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Incidence of *Pseudomonas aeruginosa* Bacteremia: A Population-Based Study

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Abstract

Background—The incidence of *Pseudomonas aeruginosa* bacteremia has not been defined in a population-based investigation.

Methods—Retrospective, population-based incidence study using resources of Rochester Epidemiology Project of Olmsted County, Minnesota. We identified all Olmsted County residents with *P. aeruginosa* bacteremia between 1/1/1997 and 12/31/2006 by microbiology records in the only two laboratories in the county. Medical records were reviewed to confirm diagnosis, residency status, and clinical characteristics.

Results—Age-adjusted incidence per 100,000 person-years for total *P. aeruginosa* bacteremia was 10.8 (95% confidence interval [CI], 7.5-14.0) in males and 3.7 (95% CI, 2.2-5.2) in females; and for monomicrobial *P. aeruginosa* bacteremia was 8.4 (95% CI, 5.5-11.2) in males and 2.5 (95% CI, 1.3-3.8) in females. There was no significant change in incidence of total *P. aeruginosa* bacteremia over the past decade (p=.418). Incidence increased exponentially with age; with greater magnitude of increase in males compared to females for total and monomicrobial *P. aeruginosa* bacteremia (p=.007 and p=.015, respectively). In patients with monomicrobial *P. aeruginosa* bacteremia, median age was 69 years; and 78.4% of cases were either nosocomial or health care-associated. Most patients had multiple comorbid conditions. The urinary tract was the most common primary source of infection. The 28-day all-cause mortality of monomicrobial *P. aeruginosa* bacteremia was 25.5%. In vitro susceptibility to ciprofloxacin was 95.3%.

Conclusions—To our knowledge, this is the first population-based incidence study of *P. aeruginosa* bacteremia. The incidence of *P. aeruginosa* bacteremia has remained stable over the past decade. Fluoroquinolone susceptibility is high among local *P. aeruginosa* bacteremia isolates.

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MNA have full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Keywords

bacteremia; epidemiology; mortality; antibiotic susceptibility; *Pseudomonas aeruginosa*

INTRODUCTION

The incidence of *Pseudomonas aeruginosa* bacteremia has never been defined in a population-based investigation.[1] Data that address *P. aeruginosa* bacteremia incidence are, for the most part, derived from cross-sectional studies that have been performed at large tertiary care centers where referral bias is a major limitation. *P. aeruginosa* is the third most common gram-negative pathogen causing bloodstream infections. Estimates from a cross-sectional study performed in tertiary care centers in North and Latin America published by the SENTRY Antimicrobial Surveillance Program showed that *P. aeruginosa* contributed to 10.6% of gram-negative nosocomial and community-acquired bloodstream infections in 1997.[2]

Increasing resistance of *P. aeruginosa* to fluoroquinolones and other antimicrobial agents has greatly impacted management decisions in patients with this infection. Oral therapy is no longer a treatment option in many patients and, in others, there may be no safe and active parenterally administered antibiotic available for use. It is estimated that resistance to ciprofloxacin in *P. aeruginosa* blood isolates in intensive care units in this country have increased from 9% to 31.7% between 1995 and 2002.[3] With the increasing use of newer fluoroquinolones, resistance is expected to continue to increase. In one investigation, exposure to levofloxacin was associated with increased risk of isolation of fluoroquinolone-resistant *P. aeruginosa*.[4]

The aims of this study are to establish the incidence, certain clinical characteristics, short- and long-term outcomes, and in vitro antibiotic susceptibility patterns of *P. aeruginosa* bacteremia in patients from Olmsted County, Minnesota. To our knowledge, our work is the first incidence investigation of *P. aeruginosa* bacteremia and fluoroquinolone-resistant *P. aeruginosa* bacteremia in a population-based setting.

METHODS

Setting

Olmsted County is located in southeastern Minnesota. It has a population of 124,277 according to the 2000 census.[5] With the exception of a lower prevalence of injection drug use, a higher prevalence of middle-class individuals, and a higher proportion being employed in the health-care industry, the population characteristics of Olmsted County residents are similar to those of US non-Hispanic whites.[6-7] The Rochester Epidemiology Project (REP) is a unique medical records-linkage system that encompasses care delivered to residents of Rochester and Olmsted County, Minnesota. The microbiology laboratories at Mayo Medical Center and Olmsted Medical Center are the only two laboratories in Olmsted County. These two medical centers are geographically isolated from other urban centers. The closest competing medical centers are in Minneapolis, Minnesota (139 km to the north), LaCrosse, Wisconsin (114 km to the east), Iowa City and Des Moines, Iowa (317 and 333 km to the south, respectively), and Sioux Falls, South Dakota (376 km to the west). Although best known as a tertiary referral center, Mayo Clinic has always provided primary, secondary, and tertiary care to local residents. Because the Mayo and Olmsted Medical Centers offer care in every medical and surgical specialty and subspecialty, local residents are able to obtain health care within the community, rather than seeking health care at a distant geographic location.[6,8]

Case Ascertainment

A population-based retrospective cohort with *P. aeruginosa* bacteremia from 1/1/1997 through 12/31/2006 was identified using the microbiology databases at the Mayo Medical Center Rochester, and Olmsted Medical Center. We used complete enumeration of Olmsted County, Minnesota population. All patients with positive blood cultures for *Pseudomonas* species during the study period were considered for inclusion, regardless of age, gender, or whether they were hospitalized or in the ambulatory care setting at the time of bacteremia. Among 5,268 episodes of gram-negative bacteremia identified in both clinical microbiology laboratories during the study period, 742 (14.1%) and 656 (12.5%) were due to *Pseudomonas* species and *P. aeruginosa*, respectively. Patients with an initial episode of *P. aeruginosa* bacteremia were included for analysis; patients without valid research authorization (n=10), or lived outside Olmsted County (n=574), and those with recurrent *P. aeruginosa* bacteremia (n=3) were excluded. Medical records were reviewed by the primary investigator (M.N.A.) to confirm the diagnosis, determine patient residency status, and obtain baseline clinical features, outcome, and isolate in vitro susceptibility data. Patients were followed from the time of the initial episode of *P. aeruginosa* bacteremia until the latest health care encounter; long-term follow-up was available through the REP.

Case definition

P. aeruginosa bacteremia was defined as growth of *P. aeruginosa* in a blood culture. Monomicrobial *P. aeruginosa* bacteremia was defined as growth of *P. aeruginosa* as the only isolate in a blood culture and polymicrobial *P. aeruginosa* bacteremia as the growth of *P. aeruginosa* and other organisms in a blood culture, excluding coagulase-negative staphylococci and *Propionibacterium* spp. The term total *P. aeruginosa* bacteremia was used to describe cases of both monomicrobial and polymicrobial *P. aeruginosa* bacteremia combined. Recurrent *P. aeruginosa* bacteremia was defined as *P. aeruginosa* bacteremia occurring 90 days after the initial episode of *P. aeruginosa* bacteremia. Cases of *P. aeruginosa* bacteremia were classified into community-acquired, health care-associated, or nosocomial.[9] Blood cultures were identified using standard microbiology techniques according to the Clinical and Laboratory Standards Institute (CLSI). Both laboratories are certified by the College of American Pathologists. CLSI methods were employed to evaluate in vitro antibiotic susceptibility results of *P. aeruginosa* isolates.

Statistical Analysis

Chi-square or Fisher's exact test was used to test for associations between categorical variables and Student's t-test was used to test for differences in a continuous variable between levels of a categorical variable. The incidence rate, expressed as the number of new cases per 100,000 person-years, was calculated assuming that the entire population of Olmsted County was at risk of *P. aeruginosa* bacteremia. The 2000 Olmsted County census figures were used with a projected population growth rate after 2000 of 1.9% per year as the denominator. Analysis was restricted to the initial episode of *P. aeruginosa* bacteremia during the study period and incidence rates were directly adjusted to the US 2000 white population.[5] Ninety-five percent confidence intervals (CI) for incidence rates were estimated assuming that the rates follow a Poisson distribution.

Poisson regression was used to examine incidence trends in overall *P. aeruginosa* bacteremia and in monomicrobial and polymicrobial *P. aeruginosa* bacteremia using the SAS procedure GENMOD (version 8, SAS Institute Inc, Cary, NC). Counts for calendar years from 1997 to 2006, age, and gender were used as the unit of observation. Rate ratios (RR) and 95% CI of *P. aeruginosa* bacteremia rates in different age groups (grouped as <18 [reference], 19-59, 60-79, and ≥80 years) were estimated. Comparisons of incidence trends across age groups were performed by including the 2-way interaction term of gender with age after adjustment for all

main effects. For Kaplan-Meier analyses, the log rank test was used to detect differences in survival rates between groups using JMP (version 6.0, SAS Institute Inc, Cary, NC). The level of significance for all statistical testing was defined as $p<0.05$ (2-sided) except when testing for interactions, where $p<0.10$ were accepted.

To examine the potential effect of referral bias on in vitro susceptibility results to fluoroquinolones, we compared ciprofloxacin and levofloxacin susceptibility results for isolates from Olmsted County patients with *P. aeruginosa* bacteremia to blood culture isolates from referral patients. We matched 69 Olmsted County residents with *P. aeruginosa* bacteremia to 69 patients with first episodes of *P. aeruginosa* bacteremia who lived outside Olmsted County, but were referred to the Mayo Clinic for care. Patients were matched for the exact year of onset of *P. aeruginosa* bacteremia, gender, and closest age (82.6% of patients were matched within 5 years of age) at onset of bacteremia.

RESULTS

Among 742 (62.8% male) cases of *Pseudomonas* spp. bacteremia identified by both microbiology laboratories during the study period, 51 (69% male) and 18 (56% male) unique Olmsted County residents had monomicrobial and polymicrobial *P. aeruginosa* bacteremia, respectively. Patients with monomicrobial and polymicrobial *P. aeruginosa* bacteremia had a median age of 69 and 78 years, respectively.

Temporal trends by age and gender

Figure 1 shows age and gender-adjusted incidence rates of *P. aeruginosa* bacteremia from 1997-2006 for total, monomicrobial, and polymicrobial *P. aeruginosa* bacteremia. There was no significant change in the incidence of total *P. aeruginosa* bacteremia between 1997 and 2006 ($p=0.418$). Although not statistically significant, there was a slight upward trend in the incidence of total *P. aeruginosa* bacteremia between the years of 2001 and 2006.

Figure 2 shows that the incidence rate of total *P. aeruginosa* bacteremia increased exponentially across age for both males and females. A similar trend was seen in both monomicrobial and polymicrobial *P. aeruginosa* bacteremia. The magnitude of the increase in incidence across age was greater in males than females for both total and monomicrobial *P. aeruginosa* bacteremia ($p=0.007$ and $p=0.015$, respectively for age-by-gender interaction). Compared with the reference age (<18 age group), the rate ratios for the 19-59, 60-79, and ≥80 age groups were 0.66 (95% CI 0.18-2.44), 14.20 (95% CI 4.85-41.55), and 59.22 (95% CI 19.80-177.12), respectively, for males; and 0.96 (95% CI 0.29-3.18), 2.87 (95% CI 0.77-10.70), and 10.93 (95% CI 3.20- 37.33), respectively, for females.

The age-adjusted incidence rate per 100,000 person-years for total *P. aeruginosa* bacteremia was 10.8 (95% CI 7.5-14.0) for males and 3.7 (95% CI 2.2-5.2) for females; and for monomicrobial *P. aeruginosa* bacteremia was 8.4 (95% CI 5.5-11.2) for males and 2.5 (95% CI 1.3-3.8) for females. The age-adjusted incidence of polymicrobial *P. aeruginosa* bacteremia was much less at 2.4 (95% CI 0.9-3.9) for males and 1.2 (95% CI 0.4-2.0) for females.

Clinical characteristics of monomicrobial and polymicrobial *P. aeruginosa* bacteremia

The clinical characteristics of patients with monomicrobial and polymicrobial *P. aeruginosa* bacteremia are shown in Table 1. Patients with polymicrobial *P. aeruginosa* bacteremia were more likely to have community-acquired infection ($p=0.022$) and an abdominal or biliary source of *P. aeruginosa* bacteremia ($p=0.004$) as compared to patients with monomicrobial *P. aeruginosa* bacteremia. Over 78% of monomicrobial *P. aeruginosa* bacteremia cases were either nosocomial or health care-associated. Furthermore, there was an association between

age and classification of monomicrobial *P. aeruginosa* bacteremia. Sixty percent (15/25) of patients ≥ 70 years old had nosocomial or health care-associated *P. aeruginosa* bacteremia compared to 96.2% (25/26) of patients < 70 years old (p=0.007).

Approximately, 30% of patients with monomicrobial *P. aeruginosa* bacteremia had primary bacteremia, defined as bacteremia with no clearly established site of active infection. An ad hoc analysis showed that patients with primary monomicrobial *P. aeruginosa* bacteremia were more likely to be neutropenic (5/15 [33.3%]) as compared to those who had a known source of bacteremia (3/36 [8.3%], p=0.039). Patients with primary monomicrobial *P. aeruginosa* bacteremia were also more likely to have a central venous catheter (10/15 [66.7%]) as compared to those with a known source (11/36 [30.6%], p=0.028). This suggests that gastrointestinal translocation of *P. aeruginosa* and line-associated infections might play an important role in the pathogenesis of primary *P. aeruginosa* bacteremia.

Among the 18 patients with polymicrobial *P. aeruginosa* bacteremia, 6 (33.3%) had aerobic gram-positive organisms in the same blood culture, 5 (27.8%) had other aerobic gram-negative organisms, 5 (27.8%) had anaerobic organisms, and the remaining 2 (11.1%) had more than two organisms in a blood culture.

Mortality

Monomicrobial *P. aeruginosa* bacteremia has poor prognosis with a 28-day and 1-year all-cause mortality of 25.5% and 47.5%, respectively. Patients with a Pitt bacteremia score[10] ≥ 4 had both a higher 28-day and 1-year all-cause mortality than patients with Pitt bacteremia score < 4 (p=0.045, and p=0.002, respectively) as in Figure 3. The 28-day all-cause mortality for community-acquired, health care-associated, and nosocomial monomicrobial *P. aeruginosa* bacteremia was 9.1%, 27.6%, and 36.6%, respectively. Although nosocomial *P. aeruginosa* bacteremia had a considerable higher 28-day all-cause mortality rate than community-acquired *P. aeruginosa* bacteremia, due to the limited sample size, the difference in mortality across the three groups was not statistically significant (p=0.315). Likewise, although not statistically significant (p=0.368) patients < 70 years of age had a higher 28-day all-cause mortality rate (30.8%) in comparison to patients ≥ 70 years old (20.0%). However, the 1-year all-cause mortality was comparable across age groups; 46.2% in patients < 70 years, and 49.1% in patients ≥ 70 years (p=0.916). It is conceivable that the relatively high 28-day all-cause mortality rate in patients < 70 years old in comparison to patients ≥ 70 could be due to the higher prevalence of immunocompromise in patients < 70 years (16/26 [61.5%] vs. 4/25 [16.0%], p=0.001). Additionally, patients < 70 years old were less likely to have a urinary source of *P. aeruginosa* bacteremia compared to patients ≥ 70 years old (3/26 [11.5%] vs. 13/25 [52.0%], p=0.002) and were less likely to have community-acquired *P. aeruginosa* bacteremia compared to patients ≥ 70 years.

In vitro susceptibility of *P. aeruginosa* bacteremia

In vitro susceptibilities to ciprofloxacin and levofloxacin among *P. aeruginosa* isolates were 95.3% and 93.5%, respectively (Table 2). Only 2 isolates of 64 tested (3.1%) were resistant, and 1 isolate (1.6%) had intermediate susceptibility to ciprofloxacin. Likewise, only 2 of 62 isolates tested (3.2%) were resistant and another 2 (3.2%) had intermediate susceptibility to levofloxacin. Even when the 3 isolates from recurrent cases of *P. aeruginosa* bacteremia were included in the analysis, 62 of 67 isolates tested (92.5%) were susceptible to ciprofloxacin and 59 of 64 isolates (92.2%) were susceptible to levofloxacin.

In vitro susceptibility results for both ciprofloxacin and levofloxacin were significantly higher in isolates from patients of Olmsted County as compared to those from non-Olmsted County residents (Table 3).

DISCUSSION

Incidence

Based on an age- and gender-adjusted incidence of 6.4 per 100,000 person-years (95% CI, 4.9-8.0), we demonstrated that *P. aeruginosa* bacteremia (monomicrobial and polymicrobial) is a relatively rare syndrome. A previous study in Olmsted County from 2003 to 2005 demonstrated an age- and gender-adjusted incidence of 188.9, 93.2, 80.9, 47.7, and 32.0 per 100,000 person-years for all cases, gram-positive, gram-negative, *Escherichia coli*, and *Staphylococcus aureus* bloodstream infections, respectively.[11] The incidence of *P. aeruginosa* bacteremia was higher in males than in females, particularly after the age of 50 years. In contrast, the incidence of *E. coli* bacteremia was higher in females in all age groups.[11]

Clinical characteristics

Although this was a population-based study, the majority of patients with *P. aeruginosa* bacteremia had multiple comorbidities and is comparable to findings in other studies of *P. aeruginosa* bacteremia that were based on hospital or ICU cohorts.[12-15] This is probably because most patients, especially with monomicrobial *P. aeruginosa* bacteremia, acquired the infection in a hospital or health care setting. Many patients with *P. aeruginosa* bacteremia were acutely ill; 21.7% of patients had a Pitt bacteremia score ≥ 4, and 27.5% required ICU admission.

Mortality

The all-cause 28-day mortality of 25.5% in patients with monomicrobial *P. aeruginosa* bacteremia in the current study was less than that reported in previous investigations of *P. aeruginosa* bacteremia.[12,16-19] The 30-day mortality of *P. aeruginosa* bacteremia was as high as 39% in one recent investigation.[13] We believe that the lower mortality demonstrated in our population-based study is likely due, in part, to the exclusion of referral patients who characteristically have more complications with worse outcomes.

The prolonged follow-up (median, 581 days) described in the current investigation is a unique advantage of our work. Because advanced age and multiple comorbidities were commonplace among our cohort, a one-year all-cause mortality rate of 47.5% in patients with monomicrobial *P. aeruginosa* bacteremia is conceivable.

In vitro antibiotic susceptibility testing

Antibiotic susceptibility results of local *P. aeruginosa* blood isolates were somewhat unanticipated; 95.3% of isolates were susceptible to ciprofloxacin. This was considerably higher than that described in recent cross sectional studies from tertiary care hospitals in North America and Europe where in vitro susceptibility results to ciprofloxacin ranged from 64.4-70.8% among all *P. aeruginosa* isolates, and from 68.3-74.9% among *P. aeruginosa* blood culture isolates.[20-24] This is consistent with previous work suggested that blood isolates of *P. aeruginosa* were more susceptible to fluoroquinolones than were isolates from other sites of infection.[25]

The higher in vitro susceptibility rates of *P. aeruginosa* bacteremia isolates in Olmsted County residents compared to non-Olmsted County residents suggests that referral bias likely influenced susceptibility results reported at our institution and possibly those from other tertiary care centers. Data from the United Kingdom and Ireland that were collected from a wide geographic area by 25 clinical laboratories indicate that the low rate of ciprofloxacin resistance described in blood culture isolates from patients in Olmsted County is reflective of that (7.4%)

seen among strains from other non-referral populations.[26] In addition, susceptibility patterns can differ from one geographic area to another.

There are few limitations in our study. First, since the population of Olmsted County is fairly small, the number of patients with *P. aeruginosa* bacteremia during the study period was also small. This limited the ability to perform a multivariate model to determine risk factors for mortality. Nonetheless, we had enough statistical power to examine age and gender effects on incidence rates. Second, the population of Olmsted County consists mainly of middle class whites; therefore, the results of the study may be generalized only to communities with similar population characteristics.

CONCLUSIONS

This is the first population-based study that defines the incidence and long-term outcome of *P. aeruginosa* bacteremia. The incidence of *P. aeruginosa* bacteremia increased exponentially with age, and was higher in males than in females, especially after the age of 50 years. Most cases of monomicrobial *P. aeruginosa* bacteremia were either nosocomially-acquired or health care-associated, especially in patients under the age of 70 years. The relatively low all-cause mortality and in vitro resistance to fluoroquinolones among blood culture isolates in our population as compared to previously reported investigations from tertiary care centers is likely due to referral bias that can impact data generated from the latter institutions.

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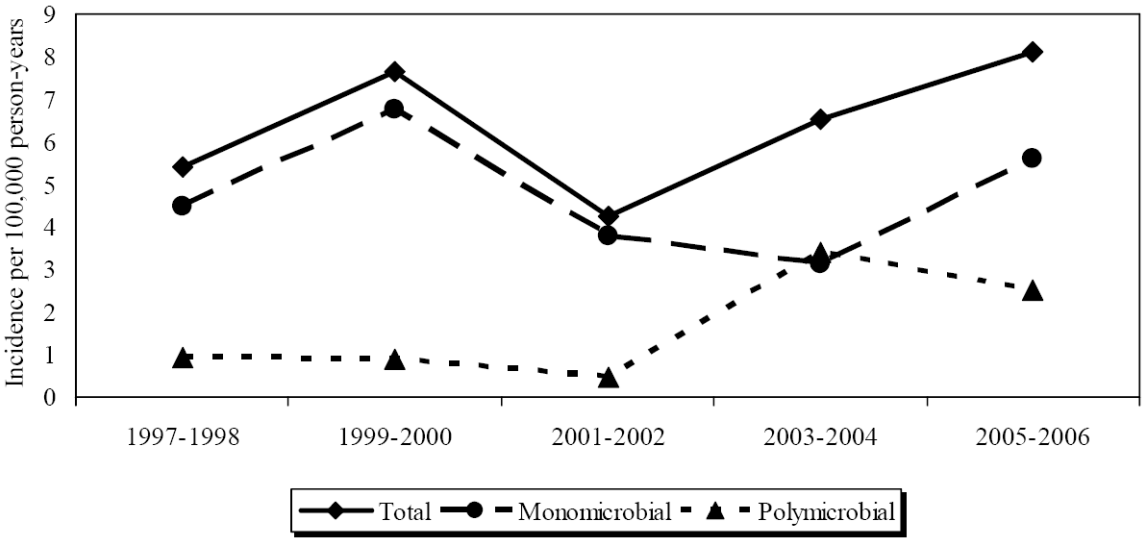
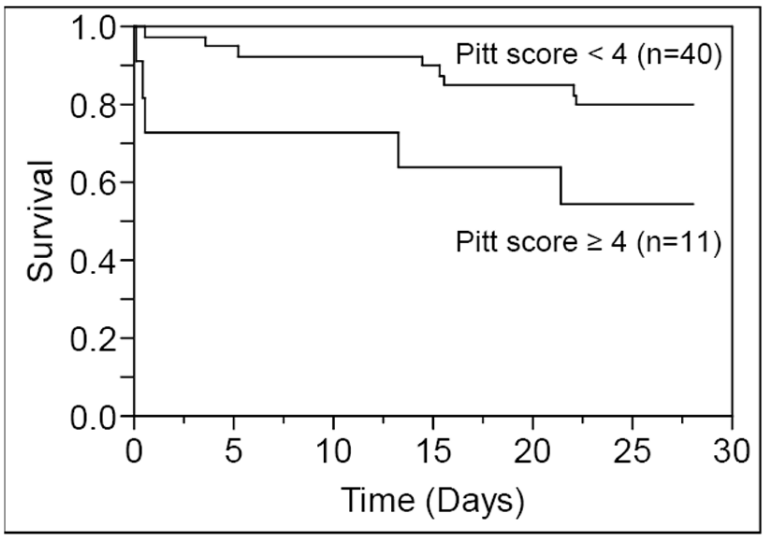


Figure 1.
Age- and gender-adjusted incidence of *Pseudomonas aeruginosa* bacteremia by calendar year

Figure 2.
Incidence of total *Pseudomonas aeruginosa* bacteremia by age group and gender: 1997-2006



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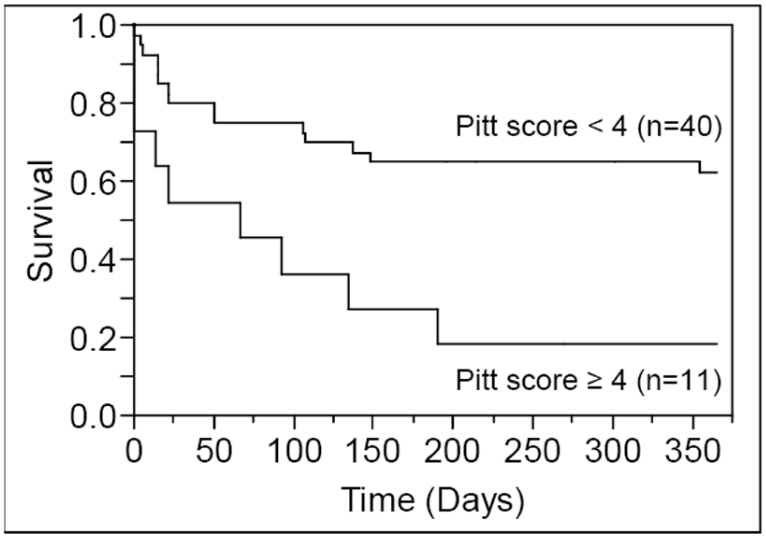

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Figure 3.

a Kaplan-Meier 28-day survival curves of patients with monomicrobial *P. aeruginosa* bacteremia by Pitt bacteremia score (p=0.045).

b Kaplan-Meier 1-year survival curves of patients with monomicrobial *P. aeruginosa* bacteremia by Pitt bacteremia score (p=0.002).

Table 1

Clinical characteristics of patients with monomicrobial and polymicrobial *P. aeruginosa* bacteremia[+]

Characteristic	Monomicrobial N=51	Polymicrobial N=18
Age	69.0 (49.0-81.0)	78.0 (64.8-82.3)
Male gender	35 (68.6)	10 (55.6)
Non-white race	2 (3.9)	2 (11.1)
Diabetes mellitus	12 (23.5)	1 (5.6)
End stage renal disease	5 (9.8)	0 (0)
Malignancy	23 (45.1)	6 (33.3)
Hematologic	10 (19.6)	3 (16.7)
Solid tumor	13 (25.5)	3 (16.7)
Immunocompromised	20 (39.2)	5 (27.8)
Chemotherapy	11 (21.6)	4 (22.2)
Corticosteroids	9 (17.6)	1 (5.6)
Neutropenia	8 (15.7)	3 (16.7)
Other immunosuppressive medications	4 (7.8)	1 (5.6)
Transplant recipients	3 (5.9)	0 (0)
Recent surgical procedure	18 (35.3)	1 (5.6)
Central venous catheter	21 (41.2)	1 (5.6)
Foley catheter	11 (21.6)	1 (5.6)
Prior antibiotic therapy	21 (41.2)	3 (16.7)
Classification:		
Nosocomial	11 (21.6)	1 (5.6)
Health care-associated	29 (56.9)	8 (44.4)
Community-acquired*	**11 (21.6)**	**9 (50.0)**
ICU admission	12 (23.5)	7 (38.9)
Hypotension	19 (37.3)	4 (22.2)
Fever/hypothermia	32 (62.7)	13 (72.2)
Leukocytosis	27 (52.9)	9 (52.9)
Leukopenia	12 (23.5)	5 (29.4)
Pitt bacteremia score ≥ 4	11 (21.6)	4 (22.2)
Source:		
Urinary tract	16 (31.4)	4 (22.2)
Abdominal/biliary**	**1 (2.0)**	**5 (27.8)**
Respiratory tract	11 (21.6)	4 (22.2)
Catheter-related	5 (9.8)	0 (0)
Skin and soft tissue	3 (5.9)	0 (0)
Primary bacteremia++	15 (29.4)	5 (27.8)
28-day all-cause mortality	13 (25.5)	4 (22.2)

[+] Continuous data are expressed as median (interquartile range), whereas categorical data are the observed number (%) for each level.

++ Primary bacteremia is defined as bacteremia with no clearly established site of active infection.

* p=0.022,

** p=0.0038 (only p values <0.05 are shown).

Table 2

Antibiotics in vitro Susceptibility of *P. aeruginosa*[+]

Antibiotic	Number of susceptible isolates/number of isolates tested	Susceptibility %
Levofloxacin	58/62	93.5
Ciprofloxacin	61/64	95.3
Gentamicin	62/64	96.9
Amikacin	63/64	98.4
Ceftazidime	63/64	98.4
Cefepime	63/63	100
Piperacillin-tazobactam	64/64	100
Imipenem	64/64	100
Meropenem	62/62	100

[+]Including both monomicrobial and polymicrobial *P. aeruginosa* bacteremia isolates.

Table 3

The effect of referral bias on reporting of *P. aeruginosa* bacteremia isolates in vitro susceptibility to fluoroquinolone antibiotics

Characteristic	Olmsted County residents N=69	Non-Olmsted County residents N=69	p-value
Year of onset of bacteremia	1997-2006	1997-2006	-
Age[+]	72 (55-82)	71 (56-79)	-
Male gender[++]	45 (65.2)	45 (65.2)	-
Ciprofloxacin susceptibility[*]	61/64 (95.3)	53/64 (82.8)	0.023
Levofloxacin susceptibility[*]	58/62 (93.5)	50/62 (80.6)	0.032

[+] Data are given as median age at onset of bacteremia in years (interquartile range)

[++] Data are given as the observed number (%).

[*] Data are given as number of susceptible isolates/number of isolates tested (%)