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Major Article

Impact of colonizing organism in the respiratory tract on the incidence, duration, and time between subsequent hospitalizations among patients with cystic fibrosis

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Key Words:

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Methicillin-susceptible *Staphylococcus aureus*
*Pseudomonas aeruginosa***Background:** This study aimed to examine the association between colonizing respiratory tract organism and frequency, duration, and time between subsequent hospitalizations among hospitalized patients with cystic fibrosis (CF).**Methods:** This retrospective cohort study of 312 CF patients from 2 New York City hospitals (2006–2016) examined the effects of colonization with *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus aureus* (MSSA) or methicillin-resistant *S aureus* (MRSA), co-colonization on incidence of hospitalization, time to next hospitalization, and total length of stay (LOS).**Results:** Annual rate of subsequent hospitalizations was highest in patients with *P aeruginosa*: adjusted incidence rate ratios (aIRRs) were 2.75 (95% confidence interval [CI], 1.72–4.41) for *P aeruginosa* versus MSSA, 2.57 (95% CI, 1.52–4.31) for co-colonization versus MSSA, and 1.77 (95% CI, 1.04–3.01) for *P aeruginosa* versus MRSA. Time to readmission was shortest for *P aeruginosa*: aIRRs were 1.75 (95% CI, 1.05–2.94) for MRSA versus *P aeruginosa*, 1.64 (95% CI, 1.03–2.59) for MSSA versus *P aeruginosa*, and 1.61 (95% CI, 1.04–2.47) for co-colonization versus *P aeruginosa*. LOS was longest for *P aeruginosa*: aIRRs were 3.41 (95% CI, 2.19–5.32) for *P aeruginosa* versus MSSA, 1.66 (95% CI, 1.01–2.75) for co-colonization versus MSSA, 2.50 (95% CI, 1.58–3.93) for *P aeruginosa* versus MRSA, and 2.05 (95% CI, 1.32–3.18) for *P aeruginosa* versus co-colonization.**Conclusions:** CF patients with *P aeruginosa* alone experienced more hospitalizations, longer LOS, and shorter time to readmission versus patients with *S aureus* or both organisms.

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Acute infection or chronic colonization of the lungs by opportunistic pathogens is a persistent complication among patients living with cystic fibrosis (CF), a multiorgan disease in which abnormal transport of electrolytes leads to thick secretions in all exocrine glands.^{1–6} Buildup of this viscous mucus in the airways leads to impaired clearance of pathogens from the respiratory tract, creating a suitable environment for bacteria, most commonly *Pseudomonas aeruginosa* and *Staphylococcus aureus*, to thrive.^{1,2,4–6} In 2016, the prevalence of *P aeruginosa* and methicillin-susceptible *S aureus*

(MSSA) in this population was approximately 46.4% and 55.0%, respectively.⁷ Additionally, in the past 2 decades, methicillin-resistant *S aureus* (MRSA) has increased in prevalence among patients with CF, rising from 0.1% in 1995 to 26.0% in 2016.^{5–7} Colonization with these species, as well as multiple other antibiotic-resistant organisms, has been associated with exaggerated inflammatory response in the lungs and decreased pulmonary function, which in turn is associated with worsening nutritional status requiring increased medical therapy and risk of hospitalization.^{4,8–14}

Although preliminary evidence suggests that outcomes for patients with CF may vary based on colonizing species, little is known about the relationship between infecting species, antimicrobial susceptibility or co-colonization, and the frequency and duration of hospitalization.^{4,9,12,13} Hence, the purpose of this study was to describe the association between respiratory colonization with *P aeruginosa*, MSSA,

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MRSA, or co-colonization and frequency, duration, and time between subsequent hospitalizations among CF patients.

METHODS

Study design and setting

We performed a retrospective cohort study of pediatric and adult CF patients colonized with at least 1 common organism (*P aeruginosa* or *S aureus*) and admitted the patients to either the pediatric or adult hospital of an accredited CF Foundation care center, which is part of a large academic health system in Manhattan, New York. During our 11-year study period, the annual number of patients treated at the center ranged from 187 in 2006 to 352 in 2016. Infection control guidelines throughout the study were consistent with CF Foundation recommendations. This study was approved by the Columbia University institutional review board.

Data source

Data were extracted from a larger federally-funded study (Nursing Intensity of Patient Care Needs and Rates of Healthcare-Associated Infections, R01 HS024915), which includes a comprehensive database developed from all patient discharges in the study hospitals between January 1, 2006, and December 31, 2016.

Study sample

CF patients were initially identified if the electronic medical record indicated any of the following CF-related ICD-9-CM diagnosis codes: 277.00 (CF without mention of meconium ileus), 277.01 (CF with meconium ileus), 277.02 (CF with pulmonary exacerbation), 277.03 (CF with gastrointestinal manifestations), and 277.09 (CF with other manifestations). Patients were excluded if they did not have complete data on colonizing organisms of interest for at least 1 hospitalization during the study period, or if the only hospitalization with complete colonization data included lung transplant.

Baseline patient characteristics

Clinical and demographic variables at initial hospitalization were extracted, including sex, age, race, insurance plan, admission and discharge dates for each hospitalization during the study period, all inpatient respiratory culture results for *P aeruginosa*, MSSA, and MRSA, and dates of lung transplant and death. Patient age was categorized into CF-specific life course stages of <16 years old, 16–21 years old, and >21 years old. To account for variability in economic status, insurance plan was defined as either commercial (including self-pay), Medicare, or Medicaid.

Exposure

A patient was considered colonized with *P aeruginosa*, MSSA, MRSA, or co-colonization (*P aeruginosa*+MSSA or *P aeruginosa*+MRSA) if 1 or more respiratory cultures were positive. We included all positive cultures, regardless of whether they were taken for surveillance purposes or clinical indication. Policies regarding surveillance cultures varied by unit and throughout the study period. Patients may have also been colonized with other CF-related pathogens, however, these data were not analyzed as they were not the focus of this study. A patient's initial colonization was considered to be the earliest hospitalization, with a positive culture for any of the organisms of interest. All microbiologic diagnostics were ascertained by respiratory culture, collected via expectorated sputum or throat

swab, and processed by the clinical microbiology laboratory of the study institution.

Outcomes

Frequency of subsequent hospitalizations included all admissions for any CF-related diagnosis within the study period after the initial hospitalization. Hospitalizations occurring after admission for lung transplant were excluded. Follow-up time contributed by each patient started from the discharge date of the initial hospitalization and ended at the end of the study period, date of admission for lung transplant, or date of death, whichever occurred first. Time to next hospitalization was defined as days between date of discharge from initial hospitalization and date of admission for the next subsequent hospitalization. Total length of stay (LOS) was the cumulative number of days a patient spent hospitalized during the study period, beginning with the initial hospitalization and ending before admission for lung transplant, if applicable.

Statistical analysis

Demographic and clinical characteristics of the cohort were summarized using descriptive statistics. Differences in baseline characteristics, frequency of hospitalization, time to next hospitalization, and total LOS stratified by colonizing organism were analyzed. The χ^2 tests were used to compare differences between categorical variables, 1-way analysis of variance F tests were used for normally distributed continuous variables, and the Kruskal-Wallis nonparametric tests were used for non-normally distributed continuous variables. Frequency of subsequent hospitalizations, time to next hospitalization, and LOS were analyzed using negative binomial regression after evidence of overdispersion and superior model fit when compared to Poisson regression.¹⁵ Confounders were identified by bivariate analysis or if there was >10% change in beta parameters. A *P* value of .05 was considered significant. All analyses were conducted using SAS 9.4 software (SAS Institute Inc, Cary, NC).

RESULTS

A total of 644 CF patients were identified from the database, 376 of whom had complete data on colonization. After excluding patients with incomplete data on colonizing organisms for at least 1 hospitalization prior to admission for lung transplant (*N* = 47) or who were not colonized with at least 1 organism of interest (*N* = 17), 312 patients with 990 hospitalizations were identified for analysis.

The baseline demographic and clinical characteristics of the cohort are shown in Table 1. The greatest proportion of patients were colonized with *P aeruginosa* (43.6%), followed by MSSA (23.7%), co-colonization (16.7%), and MRSA (16.0%). The mean age of this cohort was 24 years, with mean age differing significantly between colonizing organism. Patients colonized with *P aeruginosa* had the highest mean age (30 years), followed by co-colonization (26 years), MRSA (20 years), and MSSA (16 years). The majority of the patients were women, white, and had a commercial insurance plan. During the study period, patients colonized with *P aeruginosa* had the highest proportion of lung transplantation and death.

Of the 312 patients, 294 remained at risk of readmission after initial hospitalization and were included in analysis of the annual rate of subsequent hospitalizations by colonizing organism. Patients colonized with *P aeruginosa* experienced the highest rates of hospitalization (1.09 hospitalizations per year), followed by co-colonization (1.02 hospitalizations per year), MRSA (0.62 hospitalizations per year), and MSSA (0.40 hospitalizations per year), adjusting for age, race, and insurance plan (Table 2). Patients colonized with *P*

Table 1
Demographic and clinical variables by colonizing organism

Characteristic	Colonizing organism					P value
	All patients (n = 312)	<i>Pseudomonas aeruginosa</i> (n = 136)	MSSA (n = 74)	MRSA (n = 50)	Co-colonization (n = 52)	
All patients (%)	100	43.6	23.7	16.0	16.7	<.0001
Mean age, y (SD)	24.45 (12.8)	29.96 (11.4)	15.82 (10.3)	20.46 (11.7)	26.12 (12.8)	<.0001
Age (at date of initial hospitalization), n (%)						
<16	73 (23.4)	7 (5.2)	41 (55.4)	14 (28.0)	11 (21.2)	<.0001
16–21	64 (20.5)	24 (17.7)	13 (17.6)	18 (36.0)	9 (17.3)	—
>21	175 (56.1)	105 (77.2)	20 (27.0)	18 (36.0)	32 (61.5)	—
Female, n (%)	169 (54.2)	81 (59.6)	35 (47.3)	27 (54.0)	26 (50.0)	.3
Race (white), n (%)	208 (89.7)	99 (95.2)	44 (86.3)	36 (90.0)	29 (78.4)	.0274
Insurance, n (%)						
Commercial	174 (55.77)	78 (57.35)	42 (56.8)	29 (58.0)	25 (48.1)	.0004
Medicare	55 (17.63)	36 (26.47)	4 (5.4)	6 (12.0)	9 (17.3)	—
Medicaid	83 (26.60)	22 (16.18)	28 (37.8)	15 (30.0)	18 (34.6)	—
Inhaled Tobramycin, n (%)	88 (28.21)	38 (27.94)	15 (20.3)	21 (42.0)	14 (26.9)	.07
Frequency of rehospitalization median, (min-max)	1 (0–35)	1 (0–35)	1 (0–12)	1 (0–9)	1.5 (0–23)	.07
Number of d between subsequent hospitalizations median, (min-max)	203 (1–2,487)	148 (1–1,203)	247 (13–1,622)	197.5 (11–2,487)	202 (1–1,824)	.06
Total d hospitalized Median, (min-max)	17 (1–550)	17 (2–550)	15 (1–139)	17 (2–243)	18.5 (1–421)	.1
Lung transplantation, n (%)	34 (11.2)	24 (17.7)	1 (1.4)	5 (10.0)	4 (7.7)	<.0001
Died, n (%)	35 (10.9)	24 (17.7)	1 (1.4)	5 (10.0)	5 (9.6)	<.0001

Max, maximum; min, minimum; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*.

aeruginosa had 2.75 times the rate of annual readmissions compared with patients colonized with MSSA (95% CI, 1.72–4.41), patients with co-colonization had 2.57 times the rate of annual readmissions compared with patients colonized with MSSA (95% CI, 1.52–4.32), and patients colonized with *P aeruginosa* had 1.77 times the rate of annual readmissions compared with patients colonized with MRSA (95% CI, 1.04–3.01) (Table 2).

Of the 294 patients at risk of readmission, 184 patients with at least 1 readmission were included in the analysis assessing the number of days to next hospitalization stratified by colonizing organism. Patients colonized with *P aeruginosa* had the shortest time to subsequent hospitalization with 207 days, followed by co-colonization (333 days), MSSA (339 days), and MRSA (363 days), adjusting for age, race, and insurance plan (Table 3). Patients colonized with MRSA had 1.75 times the number of days to subsequent hospitalization compared with patients colonized with *P aeruginosa* (95% CI, 1.05–2.94), patients colonized with MSSA had 1.64 times the number of days to subsequent hospitalization compared with patients colonized with *P aeruginosa* (95% CI, 1.03–2.59), and patients with co-colonization had 1.61 times the number of

days to subsequent hospitalization compared with patients colonized with *P aeruginosa* (95% CI, 1.04–2.47) (Table 3).

Of the 312 patients in our sample, the total LOS per year was highest in patients colonized with *P aeruginosa* (33 days), followed by co-colonization (16 days), MRSA (13 days), and MSSA (9 days), adjusting for age, race, and insurance plan (Table 4). Patients colonized with *P aeruginosa* had 2.50 times the annual LOS compared to MRSA (95% CI, 1.58–3.93), patients colonized with *P aeruginosa* had 3.41 times the annual LOS compared with patients colonized with MSSA (95% CI, 2.19–5.32), patients colonized with *P aeruginosa* had 2.05 times the annual LOS compared with patients with co-colonization (95% CI, 1.32–3.18), and patients with co-colonization had 1.66 times the annual LOS compared with patients colonized with MSSA (95% CI, 1.01–2.75).

DISCUSSION

In this retrospective cohort study, the largest proportion of the 312 CF patients were colonized with *P aeruginosa* in the respiratory tract, followed by MSSA, co-colonization, and MRSA. The age range of

Table 2
Incidence rate ratios comparing mean subsequent hospitalizations per year by colonizing organism

Colonizing organism	Mean subsequent hospitalizations per year IR (95% CI)	Unadjusted model*		Mean subsequent hospitalizations per year [†] IR (95% CI)	Adjusted model ^{†,‡}	
		IRR (95% CI)	P value		IRR (95% CI)	P value
MSSA	0.98 (0.75–1.28)	1.00 (REF)	—	1.09 (0.80–1.50)	1.00 (REF)	—
<i>Pseudomonas aeruginosa</i>	0.41 (0.29–0.58)	2.39 (1.54–3.71)	.0001	0.40 (0.27–0.58)	2.75 (1.72–4.41)	<.0001
MRSA	0.58 (0.38–0.90)	1.43 (0.82–2.49)	.2	0.62 (0.39–0.99)	1.55 (0.89–2.72)	.1
Co-colonization	1.02 (0.70–1.49)	2.49 (1.49–4.16)	.0005	1.02 (0.68–1.51)	2.57 (1.52–4.32)	.0004
MRSA	—	1.00 (REF)	—	—	1.00 (REF)	—
<i>P aeruginosa</i>	—	1.67 (1.01–2.79)	.0473	—	1.77 (1.04–3.01)	.03
Co-colonization	—	1.75 (0.98–3.10)	.06	—	1.65 (0.91–2.99)	.1
Co-colonization	—	1.00 (REF)	—	—	1.00 (REF)	—
<i>P aeruginosa</i>	—	0.96 (0.60–1.53)	.9	—	1.07 (0.67–1.71)	.8

CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; REF, reference.

*Results of negative binomial regression.

[†]Model is adjusted for age category, race, and insurance plan.

Table 3
Incidence rate ratios comparing mean days to subsequent hospitalization by colonizing organism

Colonizing organism	Mean to subsequent hospitalization (d) Count (95% CI)	Unadjusted model*		Mean to subsequent hospitalization (d) [†] Count (95% CI)	Adjusted model* [‡]	
		IRR (95% CI)	P value		IRR (95% CI)	P value
<i>Pseudomonas aeruginosa</i>	248.8 (192.59–321.42)	1.00 (REF)	—	207.1 (152.19–281.85)	1.00 (REF)	—
MRSA	405.9 (292.32–563.54)	1.91 (1.16–3.15)	.01	339.3 (237.20–485.24)	1.75 (1.05–2.94)	.033
MSSA	475.0 (308.49–731.51)	1.63 (1.08–2.47)	.02	362.9 (232.73–565.70)	1.64 (1.03–2.59)	.035
Co-colonization	385.0 (270.61–547.75)	1.55 (1.00–2.39)	.049	332.8 (225.28–491.51)	1.61 (1.04–2.47)	.03
Co-colonization	—	1.00 (REF)	—	—	1.00 (REF)	—
MRSA	—	1.23 (0.71–2.15)	.5	—	1.09 (0.62–1.93)	.8
MSSA	—	1.05 (0.65–1.71)	.8	—	1.02 (0.61–1.70)	.9
MSSA	—	1.00 (REF)	—	—	1.00 (REF)	—
MRSA	—	1.17 (0.68–2.01)	.6	—	1.07 (0.62–1.85)	.8

CI, confidence interval; IRR, incidence rate ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; REF, reference.

[†]Results of negative binomial regression.

[‡]Model is adjusted for age category, race, and insurance plan.

patients colonized with each organism followed the known biological progression of disease in this population.^{7,16,17} MSSA is the organism most frequently cultured from CF patients in childhood and adolescence, and as such, 55.4% of the patients colonized with this bacterium alone in our study were <16 years old. This life stage is also the beginning of colonization with *P aeruginosa*. In our sample, we found that only 5.2% of the patients colonized with *P aeruginosa* were <16 years, a prevalence much lower than recent national estimates.⁷ However, children are often co-infected with *P aeruginosa* and *S aureus* (MSSA or MRSA). When combining patients colonized with both organisms and *P aeruginosa* alone, 24.7% of the patients who were <16 years of age were colonized with *P aeruginosa*, which is similar to the 2016 estimate of 29.1% for any *P aeruginosa* colonization in this age category.⁷ The majority of patients colonized with MRSA were >16 years of age, whereas those co-colonized were more likely to be >21 years of age. By the time patients reach adulthood, the lung microbiome may be dominated by *P aeruginosa*. In our sample, 77.2% of patients colonized with *P aeruginosa* alone were >21 years of age.

Recent studies have advanced our understanding of the interconnectedness of nutrition, gastrointestinal disorders, CF-related diabetes, and the lung and gut microbiome together in contributing to clinical outcomes among CF patients.^{18–22} By assessing the frequency of any subsequent CF-related hospitalizations, rather than pulmonary exacerbations alone, we gain insight into the impact of colonizing organism on overall disease progression and severity.

We found that the annual rate of hospitalization was significantly higher for *P aeruginosa* patients compared to MRSA, *P aeruginosa* compared to MSSA, and co-colonization compared to MSSA. In a similar

study, Hubert et al¹³ reported that the rate of any hospitalization was higher for patients coinfecting with MRSA and *P aeruginosa* versus MRSA alone, but that the number of intravenous antibiotics course per year was highest for those colonized with *P aeruginosa* only.²² However, these measures were not adjusted for clinical or demographic variables. In addition, Ahlgren et al²³ reported a significant increase in pulmonary exacerbations among patients colonized with *P aeruginosa* alone compared to *S aureus* alone but did not differentiate between MSSA and MRSA. Similar to our study, colonization with *P aeruginosa* itself or in coinfection with MSSA or MRSA resulted in worse outcomes than colonization with antibiotic-susceptible or resistant *S aureus* alone.

CF patients colonized with *P aeruginosa* had a significantly shorter time to readmission and longer total stay when compared with all other organisms (MSSA, MRSA, and co-colonization) in our study. After establishing itself in the respiratory tract as a biofilm, this organism has been found almost impossible to eradicate, even with extended courses of antibiotics.^{23,24} Chronic infection further elicits a strong inflammatory response that results in decreased lung function, poorer prognosis, and subsequently more frequent, and shorter time to, medical attention.^{23,24}

Our findings may differ from others regarding the association between co-colonization with *P aeruginosa* and *S aureus* and patient outcomes. In a laboratory setting, Orazi and O'Toole²⁵ found that adding *P aeruginosa* supernatant to *S aureus* increased the latter's tolerance for a variety of antibiotics and selected for more virulent *S aureus* colonies, suggesting increased pathogenesis with co-colonization.²⁴ However, unlike our study in which *P aeruginosa* alone most negatively impacted clinical outcomes, Hubert et al¹³ found no significant differences in

Table 4
Incidence rate ratios comparing mean LOS per year by colonizing organism

Colonizing organism	Mean LOS per year (d) IR (95% CI)	Unadjusted model*		Mean LOS per year (d) [†] IR (95% CI)	Adjusted model* [‡]	
		IRR (95% CI)	P value		IRR (95% CI)	P value
MSSA	30.08 (23.67–38.23)	1.00 (REF)	—	33.32 (24.96–44.46)	1.00 (REF)	—
<i>Pseudomonas aeruginosa</i>	9.88 (7.29–13.37)	3.05 (2.07–4.48)	<.0001	9.76 (6.87–13.89)	3.41 (2.19–5.32)	<.0001
MRSA	11.67 (7.90–17.24)	1.18 (0.72–1.94)	.5	13.35 (8.84–20.16)	1.37 (0.83–2.26)	.2
Co-colonization	21.59 (14.95–31.18)	2.19 (1.36–3.52)	.001	16.25 (11.10–23.77)	1.66 (1.01–2.75)	.047
MRSA	—	1.00 (REF)	—	—	1.00 (REF)	—
<i>P aeruginosa</i>	—	2.58 (1.63–4.07)	<.0001	—	2.50 (1.58–3.93)	<.0001
Co-colonization	—	1.85 (1.08–3.16)	.02	—	1.22 (0.71–2.08)	.5
Co-colonization	—	1.00 (REF)	—	—	1.00 (REF)	—
<i>P aeruginosa</i>	—	1.39 (0.90–2.16)	.1	—	2.05 (1.32–3.18)	.0013

CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; REF, reference.

*Results of negative binomial regression.

[‡]Model is adjusted for age category, race, and insurance plan.

duration of hospitalization between patients coinfecting with *P aeruginosa* and MSSA/MRSA compared with patients colonized by each organism separately, although these measures were left unadjusted. Thus, the effect and mechanisms of respiratory colonization with *P aeruginosa* and MSSA/MRSA alone or in combination on overall disease progression in CF patients is a topic primed for further research.

In this study, we were limited to inpatient data captured by our electronic database. As such, information on exposure, outcomes, demographic and clinical variables, including positive cultures, may have been incomplete given that clinical data is often collected during out-patient visits as part of routine care, or may have occurred at another institution, although care seeking at other institutions in this specialized population is rare. Although this study reflects only a single CF center, it is a large center with a diverse patient population. CF patients were initially identified for enrollment using ICD-9 codes, which have variable sensitivity and specificity, depending on the condition. Because respiratory cultures were not obtained for some patients during inpatient hospitalization, it is possible that they were also colonized with organisms of interest during our study period, or for some time prior to initial hospitalization. In addition, we did not have data on other colonizing organisms in the respiratory tract, which could be confounders in our study. Further, although descriptions of race were provided in the database, there were many patients who were identified as “other” or “not-specified.” This is problematic when investigating a disease in which prevalence may vary by race, such as CF being more prevalent in “white” patients.⁷

Strengths of our study include access to a database of all CF hospitalizations from a metropolitan CF clinic over an extended period. Considering that CF patients tend to receive continuous care from CF care centers, the frequency of hospitalizations and time to next hospitalization should be accurately reflected in this study cohort.

CONCLUSIONS

Our study found that patients colonized with *P aeruginosa* alone had more frequent, longer, and shorter time to subsequent hospitalizations for any CF-related diagnoses. Further research is needed to investigate the specific effects and pathogenesis of colonizing organism in the respiratory tract on other body systems and how this impacts overall CF disease progression.

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