day 14 of infection histology was markedly improved in both WT and CF mice. However, the WT mice continued to show very mild edema, mild neutrophilic inflammation, and mild epithelial damage while CF mice showed minimal edema,

mild neutrophilic inflammation, and no epithelial damage. CF mice have notably decreased evidence of disease on histology. The reduced cecum pathology and the lack of clinical symptoms of disease on Day 3 paired with the high toxin burden highlights an extraordinary phenomenon occurring in CF mice.

DISCUSSION

Clostridioides difficile bacterium is the most common cause of antibiotic associated diarrhea. People with CF (PwCF) are frequently treated with IV antibiotic therapy to decrease bacterial load of chronic pulmonary infections [8]. Treatment of pulmonary infections often includes 2-4 different classes of intravenous antibiotics with an average duration 10-21 days of in-patient therapy. Current published literature shows conflicting evidence on the risk CDI poses to PwCF. In the presented work we investigated if CF mice are a good model for studying CDI in PwCF, and we found that CF mice are an excellent model for studying CDI.

All mice were challenged with $1x10^5$ CFU of a virulent strain of *C. difficile*, a standardized dose off *C. difficile* that is sufficient to induce moderate disease [14, 20]. By Day 14, CF mice had successfully cleared enough bacteria to have low burden of *C. difficile* colonization, while WT mice maintained a moderate burden of *C. difficile* colonization. Our results support that CFTR dysfunction positively correlates with improved response to *C. difficile* infection. The observed differences in toxin burden are consistent with the bacterial burden present. CF mice already had reduced bacterial load by Day 10 and showed little to no toxin present, likely reflecting an insufficient bacterial population to sustain toxin production. In contrast, WT mice maintained a level of colonization capable of supporting continued toxin production and likely contributing to pathogenic effects seen in histology on Day 14. Genotype differences are a clear distinguishing factor between these groups. The presented data supports the hypothesis that CFTR dysfunction alters the host response in a way that promotes more effective clearance of *C. difficile* infection. We see this positively reflected in clinical symptoms and histology as well.

Similar to the phenomena experienced in PwCF, CF mice had little evidence of disease. All WT mice in our study experienced diarrhea between Days 1-3 and 46% of WT experienced severe diarrhea, yet not a single CF mouse experienced any diarrhea. In fact, only 20% of CF mice experienced symptoms at all throughout the study, with none experiencing the same symptom and only on Day 3. WT mice had a total symptom score ranging 1-6 on Days 1-3 while CF mice had a total symptom score 0-1 and only on Day 3. The lack of CF mouse symptoms compared to WT is quite similar to what has been observed in people with CF who also show no signs of diarrhea even if colonized and toxigenic positive. Histologic evaluation further supports that *C. difficile* induces less damage to the CF gut compared to WT. CF mice have notably decreased evidence of disease on histology with only mild edema and epithelial damage compared to mild edema, moderate neutrophilic infiltration, moderate to severe epithelial damage in WT. The reduced histologic disease paired with the lack of clinical symptoms of disease highlights an extraordinary phenomenon occurring in CF mice.

CF mice are a good model for studying *C. difficile* infection as they mimic human disease by colonizing with toxic *C. difficile* after challenge with antibiotics, yet much like PwCF, CF mice also show no to few signs of disease, supported by mild changes to histology. The significantly faster clearance of *C. difficile* suggests that CFTR dysfunction causes alterations in the intestinal environment that may play a role in reduced risk of gut infection.

Together, the data presented supports our primary hypothesis is that CFTR dysfunction leads to reduced risk for development of symptomatic CDI in CF due to alterations in the intestinal microenvironment that lead to rapid clearance of colonization and reduced impact of toxin. Further work is needed to identify the exact mechanism of resistance to colonization.

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ETHICS APPROVAL
Ethics Approval Declaration: Institutional Animal Care and Use Committee is a federally mandated committee in the United States that oversees an institution's animal care and use program, Case Western Reserve University's IACUC Approval Committee approved the protocol for animal research prior to the start of the research project, approval #2024-0036. All animal handling was conducted in accordance with the IACUC protocols and all authors received specialized animal ethics and handling training. Consent to Participate declaration not applicable.

CONFLICTS OF INTEREST
The authors EG, ZT, LC, BH, CK, EB, CD, and CAH have no conflicts of interest to report.

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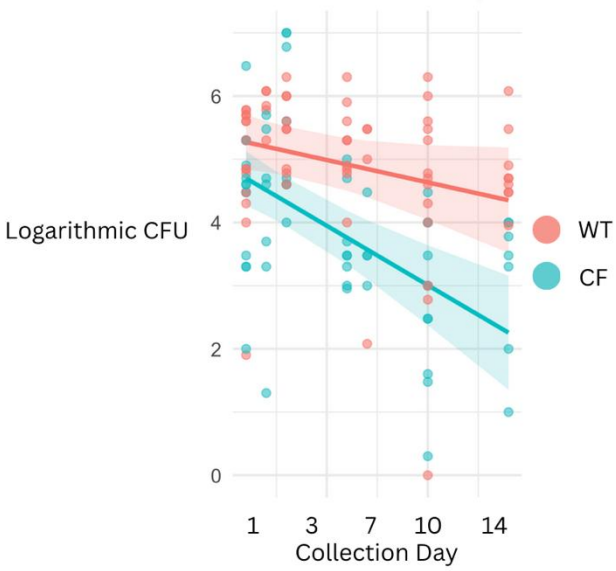


Figure 1, Logarithmic Colony Forming Units Collected over 14 Days. Mice were orally gavaged with 1x10^{5}CFU of C. difficile after 5 days of antibiotic exposure. Stool were collected for 14 days and plated anaerobically on selective media. Points may represent more than one mouse.

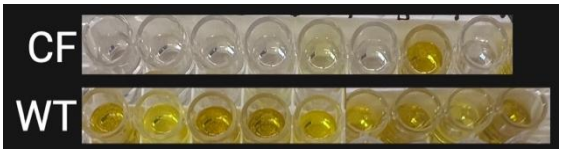


Figure 2, Visual representation of toxin positive sample on Day 10. Mice were orally gavaged with $1x10^5$CFU of C. difficile after 5 days of antibiotic exposure. Stool were collected for 14 days and plated anaerobically on selective media and toxin level was analyzed. Day 10 sample collection showed that along with CF mice having decreased CFU on selective media they also had significantly less detectable toxin present in their stool. Increased yellow color intensity represents more C. difficile toxin present. Clear represents no detectable toxin present

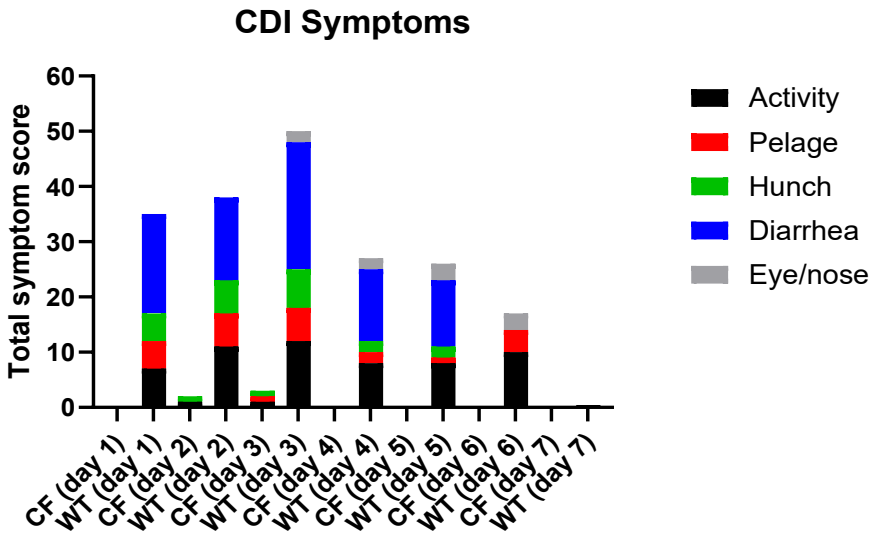


Figure 3, Five symptoms experienced by WT and CF mice over first 7 days of study infection. The figure portrays all symptoms experienced by WT and CF mice on each study day. CF mice had little to no symptoms, compared to WT mice who had experienced mild to severe symptoms. All WT mice experienced diarrhea while no CF mouse did. Repeated-ANOVA p<0.001

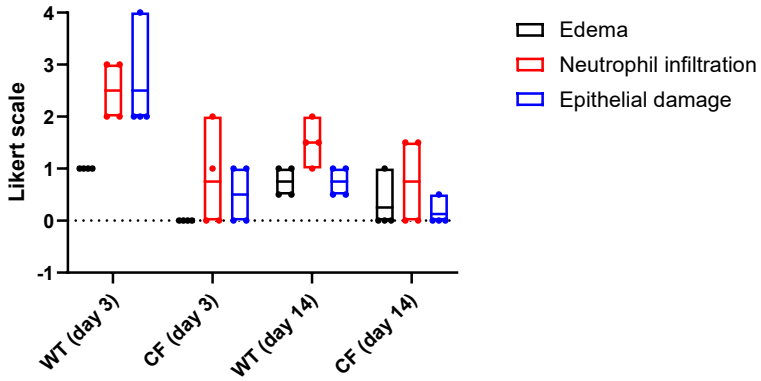


Figure 4. Histology score averages Day 3 and Day 14 post infection. CF mice had significantly less tissue damage on Day 3 and Day 14 than WT on histology. This correlates well with the decreased CFU seen over 14 days and significantly less toxin present by Day 10 and 14 of the study infection. The difference in histology, paired with the results that CF mice have less CFU and toxin over 14 days, supports that CF mice may have innate protection provided by their unique genetic makeup.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.docx