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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



Incidence and Risk Factors for Multiple Antibiotic-Resistant *Pseudomonas aeruginosa* in Cystic Fibrosis*

Christian A. Merlo, MD, MPH; Michael P. Boyle, MD, FCCP;
Marie Diener-West, PhD; Bruce C. Marshall, MD;
Christopher H. Goss, MD, MS, FCCP; and Noah Lechtzin, MD, MHS, FCCP

Background: Infection with multiple antibiotic-resistant *Pseudomonas aeruginosa* (MARPA) in individuals with cystic fibrosis (CF) has caused much concern among caregivers, yet little is known about the risks associated with acquiring resistance. The main objective of the study was to estimate the incidence and identify risk factors for the acquisition of MARPA among individuals with CF.

Methods: Five-year cohort study of individuals followed in the Cystic Fibrosis Foundation Registry from 1998 through 2002.

Results: Demographics, anthropometrics, spirometry, respiratory culture results, comorbidities, antibiotic usage, and hospitalizations were collected. Of the 4,293 patients with *P aeruginosa* infection during the study period, MARPA developed in 341. The overall incidence of MARPA was 1.8%/yr. Independent risk factors for MARPA included CF-related diabetes mellitus (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.11 to 2.43), long-term inhaled tobramycin usage (HR, 2.08; 95% CI, 1.56 to 2.77), and care at a CF center with a baseline MARPA prevalence in the top quartile (HR, 2.00; 95% CI, 1.31 to 3.04). Frequent courses of IV antibiotics and repeated hospitalizations were also found to independently increase the risk for MARPA.

Conclusions: Infection with MARPA is common among patients with CF. Diabetes, long-term inhaled tobramycin usage, and frequent acute pulmonary exacerbations requiring hospitalization or IV antibiotics increase the risk for MARPA. Receiving CF care at a center with a high prevalence of resistant *Pseudomonas* also increases the risk for MARPA in patients with CF. Further study is needed to investigate the mechanisms of acquiring resistant strains and the clinical impact of MARPA on CF outcomes. (CHEST 2007; 132:562–568)

Key words: antibiotic resistance; cystic fibrosis; incidence; *Pseudomonas aeruginosa*; risk factors

Abbreviations: BMI = body mass index; CF = cystic fibrosis; CFF = Cystic Fibrosis Foundation; CI = confidence interval; HR = hazard ratio; MARPA = multiple antibiotic-resistant *Pseudomonas aeruginosa*

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease among whites. Respiratory disease caused by chronic bacte-

rial infection is the leading cause of morbidity and mortality in CF. By the age of 18 years, approximately 80% of individuals with CF have *Pseudomo-*

*From the Department of Medicine, Division of Pulmonary and Critical Care Medicine (Drs. Merlo, Boyle, Marshall, and Lechtzin), The Johns Hopkins University School of Medicine, Baltimore, MD; Department of Biostatistics (Dr. Diener-West), The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; and Department of Medicine, Division of Pulmonary and Critical Care Medicine (Dr. Goss), University of Washington Medical Center, Seattle, WA. Dr. Merlo is a Harry Shwachman CF Clinical Investigator of the CFF. Support was provided by the CFF (CFFT # MERLO04A0).

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nas aeruginosa infection.¹ At the time of the initial infection, most isolates of *Pseudomonas* are sensitive to multiple classes of antibiotics, but over time antibiotic resistance can develop. With the growing adult population, infection with highly resistant bacteria has led to much concern among patients, caregivers, and infection-control policy makers.

Resistant *Pseudomonas* has received particular attention because of the fear that infection with multiple antibiotic-resistant *P aeruginosa* (MARPA) may result in worse clinical outcomes. This concern is magnified by worries that resistant *Pseudomonas* may also be transmissible between patients.²⁻⁴ This has resulted in the development and implementation of extensive guidelines on infection control designed to standardize clinical microbiology and infection control practices in US CF care centers.⁵

This growing awareness and concern about MARPA may be warranted. First, the prevalence of infection with MARPA among patients with CF appears to be increasing.¹ Second, there is preliminary evidence suggesting that MARPA may contribute to worse clinical outcomes. One single-center study⁶ suggested that among patients with CF, infection with MARPA is associated with more severe lung disease and more rapid decline in FEV₁ but does not lead to short term worsening in clinical outcomes. A second single-center report⁷ suggested that infection with MARPA is associated with a need for more frequent and more prolonged antibiotic courses. However, very little is known about the incidence of and risks for infection with MARPA in patients with CF. The purpose of this study therefore is to determine the incidence and prevalence of MARPA in the US CF population and to identify the clinical characteristics associated with the development of MARPA infection.

MATERIALS AND METHODS

Participants and Study Design

This was a cohort study of individuals followed in the Cystic Fibrosis Foundation (CFF) Patient Registry from January 1, 1998, through December 31, 2002.¹ Subjects were included if they had at least two sputum or throat culture findings negative for *P aeruginosa* during the first year of the study and subsequently had *P aeruginosa* infection during the study period. Subjects were censored if they were not available for follow-up, died, or underwent solid-organ transplantation. The primary outcome of interest was the onset of infection with MARPA. MARPA was defined as any strain of *P aeruginosa* resistant to at least two of the following antibiotics: tobramycin, ciprofloxacin, and/or meropenem.

Respiratory culture results with associated antibiotic resistance profiles were recorded, with the most resistant isolate used if more than one culture was performed per quarter. The highest FEV₁ per quarter was recorded. Pancreatic insufficiency was

defined as pancreatic enzyme usage. Diabetes mellitus was defined as CF-related diabetes with or without fasting hyperglycemia. An acute pulmonary exacerbation was defined as a change in clinical status requiring hospitalization or IV antibiotics. Follow-up time was the period from entry to study end or censoring. Other clinical information collected included concomitant organisms, inhaled tobramycin usage, as well as total number of hospitalizations, hospital days, courses of IV antibiotics, days of IV antibiotics, and acute exacerbations per year.

Statistical Analysis

A descriptive analysis was performed with calculation of means, SDs, and medians for continuous variables and proportions for categorical variables. Bivariate analyses were conducted using *t* tests or the Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher exact test for categorical variables. A time-to-event analysis for development of MARPA was performed. The Kaplan-Meier product limit estimator was used to evaluate the cumulative risk for MARPA infection. Multivariable Cox proportional hazards models were constructed to identify risk factors for MARPA. Covariates for multivariable models were chosen based on clinical reasoning and statistical significance in bivariable analyses. Collinearity between independent variables was assessed using the variance inflation factor. Testing of the proportional hazards assumption was performed using generalized linear regression of scaled Schoenfeld residuals on functions of time.⁸ The variables age, height, body mass index (BMI) percentile, FEV₁, diabetes, inhaled tobramycin usage, acute pulmonary exacerbations, hospitalizations, hospital days, courses of IV antibiotics, days of IV antibiotics, and concomitant infections were modeled as time-dependent covariates in order to evaluate the effect of each on MARPA developing at multiple time points. Because resistance profiles were not available for all study subjects; multiple imputation using regression techniques was performed for cultures missing antibiotic-resistance profiles.^{9,10} Results with and without imputation did not differ quantitatively, and only the results without imputation are shown. A secondary analysis defining "MARPA positive" as at least two sputum cultures obtained within a 12-month period was also performed.¹¹ Results of this sensitivity analysis did not differ significantly, and only results of the primary analysis are shown.

A *p* value < 0.05 was considered statistically significant for all analyses. Analyses were performed using statistical software (STATA 9.0, Special Edition; Statacorp; College Station, TX). The study was approved by the Institutional Review Board at the Johns Hopkins University School of Medicine.

RESULTS

There were 26,589 individuals with CF followed up in the CFF Patient Registry from January 1, 1998, through December 31, 2002. Of these, 19,170 patients had culture findings positive for *P aeruginosa*, and 4,842 subjects had infection with MARPA at some point during the study period. The yearly prevalence of MARPA rose from 13.7% in 1998 to 19.2% in 2002 and ranged by CF center from 0 to 100% (interquartile range, 10 to 22%). Of the 4,651 new cases of infection with *P aeruginosa*, associated resistance profiles were unavailable for 358 patients (7.7%). Of the remaining 4,293 cases of new *P aeruginosa* infection with available resistance pro-

files, 341 patients subsequently had MARPA infection (Fig 1). Of the group of patients with MARPA infection, a total of 89 patients (26%) acquired MARPA with their first culture of *P aeruginosa*.

The 341 patients with MARPA infection were compared with the 3,952 patients who had *Pseudomonas* but did not have infection with MARPA (Table 1). At baseline, patients with MARPA infection were older, had lower FEV₁, had lower BMI percentile, were more likely to have CF-related diabetes, and were more likely to have been treated at a CF center with a baseline prevalence of MARPA in the highest quartile when compared with those patients who did not have MARPA infection. Patients with MARPA infection were more likely to have been treated with long-term inhaled tobramycin and, on average, had higher annual rates of acute pulmonary exacerbations and hospitalizations, with more frequent courses of IV antibiotics when compared with those who did have MARPA infection.

The overall incidence of MARPA in the US CF population was 1.8 per 100 patients per year. Incidence increased steadily with age from 1.1 cases per 100 patients among individuals < 10 years of age, 2.6 cases per 100 patients among individuals between 10 and 20 years of age, 3.5 cases per 100 patients among individuals between 20 and 30 years of age, to 4.8 cases per 100 patients among individuals > 30 years of age. The risk of acquiring MARPA for patients without previous *P aeruginosa* infection increased steadily over time, and was approximately 4% at 3 years, 6% at 4 years, and 10% at 5 years.

A time-to-event analysis using Cox proportional hazards modeling with repeated measures was used to assess risk while adjusting for differences between those patients who had MARPA infection and those who did not. After adjusting for age, sex, height, BMI percentile, FEV₁, pancreatic insufficiency, and co-

infection with *S maltophilia* or *B cepacia* (Table 2), independent risk factors for MARPA infection included CF-related diabetes (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.11 to 2.43), long-term inhaled tobramycin usage (HR, 2.08; 95% CI, 1.56 to 2.77), and receiving care at a CF center with a baseline MARPA prevalence in the top quartile (HR, 2.00; 95% CI, 1.31 to 3.04). Higher FEV₁ was associated with less risk for MARPA infection (HR, 0.59; 95% CI, 0.45 to 0.76).

Significant collinearity was identified between the independent variables of acute exacerbations, IV antibiotic courses, and hospitalizations. Because of this, separate Cox proportional hazards models were used to evaluate the effect of each on the risk for MARPA (Table 3). In general, increasing rates of acute exacerbations, IV antibiotic courses, and hospitalizations per year were associated with increased risk for MARPA after adjusting for age, sex, height, BMI percentile, FEV₁, pancreatic status, inhaled tobramycin use, diabetes, center MARPA prevalence, and *B cepacia* infection.

DISCUSSION

Development of infection with MARPA is common among CF patients, and as expected, incidence rises cumulatively over time. Patients with CF who have lower FEV₁, CF-related diabetes, and those who receive long-term inhaled tobramycin appear to have increased risk for MARPA infection. Likewise, more frequent hospitalizations and courses of IV antibiotics, as well as more frequent acute pulmonary exacerbations, increase the risk for MARPA over time among patients with CF. Receiving care at a CF center with a high baseline prevalence of MARPA increases the risk for MARPA infection.

The results suggest that patients with CF-related diabetes are at increased risk for MARPA infection when compared with those CF patients without impaired glucose tolerance. This adds to the growing body of evidence concerning the potential detrimental effects of diabetes in CF. Marshall and colleagues¹² reported that patients with CF-related diabetes in general had more severe pulmonary disease, more frequent exacerbations requiring IV antibiotics, and worse nutritional status when compared to those without diabetes. It has also been demonstrated that impaired glucose tolerance and CF-related diabetes are directly related to high rates of decline in lung function.^{13,14} Therapy with insulin has been shown to reverse both pulmonary and nutritional decline in patients with CF-related diabetes, suggesting that diabetes is not simply a marker for worse disease, but rather directly contributes to

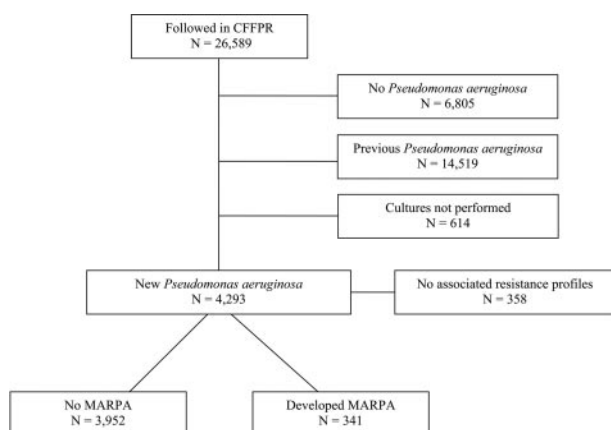


FIGURE 1. Diagram of study population.

Table 1—Baseline Characteristics of CF Patients With *Pseudomonas* Infection Who Subsequently Had MARPA Compared With Those Who Did Not*

Characteristics	Subsequently Become MARPA Positive	Remained MARPA Negative	p Value
Patients, No.	341	3,952	
Age, yr	15.4 ± 10.4	9.6 ± 9.2	< 0.0001
Female gender	174 (51)	1,928 (49)	0.43
Height, cm	141.4 ± 28.6	118.5 ± 36.8	< 0.0001
BMI percentile, %	37.0 ± 26.2	44.4 ± 27.8	< 0.0001
FEV ₁ , L	1.75 ± 0.80	1.87 ± 0.88	0.03
FEV ₁ , % predicted	70.0 ± 23.5	83.5 ± 23.1	< 0.0001
Pancreatic insufficiency	326 (96)	3,736 (95)	0.46
Diabetes	22 (6.5)	115 (2.9)	< 0.0001
Inhaled tobramycin usage	118 (35)	473 (12)	< 0.0001
Acute pulmonary exacerbations†	1.05 ± 1.74	0.48 ± 1.14	< 0.0001
Total hospitalizations†	0.74 ± 1.17	0.48 ± 0.97	< 0.0001
Total hospital days†	16.7 ± 16.8	14.7 ± 17.7	0.22
IV antibiotic courses†	0.39 ± 0.88	0.13 ± 0.50	< 0.0001
Days receiving IV antibiotics†	27.5 ± 42.9	20.9 ± 33.0	0.14
Infection with <i>Burkholderia cepacia</i>	6 (3.0)	57 (2.5)	0.67
Infection with <i>Stenotrophomonas maltophilia</i>	19 (9.6)	105 (4.7)	0.002
Infected with methicillin-resistant <i>Staphylococcus aureus</i>	8 (4.0)	50 (2.2)	0.11

*Data are presented as mean ± SD or No. (%) unless otherwise indicated.

†Indicates rate during the first year of study.

clinical deterioration.¹⁵ Furthermore, there is evidence that hyperglycemia results in neutrophil dysfunction,^{16,17} which may increase the risk of infection. More frequent infection may result in more frequent use of antibiotics, increasing the risk for MARPA.

The association between long-term use of inhaled tobramycin and the development of MARPA is complex. Long-term inhaled tobramycin has been shown to alter antibiotic resistance among CF patients with *P aeruginosa*. When inhaled tobramycin

is used for 3 months continuously, the majority of patients with tobramycin-susceptible *P aeruginosa* demonstrate a rise in *Pseudomonas* tobramycin minimal inhibitory concentrations.¹⁸ Similarly, in the Cystic Fibrosis Inhaled Tobramycin Study,¹⁹ tobramycin-resistant *Pseudomonas* increased slightly in the treatment group over time when compared with patients in the placebo group. Our results suggesting inhaled tobramycin usage as an independent risk factor for development of MARPA should be used with caution, however. Data on how inhaled tobra-

Table 2—Risk Factors for MARPA

Factors	Unadjusted HR	95% CI	Adjusted* HR	95% CI
Age	1.05†	1.04–1.06	1.01	0.99–1.03
Female gender	1.07	0.87–1.33	1.17	0.89–1.54
Height	1.02†	1.02–1.03	1.02†	1.01–1.04
BMI percentile	0.99†	0.98–0.99	1.00	0.99–1.00
FEV ₁	0.73†	0.62–0.86	0.59†	0.45–0.76
Pancreatic insufficiency	1.21	0.70–2.12	1.56	0.74–3.27
Long-term inhaled tobramycin usage	2.38†	1.92–2.95	2.08†	1.56–2.77
CF-related diabetes	2.65†	1.96–3.59	1.64†	1.11–2.43
CFF center MARPA prevalence				
Quartile 1	1.00	NA	1.00	NA
Quartile 2	0.84	0.61–1.17	0.96	0.61–1.52
Quartile 3	1.17	0.86–1.59	1.57†	1.04–2.36
Quartile 4	1.82†	1.33–2.50	2.00†	1.31–3.04
<i>S maltophilia</i> co-infection	1.10†	1.02–1.20	1.01	0.92–1.11
<i>B cepacia</i> co-infection	1.27†	1.13–1.44	0.96	0.85–1.16

*Multivariable Cox proportional hazards model adjusting for age, sex, height, BMI percentile, FEV₁, pancreatic status, long-term inhaled tobramycin usage, diabetes, CFF center baseline MARPA prevalence, and co-infection with *S maltophilia* and *B cepacia*. NA = not applicable. †p < 0.05.

Table 3—Risk Factors for MARPA

Variables	Unadjusted HR	95% CI	Adjusted* HR	95% CI
Acute exacerbations/yr				
< 1	1.00	NA	1.00	NA
1–5	4.11	3.24–5.19	3.31	2.32–4.71
> 5	10.6	7.16–15.7	6.93	4.06–11.9
IV antibiotic courses/yr				
< 1	1.00	NA	1.00	NA
1–5	3.31	2.64–4.13	1.98	1.43–2.75
> 5	6.80	2.15–21.5	4.13	1.31–13.0
IV antibiotic days/yr				
< 1	1.00	NA	1.00	NA
1–21	2.89	2.23–3.75	2.06	1.47–2.90
> 21	4.59	3.34–6.29	1.88	1.17–3.03
Hospitalizations/yr				
< 1	1.00	NA	1.00	NA
1–5	3.25	2.61–4.03	2.48	1.79–3.45
> 5	5.96	2.43–14.6	3.75	1.36–10.3
Hospital days/yr				
< 1	1.00	NA	1.00	NA
1–14	2.40	1.84–3.14	2.14	1.47–3.12
> 14	4.77	3.71–6.14	3.51	2.36–5.20

*Multivariable Cox proportional hazards model adjusting for age, sex, height, BMI percentile, FEV₁, pancreatic status, long-term inhaled tobramycin usage, diabetes, CFF center baseline MARPA prevalence, and co-infection with *S maltophilia* and *B cepacia*. See Table 2 for expansion of abbreviation.

mycin was used in our group (intermittent vs continuous) were not available, which may modify the risk of developing resistance. Data were also not available to investigate long-term usage of oral antibiotics such as fluoroquinolones in combination with inhaled tobramycin, which may also significantly affect the risk of resistance developing to multiple antibiotics. Ultimately, however, the clinician will have to decide the right balance between the well-demonstrated clinical benefits of regular inhaled tobramycin usage and the increased risk of resistance developing.

The results of our study show a clear connection between IV antibiotic courses, length of IV antibiotic treatments, hospitalizations, and days spent in the hospital with risk of MARPA developing. This is in agreement with previous studies^{20,21} in non-CF patients that demonstrate an association between MARPA and lengthy hospitalizations and prolonged exposure to antipseudomonal antibiotics. However, the beneficial effects of IV antibiotic therapy for acute pulmonary exacerbations in CF has been clearly demonstrated,^{22–25} and current evidence suggests that aggressive treatment should not be withheld in fear of resistance developing.

Finally, *Pseudomonas* resistance has been shown to develop not only during antimicrobial therapy but also through transmission of epidemic clones. However, this epidemiologic study did not utilize molecular typing of MARPA strains. It is therefore not possible to use these data to evaluate the potential

role of person-to-person spread while being hospitalized or in an outpatient CF setting. However, the results suggest that a significant proportion of patients acquire MARPA with their first culture of *P aeruginosa*, and there appears to be an association between CF care centers with higher baseline MARPA prevalence and greater risk for MARPA. One possible conclusion from this is that centers with higher baseline prevalence are more likely to aggressively treat patients with IV antibiotics to maintain lung function. This is consistent with results from a study²⁶ that identified a greater prevalence of MARPA at US CF centers that used more frequent and longer courses of IV antibiotics. Alternatively, microbiology lab techniques may vary between centers, leading to differences in the frequency of identification of resistant organisms. A final possibility is that centers with higher baseline MARPA prevalence have infection-control practices that increase the risk of person-to-person spread of MARPA. Although the answer is impossible to discern from this study, the observation underscores the need for further investigation into the mechanisms of resistance developing and transmission of epidemic-resistant strains.

While the results suggest clear risk factors for the development of MARPA, there are several limitations of our study that should be considered. The potential for surveillance bias exists because healthier, non-sputum-producing individuals may not have cultures performed as frequently as sicker patients,

decreasing the likelihood of detecting MARPA. Similarly, cultures may have been performed more frequently in sicker patients during exacerbations and IV antibiotic use, potentially increasing the detection rate of MARPA in particularly ill subjects. A second possible limitation of this study surrounds the definition of MARPA. The 1994 CFF Microbiology and Infectious Diseases Consensus Conference defined MARPA as “resistance to all of the agents in two or more of the following antimicrobial categories: β -lactam antibiotics, aminoglycosides, and/or the fluoroquinolone ciprofloxacin.”²⁷ We defined MARPA based on sensitivity to meropenem, tobramycin, and ciprofloxacin because other sensitivities were not available in the CFF Patient Registry. We recognize this as a potential for bias even though resistance to ciprofloxacin, meropenem, and tobramycin likely is associated with resistance to other fluoroquinolones, β -lactams, and aminoglycosides. Furthermore, one study²⁸ suggests that there is considerable variability in antimicrobial susceptibility of *P aeruginosa* across different laboratories and even within a single morphotype. This could potentially have led to an underestimate of MARPA and biased the results of this study. Finally, although we utilized robust multivariable Cox proportional hazards modeling in an attempt to limit confounding, it is understood that residual confounding may remain even after accounting for physiologic factors, infectious complications, and markers of severity of disease.

Despite the potential limitations, this investigation is the first to determine the incidence of MARPA and to identify clinical risk factors for the development of MARPA in a large, diverse CF population. The results emphasize the need for awareness of the potential detrimental effects of CF-related diabetes, close monitoring of the effects of prolonged antibiotic courses, and continued attention to infection-control measures. Continuing investigation into the mechanisms behind the development and transmission of MARPA in CF, as well greater understanding of the full clinical impact of MARPA on CF outcomes are essential.

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