

Supplementary Material

Importance of Beta-Lactam Pharmacokinetics and Pharmacodynamics on the Recovery of Microbial Diversity in the Airway of Persons with Cystic Fibrosis

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Supplemental Table 1. Breakdown of Sample Type by Time Point and Time Above the Minimum Inhibitory Concentration

	<i>f</i> T>MIC sufficient (n=14)*	<i>f</i> T>MIC not sufficient (n=13)
Exacerbation: Ratio OP swab:sputum	12:2	6:6
Treatment: Ratio OP swab:sputum	7:3	9:2
Follow up: Ratio OP swab:sputum	11:1	6:6

OP, oropharyngeal

*Missing data as only samples collected that were successfully sequenced are included in the total counts.

Supplemental Table 2. Richness and Alpha Diversity by Time Point

	<i>f</i> T>MIC sufficient (n=14)	<i>f</i> T>MIC not sufficient (n=13)	P value
OTUs observed: Exacerbation (predicted mean, SE)*	39.0 (5.8)	37.4 (6.3)	0.860
OTUs observed: Treatment (predicted mean, SE)*	26.4 (3.2)	22.5 (3.1)	0.388
OTUs observed: Follow up (predicted mean, SE)*	37.6 (6.5)	48.8 (6.5)	0.250
Inverse Simpson Index: Exacerbation (predicted mean, SE)**	5.04 (0.78)	3.50 (0.85)	0.201
Inverse Simpson Index: Treatment (predicted mean, SE)*	2.91 (0.30)	2.80 (0.28)	0.791
Inverse Simpson Index: Follow up (predicted mean, SE)**	3.58 (0.77)	4.97 (0.77)	0.226
Shannon Diversity: Exacerbation (predicted mean, SE)*	1.82 (0.21)	1.49 (0.22)	0.303
Shannon Diversity: Treatment (predicted mean, SE)*	1.41 (0.15)	1.38 (0.14)	0.873
Shannon Diversity: Follow up (predicted mean, SE)*	1.68 (0.20)	1.93 (0.20)	0.405

SE, standard error

*General linear model with Gaussian family and identity link, controlling for sample type (sputum vs oropharyngeal swab)

#Log transform

Supplemental Table 3. Changes in Richness, Alpha Diversity, and Beta Diversity Across Time Points

	<i>f</i> T>MIC sufficient (n=14)	<i>f</i> T>MIC not sufficient (n=13)	P value
OTUs observed: Exacerbation to Treatment (predicted mean, SE)*	-9.37 (6.5)	-13.8 (6.2)	0.625
OTUs observed: Exacerbation to Follow up (predicted mean, SE)*	-5.8 (7.1)	+11.2 (7.1)	0.110
Shannon Diversity: Exacerbation to Treatment (predicted mean, SE)*†	-0.217 (0.245)	-0.146 (0.233)	0.836
Shannon Diversity: Exacerbation to Follow up (predicted mean, SE)*	-0.222 (0.208)	+0.452 (0.208)	0.031
Inverse Simpson Index: Exacerbation to Treatment (predicted mean, SE)*	-1.200 (0.719)	-0.800 (0.684)	0.691
Inverse Simpson Index: Exacerbation to Follow up (predicted mean, SE)*	-1.376 (0.858)	+1.388 (0.858)	0.032
Morisita-Horn: Exacerbation to Treatment (predicted mean, SE)*†	0.477 (0.125)	0.534 (0.119)	0.744
Morisita-Horn: Exacerbation to Follow up (predicted mean, SE)*	0.528 (0.098)	0.471 (0.098)	0.697

SE, standard error

*General linear model with Gaussian family and identity link, controlling for discordance of sample types collected between time points

†Non-normal distribution

Supplemental Table 4. Recovery of Lung Function Following Antibiotic Treatment

	fT>MIC sufficient	fT>MIC not sufficient	P value
Pulmonary Function at End of Treatment (mean, SE)*	(n=12)	(n=12)	
% predicted FEV1	80.5 (6.2)	101.6 (6.2)	0.055
% predicted FVC	83.9 (5.3)	107.1 (5.3)	0.014
% predicted FEF25-75	69.2 (14.5)	111.0 (14.5)	0.103
Normalized FEV1 [#]	92.6 (2.60)	99.9 (3.05)	0.803
Normalized FVC [†]	91.6 (2.16)	104.1 (5.49)	0.634
Normalized FEF25-75	92.5 (4.77)	100.2 (5.29)	0.830
Pulmonary Function at Follow up[‡] (mean, SE)*	(n=11)	(n=10)	
% predicted FEV1 [^]	88.8 (4.4)	97.7 (4.7)	0.218
% predicted FVC	91.6 (5.2)	102.3 (5.6)	0.262
% predicted FEF25-75	80.3 (10.9)	98.0 (11.7)	0.371
Normalized FEV1	94.2 (2.64)	96.7 (4.77)	0.887
Normalized FVC	94.5 (2.81)	99.0 (3.60)	0.829
Normalized FEF25-75	90.5 (3.62)	90.1 (6.25)	0.446

SE, standard error; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25-75, forced expiratory flow 25-75

Normalized = percent recovery compared to baseline value (e.g., end of treatment FEV1/baseline FEV1)

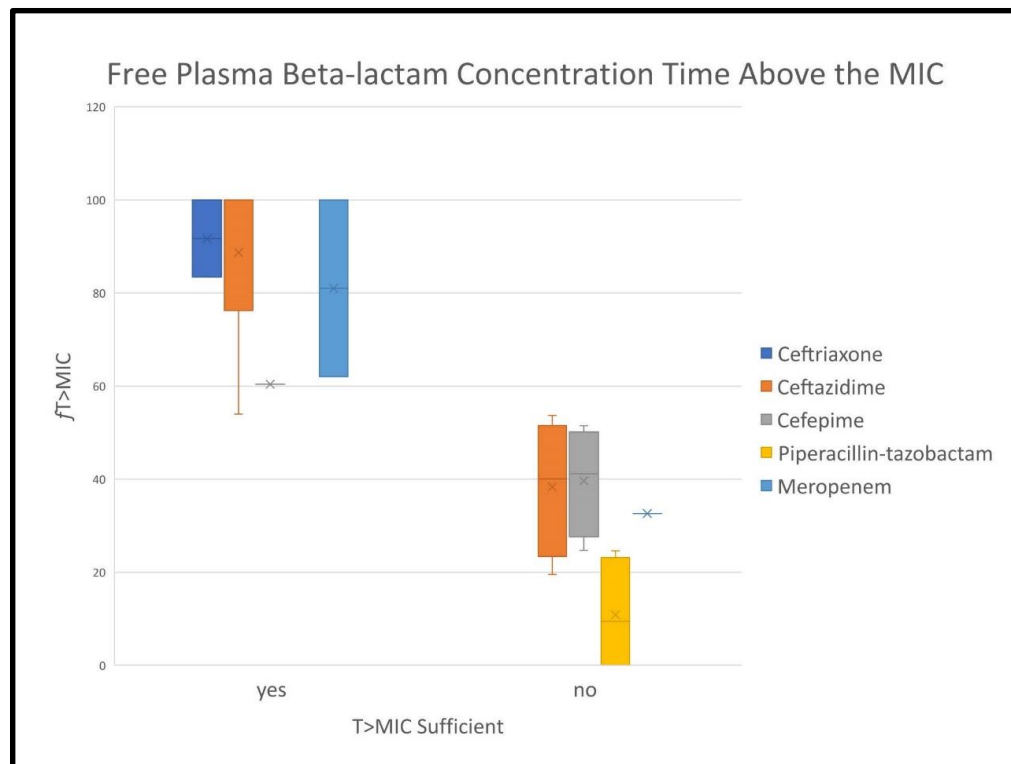
*General linear model with Gaussian family and identity link, controlling for demographic characteristics

[#]Cubic transform

[†]Inverse transform

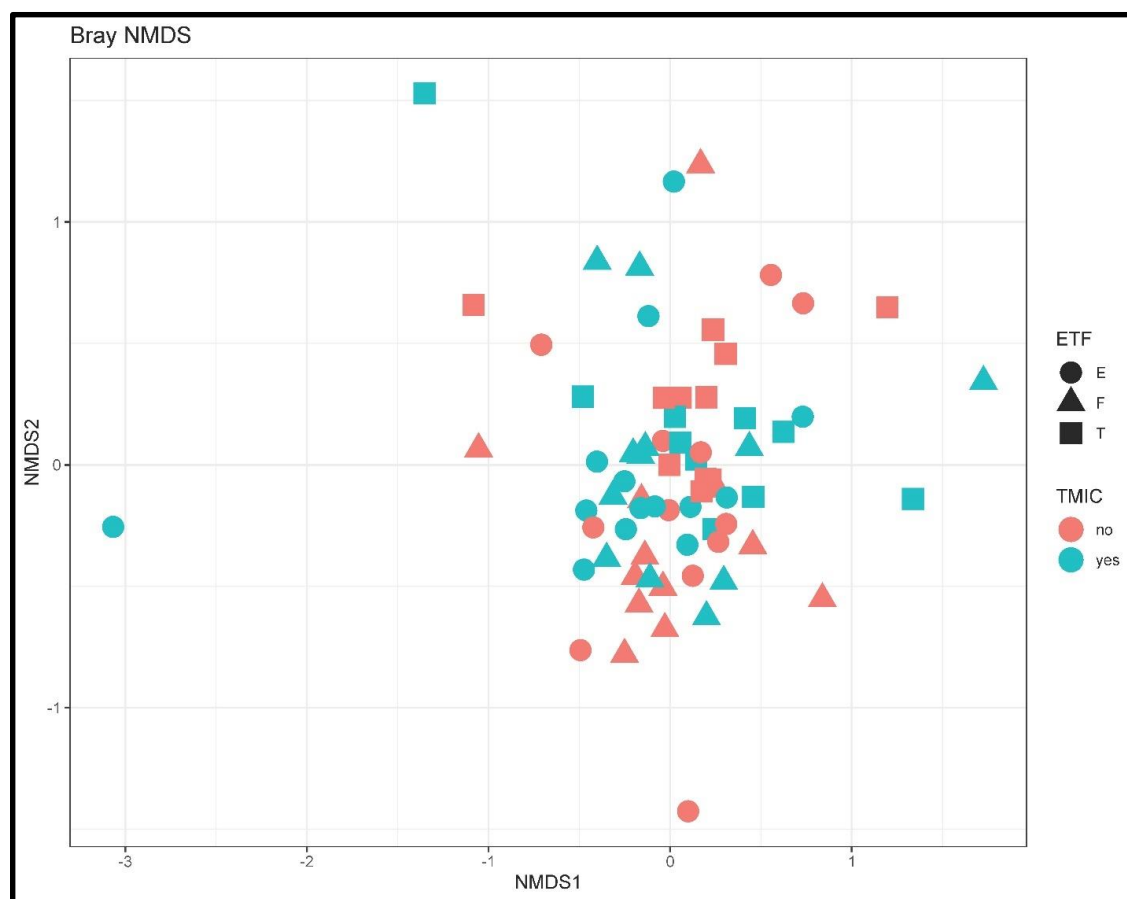
[‡]Missing data exists because PFTs had to be obtained prior to another antibiotic treatment course

[^]Square transform

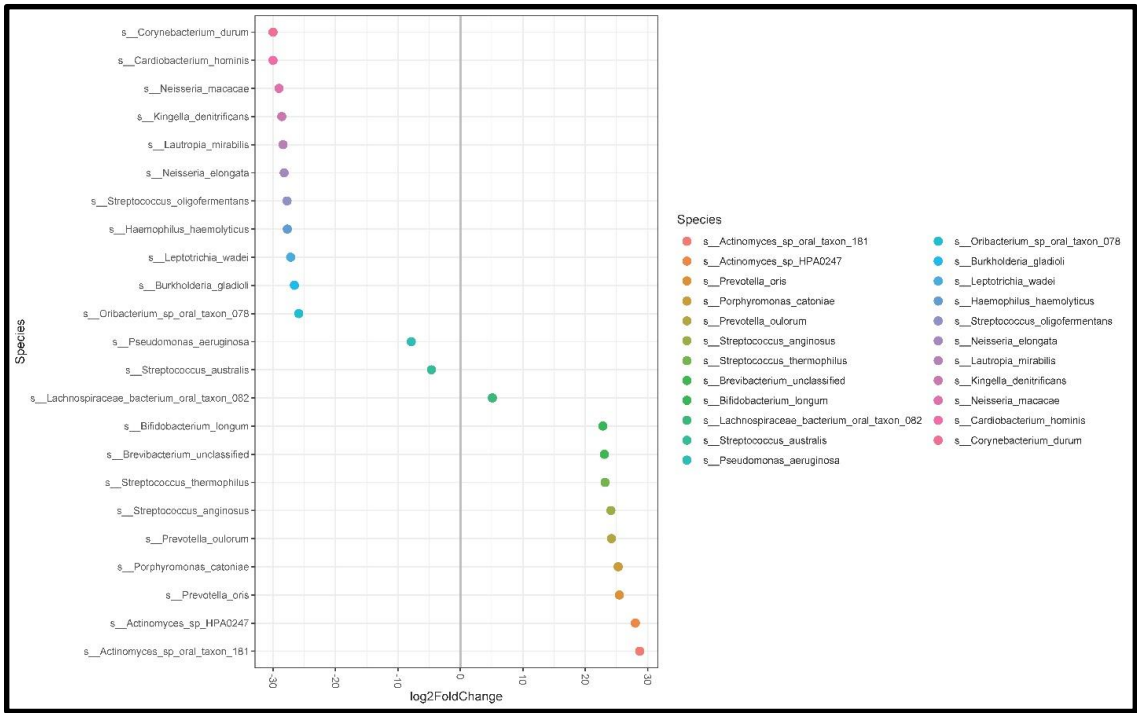


Supplemental Figure 1. Box and Whiskers Plot of Free Plasma Concentration Time above the MIC.

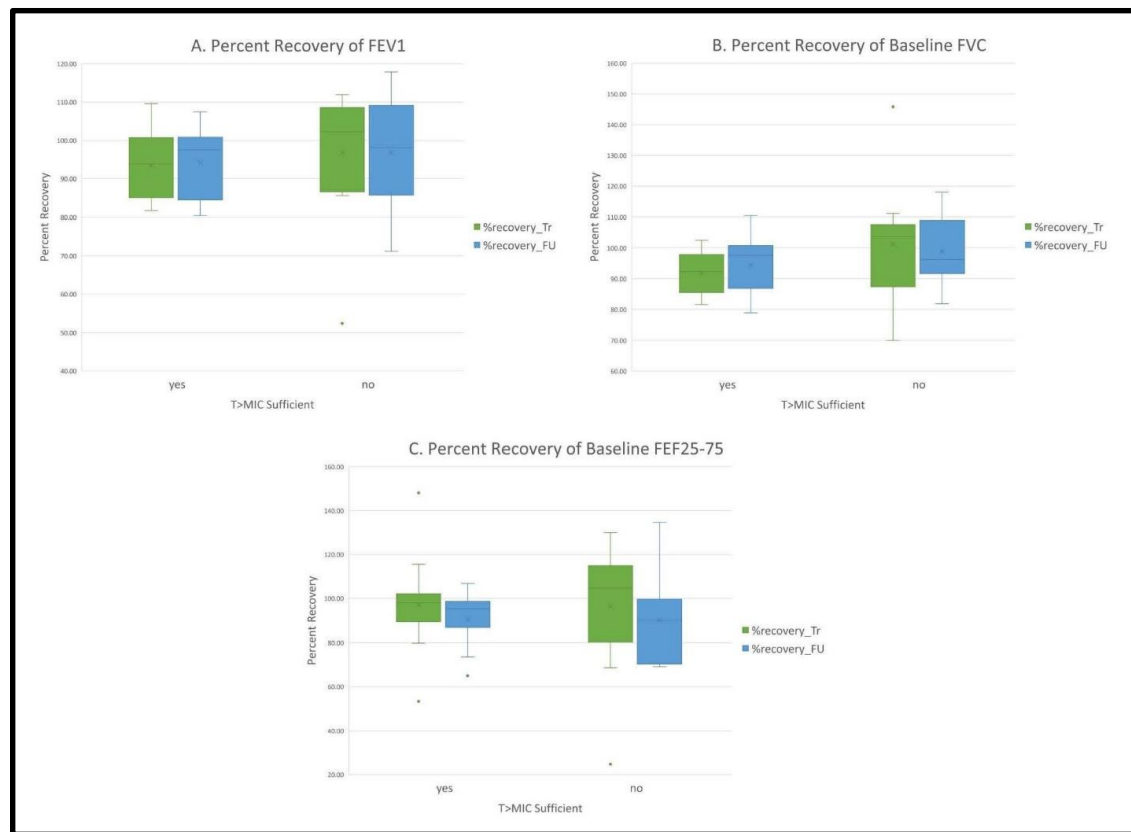
$fT>MIC$, time above the minimum inhibitory concentration; no, $fT>MIC$ not sufficient; yes, $fT>MIC$ sufficient. "x" corresponds to mean values. Center horizontal line corresponds to median. Colored boxes represent the interquartile ranges. Twenty-seven values are included in this plot; for the five study participants who received two beta-lactam antibiotics, the highest $fT>MIC$ is reported.



Supplemental Figure 2. Bray-Curtis non-metric multi-dimensional scaling plot of respiratory samples. PERMANOVA R^2 0.016, $p > 0.999$ for $fT > MIC$, controlling for repeated samples from the same study participant using the STRATA function. $fT > MIC$, time above the minimum inhibitory concentration; E, exacerbation; T, treatment; F, follow up; no, $fT > MIC$ not sufficient; yes, $fT > MIC$ sufficient.



Supplemental Figure 3. Differential abundance of bacterial taxa. All time points are included. Negative log2 fold change are more abundant in $fT > MIC$ not sufficient; positive log2 fold change are more abundant in $fT > MIC$ sufficient. All bacterial taxa shown had a p value < 0.05 .



Supplemental Figure 4. Box and Whiskers Plot of Normalized Recovery of Lung Function Compared to Baseline Following Antibiotic Treatment. Panel A. Percent Recovery of FEV1. Panel B. Percent Recovery of Baseline FVC. Panel C. Percent Recovery of Baseline FEF25-75. FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25-75, forced expiratory flow 25-75; Tr, Treatment; FU, Follow up; $fT > MIC$, time above the minimum inhibitory concentration; no, $fT > MIC$ not sufficient; yes, $fT > MIC$ sufficient. Normalized = percent recovery compared to baseline value (e.g., end of treatment FEV1/baseline FEV1). “x” corresponds to mean values. Center horizontal line corresponds to median. Colored boxes represent the interquartile ranges. Small circles represent individual values.