MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 1124-1130
DOI: 10.12659/MSM.896026

Received: 2015.09.19
Accepted: 2015.10.30
Published: 2016.04.05

The Distribution and Resistance of Pathogens Among Solid Organ Transplant Recipients with *Pseudomonas aeruginosa* Infections

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AF 1 **Aijing Luo**
BC 2 **Zhuqing Zhong**
AD 3 **Qiquan Wan**
CDF 3,4 **Qifa Ye**

1 Key Laboratory of Medical Information Research (Central South University), College of Hunan Province, Changsha, Hunan, P.R. China
2 Nursing Department, The Third Xiangya Hospital, Central South University, Changsha, Hunan, P.R. China
3 Department of Transplant Surgery, The Third Xiangya Hospital, Central South University, Changsha, Hunan, P.R. China
4 Department of Transplant Surgery, Zhongnan Hospital, Wuhan University, Wuhan, Hubei, P.R. China

Corresponding Author: Qiquan Wan, e-mail: 13548685542@163.com
Source of support: Departmental sources

Background: *Pseudomonas aeruginosa* infection remains a life-threatening complication after solid organ transplantation (SOT). We aimed to investigate the distribution and drug susceptibility of pathogens, and clinical characteristics of SOT recipients with *Pseudomonas aeruginosa* infections.

Material/Methods: A total of 55 SOT recipients who developed 61 episodes of *Pseudomonas aeruginosa* infections between January 1, 2003 and July 31, 2015 were retrospectively analyzed. The distribution and the drug susceptibility of *Pseudomonas aeruginosa* were reviewed.

Results: The most common site from which 61 *Pseudomonas aeruginosa* rods were isolated were the lungs (57.4%, n=37), followed by the blood (27.9%, n=17). There were 35, 18, and 9 recipients accompanied with a serum creatinine level of >1.5 mg/dL, lymphocyte count of <300/mm^3, and a serum albumin level of <30 g/L, respectively. Seven patients each presented with white blood cell count of >15 000/mm^3 and platelet count of <50 000/mm^3. There were 6 (10.9%) cases of septic shocks and 18 (32.7%) deaths. Antibiotic resistance rate of all *Pseudomonas aeruginosa* to 4 of 10 antibiotics investigated was more than 50%. Of these 61 *Pseudomonas aeruginosa* isolates, 47.5% were carbapenem-resistant. The rods were relatively sensitive to piperacillin-tazobactam, levofloxacin, amikacin, and cefoperazone-sulbactam (resistance rate <40%).

Conclusions: The clinical presentation of *Pseudomonas aeruginosa* infections included high body temperature, decreased platelet count, elevated white blood cell count, a high nosocomial origin and mortality, and onset in the late period after transplantation. According to our findings, piperacillin-tazobactam, levofloxacin, amikacin, and cefoperazone-sulbactam, alone or combination, are recommended to treat SOT recipients with *Pseudomonas aeruginosa* infections.

MeSH Keywords: **Bacterial Infections • Drug Resistance, Bacterial • Organ Transplantation**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896026

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Background

Significant morbidity and mortality rates are attributable to bacterial infection after solid organ transplantation (SOT) [1,2]. The incidence rate of bacterial infections has been estimated to be 23.2 cases per 100 renal transplant/years in North America [3].

Pseudomonas aeruginosa, one of the most lethal causative organisms of infection, is classified as non-lactose fermenting Gram-negative bacilli [4]. It is naturally resistant *in vitro* to some commonly used antibiotics, in addition to its striking virulence [5]. Furthermore, it is hard to treat due to the ability to acquire resistance to multiple classes of antibiotics [6].

Pseudomonas aeruginosa is an increasingly important pathogen among SOT recipients and can result in a wide range of infections, including bacteremia, pneumonia, urinary tract infection, and peritonitis. *Pseudomonas aeruginosa* pneumonia most commonly develops in lung transplant recipients, with an incidence rate of 30.3% [7].

Pseudomonas aeruginosa infection is a life-threatening complication in SOT recipients, representing 1.1–25% of lung [8–10], 6–13% of surgical site [11,12], 9.7% of urinary tract [13], and 2.3–38.9% of bloodstream infections [14–34].

The overall mortality among SOT recipients with *Pseudomonas aeruginosa* infections ranged from 28% to 47% [18,20,26,29,33,35]. Linares et al. reported that no death developed in 13 SOT recipients with *Pseudomonas aeruginosa* bacteremia [31]. A 1971 study conducted by Leigh et al. claimed that the mortality was as high as 85.7% (6/7) in renal recipients with *Pseudomonas aeruginosa* bacteremias [24].

Knowledge about *Pseudomonas aeruginosa* infections is needed to improve the global care of SOT recipients. The goal of this retrospective study was to investigate the distribution and drug susceptibility of pathogens, and clinical characteristics of SOT recipients with *Pseudomonas aeruginosa* infections.

Material and Methods

Study population

This study was performed at the Third Xiangya Hospital, Central South University, Changsha and Zhongnan Hospital, Wuhan University, Wuhan, 2 university teaching hospitals in China. Medical records of 55 SOT recipients diagnosed with *Pseudomonas aeruginosa* infections from January 1, 2003 to July 31, 2015 were retrospectively reviewed. This study investigated all SOT recipients with definite clinical signs of infection from whom *Pseudomonas aeruginosa* were isolated from clinical samples. Maintenance immunosuppression was based on calcineurin inhibitor (cyclosporine or tacrolimus) and corticosteroids, with or without mycophenolate mofetil/azathioprine. The prophylactic antibiotics used during liver transplantation included the second- or third-generation cephalosporins, semi-synthetic penicillins/beta-lactamase inhibitors, and carbapenems according to susceptibility patterns of the bacteria isolated before operation. The prophylactic antibiotics used during renal transplantation included the second- or third-generation cephalosporins or semi-synthetic penicillins/beta-lactamase inhibitors. We retrospectively analyzed demographic, clinical, and laboratory records of these recipients. The laboratory variables, including serum creatinine and albumin levels, and white blood cell, platelet, and lymphocyte count, were collected within the first 24 h after the culture was drawn. The follow-up time was at least 2 months after the onset of *Pseudomonas aeruginosa* infections. The ethics committees of both hospitals approved this study.

Definition

Pseudomonas aeruginosa infections were defined based on the criteria established by the Centers for Disease Control and Prevention (CDC) [36]. Nosocomial infection was defined as positive cultures obtained from patients who had been hospitalized for 48 h or longer. [37] Appropriate antimicrobial use was considered if *Pseudomonas aeruginosa* were susceptible *in vitro* to empirical antibiotics, which were administered within 48 h of sampling for culture. Septic shock was diagnosed in recipients with *Pseudomonas aeruginosa* infections who presented with persistent dysfunction of more than 1 organ due to hypoperfusion unresponsive to intravenous fluid challenge [38,39]. Mortality was defined as *Pseudomonas aeruginosa* infection-associated when death was related to clinical signs of active infections without evidence of any other cause [40].

Microbiologic examination

Specimens taken from SOT recipients were immediately transported to the clinical microbiology laboratory for routine bacterial culture. The Vitek-2 system (bioMérieux, Marcyl'Etoile, France) was used for identification of *Pseudomonas aeruginosa*. Antibiotic susceptibility was determined by the Kirby-Bauer method and minimum inhibitory concentration tests. The results were interpreted according to the NCCLs manual [41] which was suitable for 2003 and the CLSI criteria [42] which was suitable for 2004–2015. Intermediate susceptibility to the antibiotics was classified as resistance. All 10 commercially available antibiotics, including aztreonam (ATM), piperacillin-tazobactam (TZP), cefoperazone-sulbactam (CFS), cefazolin (CZO), cefuroxime (CXM), ceftazidime (CAZ), cefepime (FEP), amikacin (AN), levofloxacin (LVF), and meropenem (MEM) were products of Oxoid, England.

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Results

During the 12-year study period, we performed 1571 SOT in the Third Xiangya Hospital, including 1363 kidney, 199 liver, 3 heart, 5 simultaneous liver-kidney, and 1 simultaneous kidney-pancreas transplantations, and 396 SOT in Zhongnan Hospital, consisting of 283 kidney, 111 liver, and 2 simultaneous liver-kidney transplantations. A total of 61 episodes of *Pseudomonas aeruginosa* infections occurred in 55 of 1967 (2.8%) SOT recipients. Approximately 55% (30/55) of recipients developed *Pseudomonas aeruginosa* infections beyond 2 months (60 days) after SOT transplantation. The median time to develop *Pseudomonas aeruginosa* infections was 66 days (interquartile range: 14.5–163 days) after transplantation. The sites from which 61 *Pseudomonas aeruginosa* rods were isolated were the lungs (n=37), blood (n=17), abdomen (n=3), the urinary tract (n=4), wound (n=1) and vascular catheter (n=1). Most episodes of infections were nosocomial (76.4%, n=42). Twenty-six percent (14/55) of episodes of *Pseudomonas aeruginosa* infections underwent inappropriate empiric therapy.

The mean age of these 55 SOT recipients with *Pseudomonas aeruginosa* infections was 43.8±12.0 years, with a male predominance (70.9%, n=39). There were 20.0%, 18.2%, and 18.2% of recipients with *Pseudomonas aeruginosa* infections undergoing induction therapy referred to antithymocyte globulin or antilymphocyte globulin, acute rejection, and reoperation within 3 months prior to infections, respectively. Thirty-five (63.6%), 18 (32.7%), and 9 (16.4%) recipients had *Pseudomonas aeruginosa* infections accompanied with a serum creatinine level of >1.5 mg/dL, lymphocyte count of <300/mm^3, and a serum albumin level of <30 g/L, respectively. Eight and 11 patients presented with white blood cell count of >15 000/mm^3 and platelet count of <50 000/mm^3, respectively. There were 6 (10.9%) septic shocks and 18 (32.7%) deaths in these 55 recipients. However, the mortality was up to 35.7% (5/14) when SOT recipients developed *Pseudomonas aeruginosa* bacteremia. Thirty-one patients (56.4%) had a body temperature of 38°C or higher at the onset of *Pseudomonas aeruginosa* infections. Table 1 presents demographic, laboratory, and clinical variables of 55 SOT recipients with *Pseudomonas aeruginosa* infections.

Antibiotic resistance rate of all *Pseudomonas aeruginosa* to 4 of 10 antibiotics investigated was more than 50%. More than 40% of *Pseudomonas aeruginosa* were carbapenem-, aztreonam-, cefepime-, or ceftazidime-resistant. Colistin susceptibility testing was not applied for all strains and was tested only in 11 *Pseudomonas aeruginosa* strains in both institutes. Therefore, we did not include colistin in our present investigation. Of them, 5 were susceptible to both carbapenems and colistin, 5 were resistant to carbapenems but susceptible to colistin, and 1 was resistant to both carbapenems and colistin. The rods were relatively susceptible to piperacillin-tazobactam, levofloxacin, amikacin, and cefoperazone-sulbactam (resistance rate <40%). All rods were resistant to cefazolin and cefuroxime.

The drug-resistance rate of all *Pseudomonas aeruginosa* causing bloodstream infections to 6 of 10 antibiotics was 50% or higher. However, the drug-resistance rate of *Pseudomonas aeruginosa* causing pneumonia was lower than the rate of *Pseudomonas aeruginosa* causing bloodstream infections. The resistance rate of all *Pseudomonas aeruginosa* causing pneumonia to 6 of 10 commonly used antibiotics was <50%. The antibiotic resistance rate of *Pseudomonas aeruginosa* is shown in Table 2.

Discussion

Infection is still a fatal complication in SOT and remains a significant cause of morbidity and mortality. *Pseudomonas aeruginosa,* one of the most important non-fermentative Gram-negative bacilli, is the fourth-leading microorganism causing bloodstream infections in SOT recipients [34,43].

We found that drug-resistance rate of all *Pseudomonas aeruginosa* to 6 of 10 antibiotics investigated was more than 40%. The drug susceptibility test showed that *Pseudomonas aeruginosa* was relatively susceptible to piperacillin-tazobactam, levofloxacin, amikacin, and cefoperazone-sulbactam (resistance rate <40%). Forty-eight percent of *Pseudomonas aeruginosa* were carbapenem-resistant in the present study, which was higher than the carbapenem-resistance rate of 32% reported by previous studies which targeted liver transplant recipients with *Pseudomonas aeruginosa* bacteremias [44].

In Western countries carbapenem resistant strains are usually resistant to quinolones. However, in the present study we found that the drug resistance of *Pseudomonas aeruginosa* isolates to levofloxacin was lower than that of *Pseudomonas aeruginosa* isolates to meropenem. The possible reason for this difference is that meropenem rather than levofloxacin was frequently used as a prophylactic antibiotic during liver transplantation in both centers involved. We also found that 39.3% and 47.5% of *Pseudomonas aeruginosa* were cefoperazone-sulbactam- and ceftazidime-resistant, respectively, which was also higher than the rate from the study [44] conducted by Shi et al., where 24% and 18% of *Pseudomonas aeruginosa* were cefoperazone-, sulbactam-, and ceftazidime-resistant, respectively.

We found that most positive cultures of *Pseudomonas aeruginosa* were obtained from the lungs (63.6%), followed by blood (30.9%). In contrast, in a study of 27 living-donor liver recipients with *Pseudomonas aeruginosa* infections, Hashimoto et al. reported the most common site of *Pseudomonas aeruginosa* infections to be intra-abdomen (52%) and surgical site (19%) [45].

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Table 1. Demographic, laboratory and clinical variables of 55 SOT recipients with *Pseudomonas aeruginosa* infections.

Characteristics	Value	
Age, mean years ±SD	43.8±12.0	
Sex, number of male (%)	39	(70.9)
Temperature of 38 °C or greater, no. of cases (%)	31	(56.4)
Nosocomial origin, no. of cases (%)	42	(76.4)
Inappropriate antimicrobial use, no. of cases (%)	14	(25.5)
Septic shock, no. of cases (%)	6	(10.9)
Site of infection, no. of cases (%)		
Lung	31	(56.4)
Blood	13	(23.6)
Urinary tract	2	(3.6)
Abdomen	2	(3.6)
Wound	1	(1.8)
Vascular catheter	1	(1.8)
Multiple culture-positive sites	5	(9.1)
Type of transplantation, no. of cases (%)		
Liver	15	(27.3)
Kidney	39	(70.9)
Kidney-pancreas	1	(1.8)
Time of infection onset, no. of cases (%)		
<2 months posttransplant	25	(45.5)
≥2 months posttransplant	30	(54.5)
Induction therapy, no. of cases (%)		
Yes	11	(20.0)
No	44	(80.0)
Acute rejection prior to infection, no. of cases (%)		
Yes	10	(18.2)
No	45	(81.8)
Reoperation, no. of cases (%)		
Yes	10	(18.2)
No	45	(81.8)
Laboratory variables from blood, no. of cases (%)		
Platelet count <50000/mm^3	11	(20.0)
Lymphocyte count <300/mm^3	18	(32.7)
Albumin <30 g/L	9	(16.4)
WBC count >15000/mm^3	8	(14.5)
Creatinine >1.5 mg/dL	35	(63.6)
Related mortality, no. of cases (%)	18	(32.7)

SOT – solid organ transplant; SD – standard deviation; WBC – white blood cells.

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Table 2. Resistance rates of 61 *Pseudomonas aeruginosa* isolates to 10 antibiotics according to the different sites of infections [n, (%)].

Anti-microbial drugs	Lungs (35)	Blood (17)	Abdomen (3)	Urinary tract (4)	Wound (1)	Vascular catheter (1)	Total drug resistance cases (n)
MEM	16 (45.7)	7 (41.2)	3 (100)	2 (50)	0 (0)	1 (100)	29 (47.5)
TZP	11 (31.4)	5 (29.4)	3 (100)	2 (50)	0 (0)	1 (100)	22 (36.1)
CAZ	13 (37.1)	9 (52.9)	3 (100)	3 (75)	0 (0)	1 (100)	29 (47.5)
FEP	19 (54.3)	9 (52.9)	3 (100)	2 (50)	0 (0)	1 (100)	34 (55.7)
CXM	35 (100)	17 (100)	3 (100)	4 (100)	1 (100)	1 (100)	61 (100)
CZO	35 (100)	17 (100)	3 (100)	4 (100)	1 (100)	1 (100)	61 (100)
AN	10 (28.6)	5 (29.4)	2 (66.7)	1 (25)	1 (100)	0 (0)	19 (31.1)
LVF	8 (22.9)	6 (35.3)	2 (66.7)	1 (25)	0 (0)	0 (0)	17 (27.9)
CFS	13 (37.1)	9 (52.9)	1 (33.3)	1 (25)	0 (0)	0 (0)	24 (39.3)
ATM	26 (74.3)	13 (76.5)	3 (100)	3 (75)	1 (100)	1 (100)	47 (77)

MEM – meropenem; TZP – piperacillin-tazobactam; CAZ – ceftazidime; FEP – cefepime; CXM – cefuroxime; CZO – cefazolin; AN – amikacin; LVF – levofloxacin; CFS – cefoperazone-sulbactam; ATM – aztreonam.

The present study mainly consisted of renal recipients (72%). Thus, a possible explanation for the differences in site of *Pseudomonas aeruginosa* infections in both studies might be the different constitution of transplant recipients.

We found that SOT recipients with *Pseudomonas aeruginosa* infections had a mortality rate of 32.7%; however, the mortality was up to 35.7% when SOT recipients developed *Pseudomonas aeruginosa* bacteremia. Our findings are agreement with studies reporting the mortality rate to be 38–40% in transplant recipients with *Pseudomonas aeruginosa* bacteremias [33,46]. The possible reasons to explain our findings of high mortality among SOT recipients with *Pseudomonas aeruginosa* infections include the high proportion of nosocomial infection (76.4%) and the high antibiotic-resistance rate of *Pseudomonas aeruginosa* (resistance rate of all *Pseudomonas aeruginosa* to 6/10 antibiotics investigated more than 40%). Bodro et al. also confirmed that *Pseudomonas aeruginosa* infection led to deaths due to its extensive multidrug resistance [33].

The exceedingly resistant *Pseudomonas aeruginosa* in SOT recipients poses a new therapeutic challenge. Piperacillin-tazobactam, levofloxacin, amikacin, and cefoperazone-sulbactam, alone or in combination, rather than carbapenems, were recommended in 2 centers enrolled for SOT recipients presenting with *Pseudomonas aeruginosa* infections in the past. We propose using piperacillin-tazobactam and levofloxacin as the first-line agents and emphasize preventive measures for NLF GNB bacteremias to improve the outcomes of SOT recipients. Several previous studies of liver or lung recipients have established that combination antibiotic therapies, including beta-lactam, aminoglycoside, and/or fluoroquinolone, are preferred to monotherapy for infections because of MDR *Pseudomonas aeruginosa* [47–50].

As a significant nosocomial pathogen, *Pseudomonas aeruginosa* leads to infections as a result of multiple or prolonged hospital admissions, and excessive exposure to antibiotics, with the capacity to adhere to various materials used frequently in clinical settings [51]. Measures to prevent *Pseudomonas aeruginosa* infections included taking effective isolation measures, limiting the use of invasive devices, removing unnecessary catheters at the earliest possible time, and minimizing postoperative length of stay in the hospital.

Active surveillance for *Pseudomonas aeruginosa* is also recommended in institutions with high resistance rates of *Pseudomonas aeruginosa*. In addition, detailed knowledge of the local epidemiology of *Pseudomonas aeruginosa* infections in SOT recipients is also important to help physicians prescribe adequate empirical antibiotics.

Conclusions

The clinical presentation of *Pseudomonas aeruginosa* infections included high body temperature, decreased platelet count, elevated white blood cell count, a high nosocomial origin and mortality, and onset in the late period after transplantation. The drug resistance rate of *Pseudomonas aeruginosa* to commonly

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used antibiotics was high. Piperacillin-tazobactam, levofloxacin, amikacin, and cefoperazone-sulbactam, alone or in combination, rather than carbapenem, are recommended to treat with SOT recipients with *Pseudomonas aeruginosa* infections.

Conflict of interest

None declared.

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