CHANGES IN CRP WITH TREATMENT OF PULMONARY EXACERBATION IN A MIXED CF COHORT

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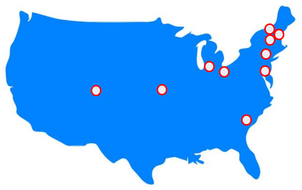
Introduction

Pulmonary exacerbations are important events in the course of CF lung disease and contribute disproportionately to decline in lung function over time. Therefore, it is important to develop tools to assess adequacy of treatment of pulmonary exacerbations and risks for early recurrence. Serum C-reactive protein (CRP), an acute-phase reactant with a short serum half-life, has been examined in a number of studies as a marker of response to pulmonary exacerbation treatment (1·3] and predictor of time until next exacerbation (TUNE) (4,5). Previous studies have been limited by small sample size, restriction to mostly adult patients, and single center design. Here, as part of an ongoing prospective study of peripherally inserted central venous catheter complications in CF patients at ten centers across the U.S. (PICC-CF), we examine CRP responses to pulmonary exacerbation treatment in a large, mixed pediatric and adult population.

Study Sites



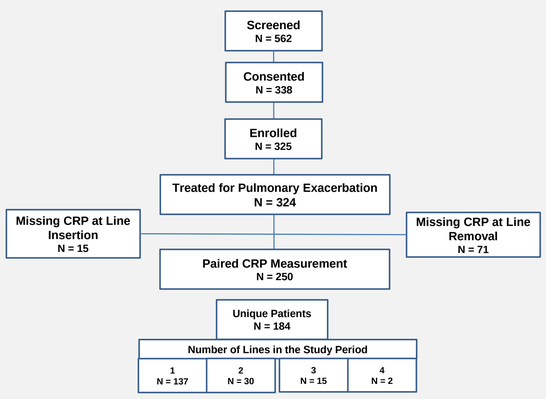
Sites	Principal Investigators	Research Coordinators
Children's Hospital Colorado	*Edith Zemanick*	*Dana Coyle*
Cleveland Clinic	*Elliott Dasenbrook*	*Dave Weaver*
Columbia University Medical Center	*Hossein Sadeghi, Emily Dimango*	*Carmen Liriano*
Dartmouth-Hitchcock Medical Center	*Alex Gifford, Margaret Guill*	*Leah McGinley*
Johns Hopkins University Medical Center	*Rebecca Dezube, Natalie West*	*Shivani Patel*
Maine Medical Center	*Jonathan Zuckerman*	*Amanda Cass*
Medical University of South Carolina	*Patrick Flume*	*Angela Millare*
University of Kansas Medical Center	*Joel Mermis, Deepika Polineni*	*Megan White*
University of Michigan Medical Center	*Shijing Jia, Samya Nasr*	*Nicole Schafer*
University of Vermont Medical Center	*Thomas Lahiri, Charlotte Teneback*	*Julie Sweet*

Epidemiologist: *Lee Lucas*
Database Manager: *Deanna Williams*
Biostatistician: *Alexandra Hinton*
Website Administrator: *Steve Prato*

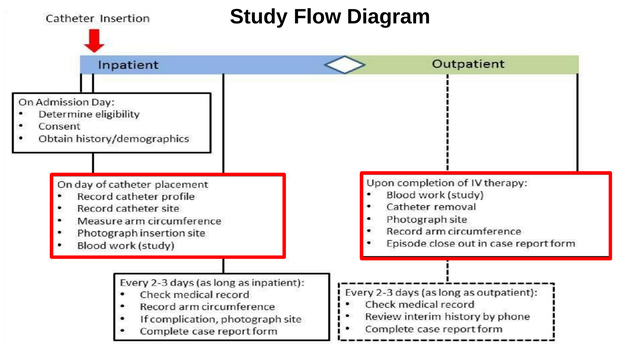
Methods

We collected clinical and demographic data from people with CF on the first hospital day, serum CRP on the day of catheter insertion and removal, and baseline lung function. We summarized demographic information about the patients using median (IQR) for continuous variables and n (%) for categorical variables. We examined relationships between CRP values by time point and age using the paired samples Wilcoxon test and age groups using the Wilcoxon rank sum test. To evaluate if the relationship between CRP and lung function, and CRP and the severity of presenting pulmonary exacerbation symptoms differed by age, we used linear regression with an interaction term and the frequency of exacerbation requiring IV antibiotic therapy using linear regression. For our analyses of TUNE, we included only patients who had multiple lines within the study period. We plotted the relationship using locally weighted scatterplot smoothing and used the Wilcoxon rank sum test to evaluate if CRP at line insertion differed for those returning within 90 days versus after 90 days.

Enrollment



Study Design



SCHEDULE OF EVENTS

Task/Procedure	Screen	Visit 1 Day 1	Visit 2 Day 3 (+/-1 day)	Visit 3 Day 5 (+/-1 day)	Visit 4 Day 7 (+/-1 day)	Visit 5 Day 9 (+/-1 day)	Visit 6 Day 11 (+/-1 day)	Visit 7 Day 14 (+/-1 day)
Informed Consent	X							
Obtain Demographics		X						
Obtain Relevant History	X	X						
Akron PES		X						
Line insertion details		X						
Confirm catheter details		X						X
CBC, INR (hospital)		X						
CRP, D-dimer (study)		X						X
Picture of insertion site		X	(X)	(X)	(X)	(X)	(X)	X
Line Management Survey			X*	X*	X*	X*	X*	X
Evaluation for Complications			X*	X*	X*	X*	X*	X
Review line removal								X

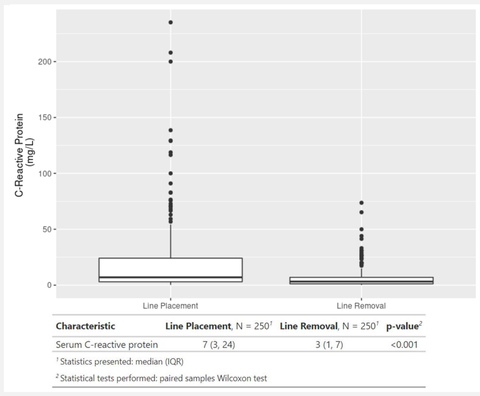
Notes: **(X)**-Optional event based on signs/symptoms of the patient. **X***-Patients who receive in-hospital care will have face-to-face follow-up evaluations. Those who are treated at home will have a check-in by phone call

Primary Endpoint The primary endpoint is the occurrence of vascular complications, defined as occlusion of the catheter requiring removal or symptomatic venous thrombosis in the extremity with the line (see Poster 743 for study definition details)

Secondary Endpoints Bacteremia, fungemia, local phlebitis or superficial thrombophlebitis, hematoma, bleeding (including incident hemoptysis after use of thrombolytic agents), site pain, arm circumference at the level of catheter insertion, catheter fracture, temporary occlusion of the catheter cleared by thrombolytic agent, non-occlusive venous thrombosis as evidenced by ultrasound or DVT at another site, blood markers of inflammation and measures of coagulation status. C-reactive protein (CRP) was drawn on the day of catheter insertion and the day of catheter removal (red boxes)

Characteristic	N =250	median (IQR); n (%)
Female	250	115 (46%)
Age (years)	250	21 (15, 28)
BMI kg/M2 for age > 21 years	125	21.6 (19.3, 24.0)
BMI percentile for age ≤ 21 years	124	31 (19, 58)
Unknown		1
Diabetes	250	90 (36%)
Genotype	246	
Homozygous F508del		129 (52%)
Heterozygous F508del		92 (37%)
Other		25 (10%)
Unknown		4
FEV1 % Predicted (best in past 12 months)	250	74 (49, 91)
Akron Pulmonary Exacerbation Score (PES)	250	10 (7, 13)
Sputum Culture (All recorded in last 12 months):		
Pseudomonas aeruginosa	250	149 (60%)
Staphylococcus aureus (MSSA)	250	104 (42%)
Staphylococcus aureus (MRSA)	250	84 (34%)
Burkholderia cepacia spp	250	9 (3.6%)
Non-tuberculous mycobacteria	250	20 (8.0%)
Other	250	136 (54%)

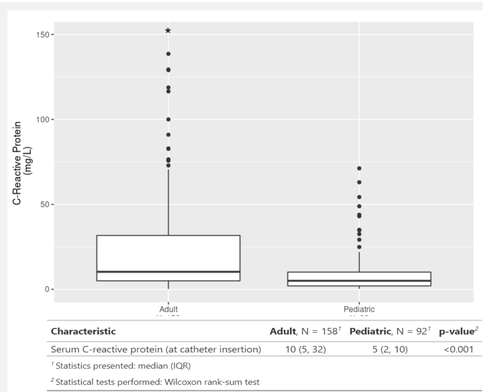
Table 1. Participant characteristics



Characteristic	Line Placement, N = 250[1]	Line Removal, N = 250[1]	p-value[2]
Serum C-reactive protein	7 (3, 24)	3 (1, 7)	<0.001

[1] Statistics presented: median (IQR)
[2] Statistical tests performed: paired samples Wilcoxon test

Figure 1. Serum C-reactive protein at the time of line insertion and removal



Characteristic	Adult, N = 158[1]	Pediatric, N = 92[1]	p-value[2]
Serum C-reactive protein (at catheter insertion)	10 (5, 32)	5 (2, 10)	<0.001

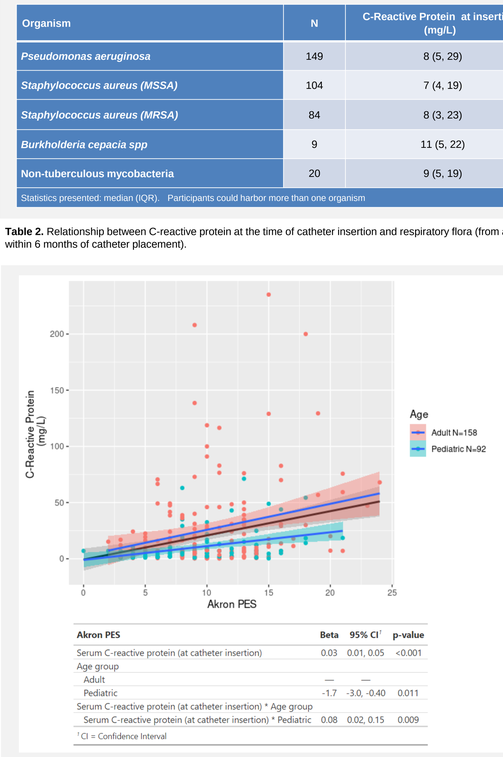
[1] Statistics presented: median (IQR)
[2] Statistical tests performed: Wilcoxon rank-sum test

Figure 2. Serum C-reactive protein at the time of line insertion in adult and pediatric participants. *-indicates off-scale value

Organism	N	C-Reactive Protein at insertion (mg/L)
Pseudomonas aeruginosa	149	8 (5, 29)
Staphylococcus aureus (MSSA)	104	7 (4, 19)
Staphylococcus aureus (MRSA)	84	8 (3, 23)
Burkholderia cepacia spp	9	11 (5, 22)
Non-tuberculous mycobacteria	20	9 (5, 19)

Statistics presented: median (IQR). Participants could harbor more than one organism

Table 2. Relationship between C-reactive protein at the time of catheter insertion and respiratory flora (from all cultures within 6 months of catheter placement).



Akron PES	Beta	95% CI[1]	p-value
Serum C-reactive protein (at catheter insertion)	0.03	0.01, 0.05	<0.001
Age group			
Adult	—	—	
Pediatric	-1.7	-3.0, -0.40	0.011
Serum C-reactive protein (at catheter insertion) * Age group			
Serum C-reactive protein (at catheter insertion) * Pediatric	0.08	0.02, 0.15	0.009

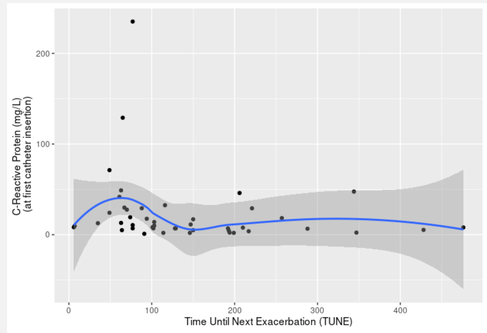
[1] CI = Confidence Interval

Figure 3. Relationship between Akron pulmonary exacerbation score (PES) and serum C-reactive protein at the time of line insertion. There was a significant interaction between age and PES.

FEV1	Beta	95% CI[1]	p-value
Serum C-reactive protein (at catheter insertion)	-0.19	-0.29, -0.09	<0.001
Age group			
Adult	—	—	
Pediatric	19	11, 26	<0.001
Serum C-reactive protein (at catheter insertion) * Age group			
Serum C-reactive protein (at catheter insertion) * Pediatric	-0.04	-0.40, 0.32	0.8

[1] CI = Confidence Interval

Figure 4. Inverse relationship between lung function (FEV1 % predicted) and serum C-reactive protein at the time of line insertion. FEV1 % predicted was the best value in the 12 months prior to line placement.



Characteristic	Time Until Next Exacerbation (TUNE) <=90 days, N = 17[1]	>90 days, N = 28[1]	p-value[2]
Serum C-reactive protein (at catheter insertion)	24 (11, 42)	7 (4, 15)	0.001

[1] Statistics presented: median (IQR)
[2] Statistical test performed: Wilcoxon rank-sum test

Figure 5. Relationship between the time until next exacerbation (TUNE) and C-reactive protein at the time of first catheter insertion for those participants who had more than one catheter placed during the study period.

Conclusions

- Very elevated CRP at pulmonary exacerbation onset is often observed in those with advanced lung disease, particularly adults
- Marked CRP elevation may portend early exacerbation recurrence
- CRP appears to be of less value as a marker in pediatric patients and those with early-stage lung disease

Future Directions

- We plan to further explore early responses of CRP to treatment initiation and potential relationships between CRP levels and CFTR modulator therapy
- For details on the study design please visit: www.picccf.org

References

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Acknowledgements:
•This study was funded by CF Foundation Grant ZUCKER18A0

• We thank all the patients who have participated in this study