ORIGINAL ARTICLE

Pseudomonas aeruginosa Colonization in the Intensive Care Unit: Prevalence, Risk Factors, and Clinical Outcomes

Anthony D. Harris, MD, MPH;[1] Sarah S. Jackson, MPH;[1] Gwen Robinson, MPH;[1] Lisa Pineles, MA;[1] Surbhi Leekha, MD, MPH;[1] Kerri A. Thom, MD, MS;[1] Yuan Wang, BS;[1] Michelle Doll, MD;[1] Melinda M. Pettigrew, PhD;[2] J. Kristie Johnson, PhD, D(ABMM)[1]

OBJECTIVE. To determine the prevalence of *Pseudomonas aeruginosa* colonization on intensive care unit (ICU) admission, risk factors for *P. aeruginosa* colonization, and the incidence of subsequent clinical culture with *P. aeruginosa* among those colonized and not colonized.

METHODS. We conducted a cohort study of patients admitted to a medical or surgical intensive care unit of a tertiary care hospital. Patients had admission perirectal surveillance cultures performed. Risk factors analyzed included comorbidities at admission, age, sex, antibiotics received during current hospitalization before ICU admission, and type of ICU.

RESULTS. Of 1,840 patients, 213 (11.6%) were colonized with *P. aeruginosa* on ICU admission. Significant risk factors in the multivariable analysis for colonization were age (odds ratio, 1.02 [95% CI, 1.01–1.03]), anemia (1.90 [1.05–3.42]), and neurologic disorder (1.80 [1.27–2.54]). Of the 213 patients colonized with *P. aeruginosa* on admission, 41 (19.2%) 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* in the current hospitalization (ICU period and post-ICU period). Of these 60 patients, 49 (81.7%) had clinical infections. Of the 1,627 patients not colonized on admission, only 68 (4.2%) had a subsequent clinical culture positive for *P. aeruginosa* in the current hospitalization. Patients colonized with *P. aeruginosa* were more likely to have a subsequent positive clinical culture than patients not colonized (incidence rate ratio, 6.74 [95% CI, 4.91–9.25]).

CONCLUSIONS. Prediction rules or rapid diagnostic testing will help clinicians more appropriately choose empirical antibiotic therapy for subsequent infections.

Infect Control Hosp Epidemiol 2016;37:544–548

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

The choice of empirical antibiotics in the intensive care unit (ICU) setting is difficult. There needs to be a balance between excessively broad coverage and too narrow coverage. Empirical 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, empirical 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 empirical 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 empirical 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) to determine the prevalence of *P. aeruginosa* colonization on ICU admission, (b) to determine risk factors for *P. aeruginosa* colonization, and (c) to 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 or surgical ICUs at the University of Maryland Medical Center from January 1, 2013, through December 31, 2013. Patients in the medical and surgical ICUs had admission,

Affiliations: 1. University of Maryland School of Medicine, Baltimore, Maryland; 2. Yale School of Public Health, New Haven, Connecticut.

Received September 16, 2015; accepted December 23, 2015; electronically published February 1, 2016

© 2016 by The Society for Healthcare Epidemiology of America. All rights reserved. 0899-823X/2016/3705-0007. DOI: 10.1017/ice.2015.346

https://doi.org/10.1017/ice.2015.346 Published online by Cambridge University Press

weekly, and discharge perirectal cultures performed as part of an active surveillance program for vancomycin-resistant enterococci infection prevention. The hospital is an 816-bed tertiary care facility. The medical ICU is a 29-bed unit that provides care to adult patients who have acute or potentially life-threatening medical conditions, including hematologic and other malignant tumors. The surgical ICU is a 19-bed unit admitting adult patients after 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 placed in tryptic soy broth (BD) 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 tryptic soy broth with 15% glycerol was placed in 5 mL tryptic soy broth and incubated overnight at 37°C. The next day, 50 μL of tryptic soy broth was plated onto cetrimide agar (Remel). After overnight incubation, colonies that were blue-green or yellow-green were identified by Vitek 2 Compact (bioMérieux).

Risk Factors Analyzed

Risk factors analyzed included comorbidities at the time of hospital admission, age, sex, antibiotics received during current hospitalization before ICU admission, and type of ICU. Antibiotic exposures were analyzed as binary variables. Comorbidities were classified using *International Statistical Classification of Disease, Ninth Revision*, codes and admission medications; underlying comorbid diseases were analyzed as individual components and as part of composite scores as determined using the Elixhauser comorbidity index and the Chronic Disease Score. We used Quan's enhanced *International Statistical Classification of Disease, Ninth Revision, Clinical Modification*, code to calculate the Elixhauser index, an aggregate comorbidity measure, using discharge codes as indicators for comorbid conditions.[6,7] The Elixhauser index contains 31 comorbid conditions and assigns each patient a score between 0 and 31. To determine the Chronic Disease Score, pharmacy records of patient medications ordered during the first 24 hours of a hospital admission were used as indicators for preexisting comorbid conditions.[8] 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 greater than 99%.[9–11] In addition, a random sample of 2% of records had all data elements validated and the accuracy of the data was 100% for this data set.

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 definitions.[12] To accomplish this, 2 infectious disease physicians (S.L. and A.D.H.) reviewed each medical record and classified each isolate detected from a clinical culture as being a true infection or a colonization.

Statistical Analysis

Initial bivariable statistical comparisons were conducted by using the χ^2 test for categorical data and the *t* test or Wilcoxon test for continuous data. We calculated odds ratios and 95% CIs using multivariable logistic regression. Because patients were allowed to enter 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 $P < .1$ 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 $P < .05$ 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).

RESULTS

During the study period, 1,840 admissions had admission perirectal cultures and were included in this study. Compliance with obtaining perianal surveillance culture samples at ICU admission was 93%. A total of 1,538 patients (84%) had only 1 ICU admission, and 135 patients had repeated admissions. Some of these 135 patients had more than 2 admissions. The cohort consisted of 1,461 admissions to the medical ICU (79.4%) and 379 admissions to the surgical ICU (20.6%). The mean age of the patients was 57.5 years. The mean (SD) comorbidity score was 5.4 (3) as measured by the Elixhauser 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 period was so short, we did not include antibiotic exposure in this 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

https://doi.org/10.1017/ice.2015.346 Published online by Cambridge University Press

TABLE 1. Chronic Disease Score (CDS), CDS-ID Components, Elixhauser Score, and Elixhauser Components for Patients With or Without *Pseudomonas aeruginosa*

Predictor variable	Entire cohort (N = 1,840)	Positive for *Pseudomonas* (n = 213)	Negative for *Pseudomonas* (n = 1,627)	*P* value
Age, mean (SD), y	57.5 (16)	62.1 (15)	56.9 (16)	<.0001
Male sex	1,016 (55)	105 (49)	911 (56)	.06
Time at risk, median (IQR), d[a]	0.19 (2)	0.12 (4)	0.20 (2)	.93
CDS, mean (SD)	7.8 (4)	7.9 (4)	7.7 (4)	.55
CDS components[b]				
Antineoplastics	108 (6)	5 (2)	103 (6)	.02
L-dopa	7 (0)	2 (1)	5 (0)	.16
Insulin and oral hypoglycemic	945 (51)	120 (56)	825 (51)	.12
Anticonvulsants	689 (37)	91 (43)	598 (37)	.09
Cromolyn	37 (2)	7 (3)	30 (2)	.16
Uric acid agents	101 (5)	3 (1)	98 (6)	.005
Cholesterol-lowering agents	296 (16)	42 (20)	254 (16)	.13
Antiretroviral agents	30 (2)	6 (3)	24 (1)	.15
Elixhauser total score, mean (SD)	5.3 (3)	5.8 (3)	5.3 (3)	.005
Elixhauser components[c]				
Congestive heart failure	389 (21)	54 (25)	335 (21)	.11
Cardiac arrhythmia	666 (36)	89 (42)	577 (35)	.07
Valvular disease	280 (15)	41 (19)	239 (15)	.08
Pulmonary circulation disorders	413 (22)	58 (27)	355 (22)	.08
Hypertension complicated	400 (22)	62 (29)	338 (21)	.006
Paralysis	71 (4)	13 (6)	58 (4)	.07
Neurologic disorders	297 (16)	51 (24)	246 (15)	.001
Diabetes uncomplicated	510 (28)	68 (32)	442 (27)	.14
Hypothyroidism	219 (12)	33 (15)	186 (11)	.09
Renal failure	477 (26)	72 (34)	405 (25)	.005
Liver disease	433 (24)	40 (19)	393 (24)	.08
Metastatic cancer	123 (7)	8 (4)	115 (7)	.07
Solid tumor without metastasis	257 (14)	22 (10)	235 (14)	.10
Obesity	267 (15)	39 (18)	228 (14)	.09
Weight loss	323 (18)	45 (21)	278 (17)	.15
Iron deficiency anemia	81(4)	15 (7)	66 (4)	.05
Alcohol abuse	297 (16)	23 (11)	274 (17)	.02
Drug abuse	169 (9)	12 (6)	157 (10)	.06

NOTE. Data are no. (%) of patients unless otherwise indicated. CDS and Elixhauser components were included in the table only if $P < .20$.
ID, infectious disease; IQR, interquartile range.
[a]Time at risk: time in hospital prior to intensive care unit admission.
[b]CDS components not shown: anticoagulants, cardiac agents (including angiotensin-converting-enzyme [ACE] inhibitors), loop diuretics, isoproterenol, beta-adrenergic, xanthine products, bronchodilators and mucolytics, epinephrine, glucocorticoid, gold salts, antihypertensives and calcium channel blockers (excludes ACE inhibitors), beta-blockers and diuretics, cimetidine, ophthalmic miotics, antitubercular agents, calcitrol, calcium acetate, hematopoetic agents, opioid agonists, narcotic antagonists, and immunosuppressive agents.
[c]Elixhauser components not shown: peripheral vascular disorder, hypertension uncomplicated, chronic pulmonary disease, diabetes complicated, peptic ulcer disease excluding bleeding, human immunodeficiency virus/AIDS, lymphoma, rheumatoid arthritis/collagen, coagulopathy, fluid and electrolyte disorders, blood loss anemia, psychoses, and depression.

among those not colonized it was 5.3 ($P = .005$). The mean Chronic Disease Score among those colonized on admission with *P. aeruginosa* was 7.9 whereas among those not colonized it was 7.7 ($P = .55$). The results of the multivariable analysis are shown in Table 2. Significant risk factors in the multivariable analysis for *P. aeruginosa* colonization were age (odds ratio, 1.02 [95% CI, 1.01–1.03]), anemia (1.90 [1.05–3.42]), and neurologic disorder (1.80 [1.27–2.54]).

Among the 213 patients colonized with *P. aeruginosa* on admission, 41 (19.2%) 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 1,840) had positive clinical cultures for *P. aeruginosa*. These 60 patients had 170 clinical cultures positive on the current hospital admission.

https://doi.org/10.1017/ice.2015.346 Published online by Cambridge University Press

TABLE 2. Adjusted Predictors of Colonization with *Pseudomonas aeruginosa* in Study of 1,840 Patients at Intensive Care Unit Admission

Predictor variables	Adjusted odds ratio (95% CI)[a]
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)

[a]Adjusted for deficiency anemia, other neurologic disorders, and age.

The sources for these 170 clinical cultures were 71 (42%) sputum, 48 (28%) bronchial culture, 15 (9%) urine culture, 10 (6%) wound culture, 7 (4%) blood, and 19 (11%) miscellaneous. Sixty-five of the 170 clinical cultures had susceptibility tests 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 half-day, another 25% within 5.2 days, another 25% within 14 days, and the remaining 25% after 14 days.

Using the National Healthcare Safety Network definitions, we found that 49 (81.7%) 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 the 1,627 patients 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 more than 6 times as likely to have a subsequent positive clinical culture than patients not colonized (incidence rate ratio, 6.74 [95% CI, 4.91–9.25]).

DISCUSSION

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, neurologic disorders, and anemia. Patients colonized with *P. aeruginosa* were more than 6 times as likely as patients not colonized to have a subsequent clinical culture (indicating likely infection) with *P. aeruginosa*. 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 empirical antibiotic therapy.

Appropriate empirical therapy for *P. aeruginosa* and other gram-negative bacteria improves patient outcomes.[13,14] 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.[15,16] 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 empirical antibiotic choice.

Other studies have analyzed risk factors for *P. aeruginosa* colonization on admission but to our knowledge, none have been done in the ICU setting of the United States. 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.[17] A small study in France among 121 ICU patients identified 1.7% as positive on admission.[18] Nesher et al[3] studied 800 stem-cell transplant patients and showed that 7.3% were colonized with *P. aeruginosa*. 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.[19] Other studies have identified age as a risk factor for antibiotic-resistant *Pseudomonas*.[20,21] We found 1 study that identified anemia as a risk factor for *Pseudomonas* bacteremia.[22] We found 1 study that identified neurologic disease as a risk factor for antibiotic-resistant *Pseudomonas* infections.[23] Anemia has previously been identified as a risk factor for bacteremia due to *Pseudomonas*[22] and neurologic disease has been identified as a risk factor for antibiotic-resistant *Pseudomonas* infection.[23] 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.

In conclusion, we envision a day in the near future where either prediction rules or rapid diagnostic testing will help clinicians more appropriately choose empirical antibiotic therapy for both susceptible and antibiotic-resistant bacteria. With this goal, our results significantly add to the literature in identifying a need to determine which ICU patients are colonized with *P. aeruginosa* on admission.

ACKNOWLEDGMENTS

Financial support. Cubist and Merck; and National Institutes for Allergy and Infectious Diseases (K24AI079040 to A.D.H. and K23AI082450 to K.A.T.).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

Address correspondence to Anthony D. Harris, MD, MPH, 10 S. Pine St, MSTF 330, Baltimore, MD 21201 (aharris@epi.umaryland.edu).

REFERENCES

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014;370:1198–1208.

https://doi.org/10.1017/ice.2015.346 Published online by Cambridge University Press

2. Thuong M, Arvaniti K, Ruimy R, et al. Epidemiology of *Pseudomonas aeruginosa* and risk factors for carriage acquisition in an intensive care unit. *J Hosp Infect* 2003;53:274–282.
3. Nesher L, Rolston KV, Shah DP, et al. Fecal colonization and infection with *Pseudomonas aeruginosa* in recipients of allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* 2015;17:33–38.
4. Green HP, Johnson JA, Furuno JP, et al. Impact of freezing on the future utility of archived surveillance culture specimens. *Infect Control Hosp Epidemiol* 2007;28:886–888.
5. Lautenbach E, Santana E, Lee A, et al. Efficient recovery of fluoroquinolone-susceptible and fluoroquinolone-resistant *Escherichia coli* strains from frozen samples. *Infect Control Hosp Epidemiol* 2008;29:367–369.
6. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–1139.
7. Manitoba Centre for Health Policy. Concept: Elixhauser comorbidity index. Manitoba Centre for Health Policy website. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1436. Updated 2014. Accessed August 3, 2015.
8. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992;45:197–203.
9. Pepin CS, Thom KA, Sorkin JD, et al. Risk factors for central-line–associated bloodstream infections: a focus on comorbid conditions. *Infect Control Hosp Epidemiol* 2015;36:479–481.
10. Harris AD, Johnson JK, Thom KA, et al. Risk factors for development of intestinal colonization with imipenem-resistant *Pseudomonas aeruginosa* in the intensive care unit setting. *Infect Control Hosp Epidemiol* 2011;32:719–722.
11. Harris AD, Fleming B, Bromberg JS, et al. Surgical site infection after renal transplantation. *Infect Control Hosp Epidemiol* 2015;36:417–423.
12. Centers for Disease Control and Prevention (CDC). CDC/NHSN surveillance definitions for specific types of infections. CDC website. http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf. Updated 2015. Accessed January 7, 2016.
13. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in gram-negative severe sepsis and septic shock: a retrospective cohort study. *Crit Care* 2014;18:596.
14. Tumbarello M, De Pascale G, Trecarichi EM, et al. Clinical outcomes of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients. *Intensive Care Med* 2013;39:682–692.
15. Zaborin A, Smith D, Garfield K, et al. Membership and behavior of ultra-low-diversity pathogen communities present in the gut of humans during prolonged critical illness. *MBio* 2014;5:e01361–14.
16. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. *J Clin Invest* 2014;124:4212–4218.
17. Sidler JA, Frei R, Tschudin-Sutter S, et al. Is admission screening for *Pseudomonas aeruginosa* useful in haematologic patients? A prospective study with 1310 patients. *Clin Microbiol Infect* 2015;21:572.e1–572.e3.
18. Agodi A, Barchitta M, Cipresso R, Giaquinta L, Romeo MA, Denaro C. *Pseudomonas aeruginosa* carriage, colonization, and infection in ICU patients. *Intensive Care Med* 2007;33:1155–1161.
19. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, enterococcus, gram-negative bacilli, *Clostridium difficile*, and *Candida*. *Ann Intern Med* 2002;136:834–844.
20. Ghibu L, Miftode E, Teodor A, Bejan C, Dorobat CM. Risk factors for *Pseudomonas aeruginosa* infections, resistant to carbapenem [in Romanian]. *Rev Med Chir Soc Med Nat Iasi* 2010;114:1012–1016.
21. Tuon FF, Gortz LW, Rocha JL. Risk factors for pan-resistant *Pseudomonas aeruginosa* bacteremia and the adequacy of antibiotic therapy. *Braz J Infect Dis* 2012;16:351–356.
22. Enoch DA, Kuzhively J, Sismey A, Grynik A, Karas JA. *Pseudomonas aeruginosa* bacteraemia in two UK district hospitals. *Infect Dis Rep* 2013;5:e4.
23. Zavascki AP, Barth AL, Gaspareto PB, et al. Risk factors for nosocomial infections due to *Pseudomonas aeruginosa* producing metallo-beta-lactamase in two tertiary-care teaching hospitals. *J Antimicrob Chemother* 2006;58:882–885.

https://doi.org/10.1017/ice.2015.346 Published online by Cambridge University Press