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Pseudomonas aeruginosa colonization in the ICU: Prevalence, risk factors and clinical outcomes

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Abstract

OBJECTIVE—Determine the prevalence of *Pseudomonas aeruginosa* colonization on ICU admission, risk factors for *P. aeruginosa* colonization, and the incidence of subsequent clinical culture with *P. aeruginosa* among those colonized and not colonized.

DESIGN—A cohort study of patients admitted to the medical or surgical intensive care units between January 1, 2013, and December 31, 2013.

SETTING—A tertiary care hospital in Maryland.

RESULTS—213 patients of 1840 patients (11.6%) were colonized with *P. aeruginosa* on ICU admission. Significant risk factors in the multivariable analysis for colonization were age (OR 1.02, 95% CI 1.01–1.03), anemia (1.90, 95% CI 1.05–3.42) and neurological disease (OR 1.80 95% CI 1.27–2.54). Among the 213 patients colonized with *P. aeruginosa* on admission, 60 (28.2%) had a subsequent clinical culture positive for *P. aeruginosa* on the current hospital admission (ICU period and post ICU period). 49 (82%) of the 60 patients had clinical infections. Among those not colonized on admission, only 68 (4.2%) had a subsequent clinical culture positive for *P. aeruginosa* on the current hospital admission. Patients colonized with *P. aeruginosa* were more likely to have a subsequent positive clinical culture than patients not colonized (IRR: 6.74, 95% CI: 4.91, 9.25).

CONCLUSIONS—These data emphasize the need to identify ICU patients colonized with *P. aeruginosa* on admission. Prediction rules or rapid diagnostic testing will help clinicians more appropriately choose empiric antibiotic therapy for subsequent infections.

Keywords

Pseudomonas; active surveillance; risk factors; HAI; antimicrobial stewardship

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BACKGROUND AND OBJECTIVES

Pseudomonas aeruginosa is an important cause of healthcare-associated infections. In the United States, it is the 6th most common cause of healthcare-associated infections, accounting for 7.1% of all hospital infections.[1]

The choice of empiric antibiotics in the ICU setting is difficult. There needs to be a balance between excessively broad coverage and too narrow coverage. Empiric antibiotic coverage that covers *P. aeruginosa* but is broader than necessary may lead to the emergence of *P. aeruginosa* and other intestinal bacteria that are resistant to those broad spectrum antibiotics. In contrast, empiric therapy that does not cover *P. aeruginosa* may lead to poor outcomes for ICU patients eventually found to have *P. aeruginosa* infection. Improvements in our understanding of which patients require broad-spectrum empiric coverage versus situations in which narrower spectrum agents may be appropriate would be valuable from an antimicrobial stewardship perspective.

Knowledge of whether a patient is colonized with *P. aeruginosa* can be helpful in guiding selection of empiric antibiotics for suspected sepsis in the ICU setting. Colonization with *P. aeruginosa* is associated with subsequent infection with the same strain of *P. aeruginosa*[2,3], but few studies have assessed the prevalence and predictors of *P. aeruginosa* colonization at admission. The objectives of this cohort study were as follows: a) Determine the prevalence of *P. aeruginosa* colonization on ICU admission; b) Determine risk factors for *P. aeruginosa* colonization; and c) Determine the incidence of subsequent clinical culture with *P. aeruginosa* among those colonized and not colonized.

METHODS

Study population and sample collection

We conducted a cohort study of patients admitted to the medical (MICU) or surgical intensive care units (SICU) at the University of Maryland Medical Center between January 1, 2013, and December 31, 2013. Patients in the medical and surgical ICUs had admission, weekly and discharge peri-rectal cultures performed as part of a vancomycin-resistant enterococci infection prevention active surveillance program. The hospital is an 816-bed tertiary care facility. The MICU is a 29-bed unit that provides care to adult patients who have acute or potentially life-threatening medical conditions, including hematologic and other malignancies. The SICU is a 19-bed unit admitting adult patients post-surgery and with surgical complications. The primary outcome was presence of *P. aeruginosa* on ICU admission swab. Patients who did not have admission swabs were excluded. Patients with multiple admissions to either of the ICUs during the study period were allowed to enter the cohort as at-risk patients multiple times, as long as they were not positive for *P. aeruginosa* on any prior ICU admissions. This study was approved by the Institutional Review Board of the University of Maryland, Baltimore.

Microbiologic methods

Swabs were frozen in Tryptic soy broth (TSB; Becton Dickinson, Sparks, MD) and 15% glycerol and frozen at −80°C. The freezing method that we used has been validated and

published.[4,5] Frozen swabs were thawed and 100 μl of TSB with 15% glycerol was placed in 5 ml TSB broth and incubated overnight at 37°C. The next day, 50μl of TSB broth was plated onto cetrimide agar (Remel; Lenexa, KS). After overnight incubation, colonies that were blue-green or yellow-green were identified by Vitek 2 Compact (bioMerieux; Durham, NC).

Risk factors analyzed

Risk factors analyzed included comorbidities at the time of hospital admission, age, sex, antibiotics received during current hospitalization prior to ICU admission, and type of ICU. Antibiotic exposures were analyzed as binary variables. Comorbidities were classified using ICD-9 codes and admission medications; presence of underlying comorbid diseases were analyzed as individual components and as part of composite scores as determined using the Elixhauser Comorbidity Index (CI) and the Chronic Disease Score (CDS). We used Quan's enhanced ICD-9-CM code to calculate the Elixhauser CI, an aggregate comorbidity measure, using discharge codes (i.e., from the International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM) as indicators for comorbid conditions.[7,8] The Elixhauser CI contains 31 comorbid conditions and assigns each patient a score between 0 and 31. To determine the CDS, pharmacy records of patient medications ordered during the first 24 hours of a hospital admission were used as indicators for pre-existing comorbid conditions.[9] Data contained within the tables of this repository have been validated for this and other research studies and were found to have positive and negative predictive values >99%.[10–12] In addition, a random sample of 2% of records had all data elements validated and the accuracy of the data was 100% for this dataset.

Subsequent clinical culture positivity

For the cohort, we assessed the proportion of clinical culture positivity with *P. aeruginosa* on the same ICU admission and on the same hospital admission. We compared these proportions between patients colonized and those not colonized with *P. aeruginosa*. We then determined what proportion of the patients with clinical culture-positive samples represented actual infection using National Healthcare Safety Network (NHSN) definitions.[13] To accomplish this, two infectious disease physicians (S.L. and A.H.) reviewed each medical record and classified each isolate detected from a clinical culture as being a true infection or colonization.

Statistical analysis

Initial bivariable statistical comparisons were conducted by using the $\chi 2$ test for categorical data and the Student's *t* test or Wilcoxon test for continuous data. We calculated odds ratios and 95% confidence intervals (CIs) using multivariable logistic regression. Because patients were allowed to enter into the study multiple times, we also assessed the need to control for the correlated error structure of the data. This correlated analysis did not yield different results. All variables that were associated with the outcome colonization in the bivariable analysis at the $p<0.1$ level were included in the model-building stages of the multivariable analysis. Variables were retained in the final model if they were significant at a $p<0.05$ level or if they were observed to have a confounding effect on the association between another predictor and *P. aeruginosa* colonization status. We calculated an incidence risk ratio with

95% CI of subsequent positive clinical culture given *P. aeruginosa* colonization at admission. Statistical analysis was performed with SAS Version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

During the study period, 1840 admissions had admission peri-rectal cultures and were included in this study. Compliance with obtaining perianal surveillance culture samples at ICU admission was 93%. 1538 (84%) patients had only one ICU admission, and 135 patients had repeat admissions. Some of these 135 patients had more than two admissions. The cohort consisted of 1461 (79.4%) admissions to the medical ICU and 379 (20.6%) admissions to the surgical ICU. The mean age of the patients was 57.5 years. The mean and standard deviation comorbidity score as measured by the Elixhauser was 5.4 (3) and 7.8 (4) as measured by the Chronic Disease Score. Median length of stay in hospital prior to ICU admission was 4.5 hours. Because this time period was so short, we did not include antibiotic exposure in this time period in the analysis.

In this cohort, 213 patients (11.6%) had the primary outcome of being colonized with *P. aeruginosa* on ICU admission. The results of the bivariable analysis are shown in Table 1. The mean Elixhauser comorbidity index among those with *P. aeruginosa* colonization on admission was 5.8 whereas those not colonized was 5.3 ($p<0.01$). The mean Chronic Disease Score among those colonized on admission with *P. aeruginosa* was 7.9 whereas among those not colonized was 7.7 ($p=0.55$). The results of the multivariable analysis are shown in Table 2. Significant risk factors in the multivariable analysis for *P. aeruginosa* colonization were age (OR 1.02, 95% CI 1.01–1.03), anemia (1.90, 95% CI 1.05–3.42) and neurological disorder (OR 1.80 95% CI 1.27–2.54).

Among the 213 patients colonized with *P. aeruginosa* on admission, 41 (19.3%) had a subsequent clinical culture positive for *P. aeruginosa* on ICU admission and 60 (28.2%) had a subsequent clinical culture positive for *P. aeruginosa* on the current hospital admission (ICU period and post ICU period). Thus, 3.3% of the entire cohort (60 of 1840) had positive clinical cultures for P. aeruginosa. These 60 patients had 170 clinical cultures positive on the current hospital admission. The sources for these 170 clinical cultures were 42% sputum, 28% bronchial culture, 9% urine culture, 6% wound culture, 4% blood and 11% miscellaneous. 65 of the 170 clinical cultures had susceptibilities performed. Susceptibilities of these clinical cultures were as follows: 35% were resistant to piperacillin-tazobactam, 26% were resistant to cefepime, 43% were resistant to imipenem. The clinical cultures occurred with the following frequency after surveillance culture: 25% occurred in the first ½ day, 25% within 5.2 days, 25% within 14 days and 25% after 14 days.

Using the NHSN definitions, we found that 49 (82%) of the 60 patients had clinical infections; 35 had pneumonia, 5 bloodstream infection, 4 intra-abdominal infection, 2 osteomyelitis, 2 surgical site infection, and 1 catheter-associated urinary tract infection.

In contrast, among those not colonized, only 31 (1.9%) had a subsequent clinical culture positive for *P. aeruginosa* on ICU admission and 68 (4.2%) had a subsequent clinical culture positive for *P. aeruginosa* on the current hospital admission. Patients colonized with *P.*

aeruginosa were thus over six times more likely to have a subsequent positive clinical culture than patients not colonized (IRR: 6.74, 95% CI: 4.91, 9.25).

CONCLUSIONS

In this study, we found that 11.6% of ICU patients were colonized with *P. aeruginosa* on admission. Among these patients, 28.2% had a clinical culture during the same hospital admission with *P. aeruginosa*. The Elixhauser comorbidity index was higher among patients colonized with *P. aeruginosa*, and independent risk factors for colonization included age, neurological disorders, and anemia. Patients colonized with *P. aeruginosa* were over six times more likely than patients not colonized to have a subsequent clinical culture (indicating likely infection) with *P. aeruginosa*. We think this latter percentage identifies the need for clinicians to have a rapid method of identifying which patients are colonized with *P. aeruginosa* to better guide empiric antibiotic therapy.

Appropriate empiric therapy for *P. aeruginosa* and other gram-negative bacteria improves patient outcomes.[14,15] This is especially true in the era of increasing antibiotic-resistance in gram-negative bacteria. However, the evidence of adverse effects of antibiotics on antibiotic resistance in the human microbiome continues to increase.[16,17] These competing risks create a difficult situation for the antibiotic-prescribing clinician, which in turn creates a need for better testing or prediction rules to help guide empiric antibiotic choice.

Other studies have analyzed risk factors for *P. aeruginosa* colonization on admission but to our knowledge, none has been done in the United States ICU setting. A study in hematology patients identified that 8.2% of patients were positive on admission for *P. aeruginosa* but less than 1% developed subsequent infection.[18] A small study in France among 121 ICU patients identified 1.7% as positive on admission.[19] Nesher et al. studied 800 stem-cell transplant patients and showed that 7.3% were colonized with *P. aeruginosa*.[3] They also showed that 32.8% of these patients had subsequent infection with *P. aeruginosa*.

Our identification of age as a risk factor is biologically plausible; increasing age places individuals at risk for certain bacteria and antibiotic-resistant bacteria.[20] Other studies have identified age as a risk factor for antibiotic-resistant *Pseudomonas*.[21,22] We found one study that identified anemia as a risk factor for *Pseudomonas* bacteremia.[23] We found one study that identified neurological disease as a risk factor for antibiotic-resistant *Pseudomonas* infections.[24] Anemia has previously been identified as a risk factor for bacteremia due to *Pseudomonas*[23] and neurological disease has been identified as a risk factor for antibiotic-resistant *Pseudomonas* infection.[24] However, the biological mechanism for this is not clear.

The major limitation of our study is that it is a single site. Another significant limitation is that we did not have accurate data as to whether a patient was admitted to the hospital from a long-term care facility or another healthcare facility, or the number of hospital admissions in the prior year which may affect the rate of admission positivity or their history of previous hospitalizations.

In conclusion, we envision a day, hopefully in the near future, where either prediction rules or rapid diagnostic testing will help clinicians more appropriately choose empiric antibiotic

therapy for both susceptible and antibiotic-resistant bacteria. With this goal, we think our results significantly add to the literature in identifying a need to identify which ICU patients are colonized with *P. aeruginosa* on admission.

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Table 1

Chronic Disease Score (CDS) and CDS-ID Components, Elixhauser Score and Elixhauser Components for Patients with or without *P. aeruginosa*

Predictor Variables	Entire Cohort N=1840	Positive for Pseudomonas n=213	Negative for Pseudomonas n=1627	p-value
Age in years, mean (SD)	57.5 (16)	62.1 (15)	56.9 (16)	<0.0001
Male sex, no. (%)	1016 (55)	105 (49)	911 (56)	0.06
Time at Risk in days (median, IQR) *	0.19 (2)	0.12 (4)	0.20 (2)	0.93
CDS, mean (SD)	7.8 (4)	7.9 (4)	7.7 (4)	0.55
CDS Components no. (%)				
Antineoplastics	108 (9)	5 (2)	103 (6)	0.02
L-dopa	7 (0)	2 (1)	5 (0)	0.16
Insulin and oral hypoglycemic	945 (51)	120 (56)	825 (51)	0.12
Anticonvulsants	689 (38)	91 (43)	598 (37)	0.09
Cromolyn	37 (2)	7 (3)	30 (2)	0.16
Uric acid agents	101 (6)	3 (1)	98 (6)	0.005
Cholesterol lower agents	296 (16)	42 (20)	254 (16)	0.13
Antiretroviral agents	30 (2)	6 (3)	24 (1)	0.15
Elixhauser Total Score, mean (SD)	5.3 (3)	5.8 (3)	5.3 (3)	0.005
Elixhauser Components				
Congestive Heart Failure	389 (21)	54 (25)	335 (21)	0.11
Cardiac Arrhythmia	666 (36)	89 (42)	577 (35)	0.07
Valvular Disease	280 (15)	41 (19)	239 (15)	0.08
Pulmonary Circulation Disorders	413 (23)	58 (27)	355 (22)	0.08
Hypertension Complicated	400 (22)	62 (29)	338 (21)	0.006
Paralysis	71 (4)	13 (6)	58 (4)	0.07
Neurological Disorders	297 (16)	51 (24)	246 (15)	0.001
Diabetes Uncomplicated	510 (28)	68 (32)	442 (27)	0.14
Hypothyroidism	219 (12)	33 (15)	186 (11)	0.09
Renal Failure	477 (26)	72 (34)	405 (25)	0.005
Liver Disease	433 (24)	40 (19)	393 (24)	0.08
Metastatic Cancer	123 (7)	8 (4)	115 (7)	0.07
Solid Tumor without Metastasis	257 (14)	22 (10)	235 (14)	0.10
Obesity	267 (15)	39 (18)	228 (14)	0.09
Weight Loss	323 (18)	45 (21)	278 (17)	0.15
Iron Deficiency Anemia	81(4)	15 (7)	66 (4)	0.05
Alcohol Abuse	297 (16)	23 (11)	274 (17)	0.02
Drug Abuse	169 (9)	12 (6)	157 (10)	0.06

*Time at risk: time in hospital prior to ICU admission

Note: CDS and Elixhauser components were only included in the table if p<0.20.
CDS components not shown: anticoagulants, cardiac agents (including ACE inhibitors), loop diuretics, isoproterenol, beta-adrenergic, xanthine products, bronchodialators and mucolytics, epinephrine, glucocorticoid, gold salts, anti-hypertensives and calcium channel blockers (excludes ACE

inhibitors), beta-blockers and diuretics, cimetidine, ophthalmic miotics, antitubercular agents, calcitrol, calcium acetate, hematopoetic agents, opiod agonitsts, narcotic antagonists, and immunosuppressive agents.

Elixhauser components not shown: peripheral vascular disorder, hypertension uncomplicated, chronic pulmonary disease, diabetes complicated, peptic ulcer disease excluding bleeding, HIV/AIDS, lymphoma, rheumatoid arthritis/collagen, coagulopathy, fluid and electrolyte disorders, blood loss anemia, psychoses, and depression.

Table 2

Adjusted Predictors of Development of ICU Admission Colonization with *P. aeruginosa* (N=1840)

Predictor Variables	**Adjusted Odds Ratio* (95% CI)**
Iron Deficiency Anemia	1.90 (1.05, 3.42)
Neurological Disorders	1.80 (1.27, 2.54)
Age (in years)	1.02 (1.01, 1.03)

*Adjusted for deficiency anemia, other neurological disorders, and age.