Published in final edited form as:

Infect Control Hosp Epidemiol. 2011 July ; 32(7): 719–722. doi:10.1086/660763.

Risk factors for Development of Intestinal Colonization with Imipenem-resistant *Pseudomonas aeruginosa* in the Intensive Care Unit Setting

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Abstract

Risk factors for development of intestinal colonization by imipenem-resistant *Pseudomonas aeruginosa* (IRPA) may differ between those who acquire the organism via patient-to-patient versus by antibiotic selective pressure. The aim of this study was to quantify potential risk factors for the development of IRPA not due to patient-to-patient transmission.

Keywords

antibiotic-resistant *Pseudomonas aeruginosa*; cohort; risk factors

Introduction

Imipenem-resistant *Pseudomonas aeruginosa* (IRPA) is an important nosocomial pathogen.¹ It is often difficult to assess risk factors for the development of intestinal colonization with antibiotic-resistant bacteria due to the requirement of a large sample size. Furthermore, most prior studies have combined patients who likely acquired a specific bacteria or antibiotic-resistant bacteria from patient-to-patient transmission with those who likely developed resistance as a result of antibiotic selective pressure.^{2–4} Both these mechanisms are important to understand and risk factors between the two may differ. We previously have published a study using this cohort to quantify the amount of colonization due to patient-to-patient transmission, hereon defined as exogenous acquisition.⁵ The aim of this study was to quantify potential risk factors for the development of intestinal colonization with IRPA not due to patient-to-patient transmission, hereon defined as endogenous acquisition.

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Potential Conflicts of Interest: All authors: None

Methods

We conducted a prospective cohort study of patients admitted to either the medical or surgical intensive care units (ICUs) at the University of Maryland Medical Center between September 1, 2001 and September 1, 2006.

Patients in the medical ICU and surgical ICU had admission, weekly, and discharge peri-rectal cultures performed as part of an ongoing vancomycin-resistant enterococci (VRE) infection prevention active surveillance and were concurrently screened for IRPA; IRPA results were not relayed to clinicians.

Patients who had the outcome (development of intestinal colonization with IRPA i.e. endogenous acquisition) were defined as patients who had an ICU admission culture negative for IRPA and had a subsequent ICU weekly or ICU discharge culture positive for IRPA on the same ICU admission. Patients who had a positive admission culture for IRPA were excluded since they were not at risk for the outcome upon cohort entry. Patients who did not have admission cultures or discharge cultures obtained were excluded. Patients admitted to either ICU for less than 48 hours were excluded because they were not at risk for development of intestinal colonization.

PFGE was performed on all IRPA isolates from patients who were admission positive and those who developed the outcome to determine which acquisitions were likely due to patient-to-patient transmission. The definition for patient-to-patient transmission has been previously described.⁵ Patients who met this definition were excluded from the statistical analysis because it was determined that these patients likely acquired the IRPA from patient-to-patient transmission i.e. exogenous acquisition.

For all patients in the study, we collected data regarding comorbidities, time at risk in the ICU, demographics, colonization pressure and antibiotic exposures while in the ICU prior to developing the outcome or prior to ICU discharge for those who did not have the outcome of interest. Antibiotic exposures were analyzed as binary variables. For patients who had endogenous acquisition, antibiotics received during the time period between ICU admission and to date of surveillance culture positivity were analyzed. For patients who did not have endogenous acquisition, antibiotic exposures received during the time period between ICU admission and ICU discharge were analyzed. Data on antibiotics received prior to ICU admission were collected but not statistically analyzed because the median number of days in the hospital prior to entering the ICU was very short (0.5 days) and thus we did not think these antibiotic exposures were relevant to the study aim. Time at risk was defined as has been previously described.⁶ Colonization pressure was measured for each patient and was defined as the number of surveillance cultures positive for IRPA divided by the total number of surveillance cultures obtained from patients other than the patient while in the cohort.

Results

The five-year cohort of patients included 3,184 unique patients who were not colonized with IRPA on admission culture and had discharge cultures obtained. Approximately 5% (n=156) of patients developed endogenous acquisition with an IRPA. Thirty-eight of these patients were excluded from the subsequent analysis because they were determined to have exogenous acquisition from patient-to-patient transmission based on PFGE.⁵ Thus, subsequent bivariable and multivariate analyses were done on a cohort of 3,146 patients, of which 118 (3.8%) had the outcome of development of endogenous acquisition with IRPA. The mean age of the patients was 55 years. The mean aggregate comorbidity score as measured by the Chronic Disease Score was 7.08 and 2.46 as measured by the Charlson Comorbidity Index. The mean length of stay in the hospital was 19.1 days (median 12.4).

The mean length of stay in the ICU was 7.9 days (median 4.7). The median number of days in the hospital prior to entering the ICU was 0.5 days. Approximately 43% of the cohort was in the MICU and 57% in the SICU.

Bivariate risk factor analysis is shown in Table 1. Results from the multivariable logistic-regression analysis are outlined in Table 2. The results demonstrate that patients who endogenous IRPA acquisition were more likely to have been exposed to imipenem (OR=6.06, 95% CI 3.97–9.24). Furthermore, time at risk greater than 4.6 days (OR=2.00, 95% CI 1.27–3.16) and colonization pressure (OR=9.58, 95% CI 5.09–18.05) were also significantly associated with endogenous acquisition.

Discussion

The identification of imipenem as a risk factor has biological plausibility in that the use of an antibiotic often leads to emergence of resistance to that particular antibiotic. A smaller European study that analyzed risk factors for carbapenem-resistant *P. aeruginosa* colonization and colonization acquisition suggested that carbapenems, fluoroquinolones, and severity of illness were possibly predictors.⁴ Another smaller European study also identified imipenem as a risk factor for IRPA acquisition.³

In our study, we chose to exclude patients who were presumed to have exogenous acquisition due to patient-to-patient transmission based on PFGE, in order to better understand the risk factors associated with development of intestinal colonization due to reasons other than patient-to-patient transmission i.e. endogenous acquisition. Despite removing these patients, we still found colonization pressure to be statistically associated with the outcome. This may suggest that for *P. aeruginosa* molecular epidemiological techniques like PFGE do not have enough discriminatory ability to account for all of the patient-to-patient transmission that is occurring. Another possibility is that colonization pressure is highly correlated with other antibiotic use or that colonization pressure may just reveal a statistical association and not a causal association. Lastly, temporal overlap of hospital stay, one criterion of our definition of patient-to-patient transmission, may not have accounted for transmission via fomites or environmental surfaces. Several studies have observed persistent contamination by *P. aeruginosa* of environmental surfaces in healthcare settings.^{7, 8}

Time at risk was also found to be an important variable. Our research group and others have demonstrated the importance of controlling for time at risk in risk factor studies of antibiotic resistance.^{6, 9} This finding supports the logical hypothesis that the longer a patient is in the ICU, the greater the chance that they are colonized with an IRPA strain. This finding may support changes in empiric antibiotic choices based on duration of ICU stay.¹⁰

A limitation of our study is that we did not have 100% compliance with obtaining admission, discharge and weekly cultures from our patients. Our compliance with admission culturing was greater than 90% and our compliance with weekly and discharge culturing was greater than 85%. In addition, our findings may not be generalizable to different ICUs since the cohort consisted only of medical and surgical ICU patients in a tertiary-care hospital. An additional potential limitation of our studies similar to other studies is that we categorized antibiotics as binary variables; future research needs to determine and help assess optimal methods of categorizing antibiotic exposures.

In conclusion, our study has identified risk factors for endogenous acquisition with IRPA in the ICU. We observed that exposure to imipenem, colonization pressure and time at risk were all statistically associated with the outcome. Future research should explore potential associations of duration or dose of antibiotic therapy and development of resistance.

Acknowledgments

We thank Colleen Reilly and Jingkun Zhu for database maintenance and abstraction and Gwen Robinson and Mary Lee for microbiological analysis.

Funding Sources: This research was supported by National Institutes of Health grants R01A1060859 and K24AI079040 (A.D.H.), K01AI071015-02 (J.P.F.), 1K12RR02350-03 (J.K.J.), and KL2RR024141 (J.C.M.), Agency for Healthcare Research and Quality grant 1K08 HS18111-01 to D.J.M. and the University of Maryland General Clinical Research Center grant M01RR16500.

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Table 1

Potential Predictors of Development of Intestinal Colonization with Imipenem-resistant *Pseudomonas aeruginosa*

Variable	Developed IRPA (n =118)	Did not Develop IRPA (n =3028)	p-value
Age, years (mean, SD)	56.7 (15.0)	55.7 (15.5)	0.46
CDS at ICU admission (mean, SD) *	9.6 (4.2)	8.7 (4.2)	0.03
Charlson Comorbidity Index (mean, SD)	2.1 (2.0)	2.5 (2.3)	0.14
Sex, female (n, %)	45 (38.1)	1312 (43.3)	0.30
Time at risk (days) (median, IQR)	8.0 (4.8–16.6)	4.51 (2.96–8.18)	<.01
Colonization pressure (median, IQR)	0.09 (0.06–0.16)	0.029 (0.0–0.08)	<.01
Antibiotic exposures [†]			
Fluoroquinolones	22 (18.6)	620 (20.5)	0.73
1 st generation Cephalosporin	13 (11.0)	412 (13.6)	0.49
3 rd generation Cephalosporin	13 (11.0)	251 (8.3)	0.31
Vancomycin	47 (39.8)	660 (21.8)	<0.01
Aminoglycosides	22 (18.6)	237 (7.8)	<0.01
Piperacillin-Tazobactam	47 (39.8)	971 (32.1)	0.09
Cefepime	14 (11.9)	158 (5.2)	<0.01
Imipenem	43 (36.4)	228 (7.5)	<0.01

* Infectious disease-specific aggregate comorbidity measure

[†] Antibiotic exposures were assessed during the period between ICU admission and either developing the outcome or being discharged from the ICU i.e. no longer being at risk

SD=Standard deviation, IQR=Interquartile range, CDS=Chronic Disease Score

Table 2

Unadjusted and Adjusted Predictors of Development of Intestinal Colonization with IRPA not due to Patient-to-patient Transmission

	Unadjusted	Final Logistic Regression Model
Variable	OR (95% CI)	OR (95% CI)
CDS at ICU admission	1.10 (1.01, 1.22)	
Time at risk (> 4.6 days) **	3.56 (2.30, 5.50)	2.00 (1.27, 3.16)
Colonization pressure (>3.2%) **	10.73 (5.74, 20.03)	9.58 (5.09, 18.05)
Vancomycin †	2.38 (1.63, 3.47)	
Aminoglycosides †	2.70 (1.67, 4.37)	
Piperacillin-Tazobactam †	1.40 (0.96, 2.04)	
Cefepime †	2.45 (1.37, 4.37)	
Imipenem †	7.04 (4.73, 10.49)	6.06 (3.97, 9.24)

** These variables were dichotomized at the median because they were not normally distributed.

† Antibiotic exposures were assessed during the period between ICU admission and either developing the outcome or being discharged from the ICU i.e. no longer being at risk