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A prospective study to evaluate serologic and immune responses to SARS-COV-2 infection in persons living with cystic fibrosis: Canadian arm of the CAR-CF study

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Background: Better understanding of SARS-CoV-2 in chronic disease populations is needed. The CAR-CF study is a large, international, multicenter study that has been undertaken to evaluate seroprevalence and vaccine response in children and adults living with CF. The objective was to describe the characteristics of the Canadian prospective cohort of the CAR-CF initiative to date.
Methods: The Canadian prospective study arm will run in 10 centers that are part of the CF Canada Accelerating Clinical Trials network. Consenting participants with a diagnosis of CF will be enrolled prospectively and followed over a 24-month period with symptom-based surveys for SARS-CoV-2 and serology to be completed at 3- to 6-month intervals. Linkage to the Canadian CF registry will provide clinical and outcome data over the study period. Approved SARS-CoV-2 assays will be implemented in alignment with international partners to assess for seroprevalence and vaccine response. Primary outcomes include SARS-CoV-2 seroprevalence, and secondary outcomes include vaccine titers and pulmonary outcomes (lung function decline, exacerbations) after SARS-CoV-2 infection.
Results: The Canadian arm of the CAR-CF study began November 3, 2020, and 87 participants (age 3–68 years, 77% <18 years; 81% students) have been enrolled to date at 5 centers. Of these, 66 participants (76%) have had baseline bloodwork done, and 53 (61%) have completed their initial surveys. Of those who completed the survey, 23 (43%) reported having had at least one SARS-CoV-2 test in the preceding 3 months. Two participants (2% of cohort) had a history of prior SARS-CoV-2 infection diagnosed by nasopharyngeal swab (self-reported); both were younger than 18, and one required admission to hospital. One participant had received a dose of vaccine, and serologic results were pending at the time of submission.
Conclusion: The Canadian arm of the CAR-CF prospective study is underway, with enrollment occurring at 5 centers and expansion to 10 shortly. Further clinical and serologic results will be available for current and upcoming participants for presentation in October 2021.

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Prospective Evaluation of nontuberculous mycobacterial Disease in Cystic fibrosis Trial (PREDICT): Colorado single center (2013–2018)

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Background: Nontuberculous mycobacteria (NTM) are important cystic fibrosis (CF) pathogens. Because of overlap of clinical symptoms and radiographic findings, exclusion of disease due to co-infection and CF comorbidities is required to determine the significance of NTM-positive cultures and the potential benefit of treatment. The lack of validated diagnostic criteria for NTM disease in CF makes treatment decisions difficult and impedes therapeutic trials. The primary objective of this study is to develop a standardized diagnostic protocol to identify NTM disease in adults and children with CF.
Methods: This is a prospective single-center observational trial at the Colorado Adult and Pediatric CF Programs (2013–2018; before multicenter expansion). All subjects undergo the same diagnostic algorithm based on CFF and European Cystic Fibrosis Society NTM Consensus Guidelines. Sputum-producing CF subjects aged 6 and older with a recent positive NTM clinical respiratory culture and not on NTM treatment are eligible for this study. Enrolled subjects are regularly monitored in clinic with assessment for NTM microbiologic criteria, evidence of an NTM clinical syndrome, radiographic evidence of disease, control of comorbidities, and quality of life. Primary endpoint is diagnosis of NTM disease. Those with NTM disease are offered treatment as part of the PATIENCE Trial.
Results: Up to the start of the multicenter trial in 2018, 42 adults and 13 children with CF were enrolled. Mean age at enrollment was 28.2 ± 13.4 (range 8.1–67.0). Of the 55 enrolled participants, 60% have *Mycobacterium avium* complex, 27% have *M. abscessus* complex, and 13% have both. Twenty-nine subjects (53%) were not diagnosed with NTM disease, including 2 with a single positive NTM culture only. Forty-seven percent were diagnosed with NTM disease. Overall distribution of CFTR mutations was 53% F508del homozygous and 40% F508del heterozygous and was not different between those with and without NTM disease. On average, subjects without NTM disease have been observed for 52.1 ± 22.5 months with 14.2 ± 8.5 (range 3–37) clinic visits in PREDICT. Subjects with NTM disease were observed for 15.0 ± 15.3 months and 6.8 ± 4.0 visits (range 2–20) until diagnosis was made. Similar proportions of subjects in the group with (23%) and without (31%) ($P = 0.56$) NTM disease had *Mycobacterium abscessus* complex. Those with NTM disease had lower $ppFEV_1$ (73%) than those without NTM disease (90%) ($P = 0.01$) at enrollment. Those with NTM disease had a similar change in $ppFEV_1$ as those without disease after enrollment initially but had greater decline after 2 years of follow-up.
Conclusion: Use of an NTM diagnostic protocol and standardized data collection method is feasible in CF. Almost half of our subjects met the criteria for NTM disease. Additional characteristics associated with diagnosis of NTM disease will be presented.
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CF innate immune defect affects CF intestinal microbiota

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Background: Cystic fibrosis (CF) intestinal disease manifests as intestinal hyperinflammation, small intestinal bacterial overgrowth, and large intestinal microbial dysbiosis. It is not clearly known whether CF-defective innate immunity contributes to these clinical outcomes. In this report, we have scrutinized the intestinal microbiota of various lines of CF mice.
Methods: Four lines of CF mice—whole-body CFTR-knockout (Pan-CF), myeloid CFTR-knockout (Mye-CF), neutrophil CFTR-knockout (Neu-CF), and macrophage CFTR-knockout (Mac-CF) mice—were co-housed with CFTR Exon-10 floxed mice (WT) for 2 months to normalize for any possible influences from environmental factors. After 2 months, fecal samples and intestinal contents were taken for 16s rRNA gene sequencing. Alpha- and beta-diversity was analyzed. Bacterial abundance from taxonomic data of each genotype and comparisons across the genotypes were performed.
Results: We found that the various CF genotypes affected intestinal bacterial populations differently. Figure 1 shows the significantly altered bacteria taxa, to the genus level, for the respective genotype comparison, with the Pan-CF model having the most significantly altered flora, accounting for 12 of the 18 significant comparisons. The Pan-CF had 15 significantly different small intestinal (SI) bacteria, 9 significantly different large intestinal (LI) bacteria, and 6 significantly different fecal bacteria than the WT mice. Mye-CF had 1 significantly different SI and fecal bacterial taxon than the WT. Mac-CF had 1 significantly different fecal taxon than WT. Pan-CF had 9 significantly different SI bacteria, 9 significantly different LI bacteria, and 7 significantly different fecal bacteria than Neu-CF. Pan-CF had 3 significantly different SI bacteria, 5 significantly different LI bacteria, and 8 significantly different fecal bacteria than Mac-CF. Pan-CF had 7 significantly different SI bacteria, 13 significantly different LI bacteria, and 7 significantly