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Risk Factors of *Pseudomonas Aeruginosa* Infection in NICU and PICU: A Matched Case Control Study

Amal Obaidallah Almutairi* and Mohammed Bakhsh

Department of Neonatal and Pediatric Intensive Care Units, King Abdulaziz Medical City, Jeddah, Saudi Arabia

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***Corresponding author:** Amal Obaidallah Almutairi, King Abdulaziz Medical City, Jeddah, Saudi Arabia, E-mail: amalobaidallah8@gmail.com

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A B S T R A C T

Introduction: *Pseudomonas aeruginosa* (*P. aeruginosa*) is a non- fermentative gram-negative rod that has been associated with nosocomial infections. Many factors were found to increase the risk of acquiring *P. aeruginosa* infection in neonatal and pediatric intensive care units. Hence, our study aims to evaluate the risk factors of acquired *Pseudomonas aeruginosa* infection or colonization after NICU and PICU admission at King Abdulaziz Medical City, in Jeddah, Saudi Arabia.

Method: This study is a matched retrospective case-control study conducted at King Abdulaziz Medical City (KAMC), Jeddah. Cases included all pediatric patients diagnosed with *P. aeruginosa* infection or colonization who met the specified criteria. For each case, two controls (1:2 basis) who were negative for *P. aeruginosa* infection were randomly selected.

Results: During the study period, a total of 31 confirmed cases of Pseudomonas bacteremia infection or colonization were identified and were matched with 62 controls. Most cases and control group's ages are between 0-1 month, with proportions of 71.7% and 72.6 %, respectively. The gender distribution was not significantly different in the two groups. Respiratory distress syndrome (p= 0.004), sepsis (p= 0.001), malnutrition (p= 0.005), heart diseases (p= 0.001 or= 10.88), neurological diseases (p= 0.021) were significantly associated with Pseudomonas identification. MDR *P. aeruginosa* isolates among cases was only reported in two cases. In univariate analysis, the factors of congenital heart disease and NICU/PICU stay duration were identified as significant factors. Multivariate analysis showed significant results in sepsis 6.44 (95% CI: 1.39-29.7, P < 0.05), congenital heart diseases 6.89 (95% CI: 1.62-29.3, P < 0.01), malnutrition 3.64 (95% CI: 1.02-13.2, P < 0.05) and surgery history 4.02 (95% CI: 1.02-15.7, P < 0.05).

Conclusion: More studies need to be conducted to evaluate both risk factors and drug resistance as the diagnostics and characteristics of the organisms are developing.

Keywords: *Pseudomonas aeruginosa*, NICU, PICU, Infection, Colonization

1. Introduction

Nosocomial infections are considered main causes of morbidity and mortality in the Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Units (PICU)[1,2]. *Pseudomonas aeruginosa (P. aeruginosa)* is a non- fermentative gram-negative rod that has been extensively associated with

nosocomial infections in NICU and PICU patients[3-5]. They are commonly associated with the development of hospital acquired pneumonia, ventilator associated pneumonia, bacteremia, catheter associated infections and surgical site infections[6,7]. In neonates, it can cause a number of serious neonatal complications, such as sepsis, meningitis, conjunctivitis and pneumonia[4]. *P. aeruginosa* has been estimated to be the causative pathogen in 7.3% of nosocomial infections[8]. In the NICU, a study reported that 23.8% of their patients were colonized by *P. aeruginosa* during their stay in the unit[3].

Many factors were identified to increase the risk of acquiring *P. aeruginosa* infection or colonization among infants in NICUs. These risk factors are mainly attributed to the ubiquity of *Pseudomonas aeruginosa* and its capability of colonizing a wide range of potential reservoirs including environmental surfaces, water systems, medical equipment, patients and healthcare workers[9]. This represents a huge challenge in the NICU setting and several outbreaks of *P. aeruginosa* in NICUs have been reported. A systematic review included 15 articles with a total of 414 infants colonized or infected with *P. aeruginosa* was done and found that the risk factors for Pseudomonas NICU outbreaks included antimicrobial use before positive blood culture and its duration, blood transfusion, umbilical venous catheter exposure, intravenous nutrition and electrolytes delivery and aging[10]. The risk of hand colonization of healthcare workers with *P. aeruginosa* increases with artificial fingernail use and it may be linked to underlying conditions like otitis externa and onychomycosis[9,10]. Furthermore, greater risk of infection and higher mortality rates from *P. aeruginosa* infection were noted in low-birth-weight preterm infants compared to older infants[10,11]. Additionally, several risk factors have been reported in adult Intensive Care Unit (ICU) which include Infection with other microorganisms, total parenteral nutrition, comorbid cerebrovascular and cardiovascular disease, ICU admission, malignancy, compromised immune system, mechanical ventilation, acute respiratory failure, infection in the respiratory tract and central vein catheter and use of multiple invasive devices[12-14]. Lastly, cystic fibrosis has been linked to the acquisition of *P. aeruginosa* in older ages[15].

Resistance to antibiotics was shown to significantly increase mortality rates and the length of stay of newborns in the NICU[16]. Infants born <32 weeks of gestation, with a birth weight <1500g and infants small for gestational age are at higher risk of infection by resistant *P. aeruginosa*[17]. Moreover, gender, co-existing or additional diseases, previous broad-spectrum antibiotics and invasive procedures were also identified as risk factors for antibiotic resistant P. aeruginosa[18,19].

The risk factors and antimicrobial susceptibility pattern of *P. aeruginosa* patients in NICU and Pediatric Intensive Care Unit (PICU) have not been adequately characterized locally. Hence, our study is aiming to address this problem. This study aims to evaluate the risk factors of positive and negative cultures of *Pseudomonas aeruginosa* in NICU and PICU patients in King Abdulaziz Medical City, in Jeddah, Saudi Arabia. Furthermore, the study evaluated the rate of multi-drug resistance of the identified Pseudomonas isolates.

2. Methods

This study is a matched retrospective case-control study conducted at King Abdulaziz Medical City (KAMC), Ministry of National Guard, Jeddah. Cases included all pediatric patients with age less than 14 years who were diagnosed with *P. aeruginosa* infection or colonization who have met the specified criteria for case selection between October 2020 and October 2022 in Neonatal Intensive Care (NICU) and Pediatric Intensive Care (PICU).

2.1. Case Patients

A retrospective review was carried out in order to identify all reports of *P. aeruginosa*-caused hospital acquired infections or colonization that happen more than 48 hours after being admitted to the NICU or PICU in which, patients did not exhibit any symptoms of infection at the time of NICU or PICU admission. Pseudomonas colonization was defined as the isolation of *P. aeruginosa* in or on the body in the absence of any symptoms or disease[20].

2.2. Control Patients

For each case, two controls (1:2 basis) who were negative for *P. aeruginosa* infection were randomly selected using systematic sampling technique from patients admitted during study period at the same ICU ward.

2.3. Data Collection

For this retrospective chart review study, demographic characteristic (age, gender), underlying conditions before the coexistence of positive pseudomonal cultures (cystic fibrosis, respiratory distress syndrome, bronchitis, asthma, pneumonia, sepsis, premature and very low birth, severe combined immunodeficiency, congenital heart disease, malnutrition, hematological diseases, malignancy, hepatobiliary diseases, nephrological diseases, urological diseases, neurological and other) , history of hospitalization, NICU/PICU stay duration, previous use of antibiotics, invasive procedures (peripheral and central lines, foley catheter, nasogastric tube, tracheostomy and mechanical ventilation), use of parenteral nutrition ,and previous history of surgery were collected through electronic chart review.

Antimicrobial susceptibility for *P. aeruginosa* positive culture was collected. Antimicrobial drugs that were tested include: carbapenems (imipenem and meropenem) and cephalosporins (cefepime, ceftazidime); quinolones (ciprofloxacin); penicillins (piperacillin/tazobactam); aminoglycoside (Gentamicin, amikacin). Multidrug resistant Pseudomonas was defined as resistance of the isolate to at least one antipseudomonal active agent in at least three different antibiotic classes[21]. The study was approved by the institutional review board.

2.4. Statistical Analysis

Percentages were used to describe categorical variables, while numerical variables were presented as means and ranges. Categorical variables were compared using the Chi-square or Fisher exact test and numerical variables by the t-test or Mann-Whitney U test, as appropriate. A P- value less than 0.05 was considered statistically significant. Logistic regression analysis was used to identify the risk factors associated with *Pseudomonas aeruginosa* infection. The odd ratio was calculated with 95% confidence interval. The data was analyzed using JMP software version.

3. Results

During the study period, a total of (31) confirmed cases were identified and included in the study. For each case, two controls were chosen (62). Table 1 shows the characteristics of these 31

cases and 62 controls. Twenty-two cases were from the NICU and nine were from the PICU. Eighteen of the controls were from the PICU and 44 were from the NICU. Most cases and control group's ages are between 0-1 month, with proportions of 71.7% and 72.6 %, respectively. The gender distribution was not significantly different in the two groups.

Univariate analysis comparing *P. aeruginosa* infected or colonized cases with controls identified that prematurity and low birth weight were statistically significant with p-value of 0.002. Furthermore, the rate of respiratory distress syndrome (58.1% *vs.* 27.4%; p= 0.004), sepsis (48.4% *vs.* 16.1%; p= 0.001), malnutrition (51.6% *vs.* 22.6%; p= 0.005), heart diseases (58.1% *vs.* 11.3%; p= 0.001, neurological diseases (41.9p % vs. 19.4%; p= 0.021) were significantly higher in subjects who developed Pseudomonas infection or colonization (Table 2). Moreover, cases with longer duration of hospital stay, ranging from 15 to 30 days, were significantly higher in subjects who acquired Pseudomonas infection or colonization compared to controls (71.0% *vs.* 32.3%; P= 0.001). In addition, history of surgery was significantly higher in cases compared to controls (48.4% *vs.* 14.5%; p= 0.001).

Table 3 shows the susceptibility profile of various antimicrobial drugs used for treatment of cases diagnosed with *P. aeruginosa.* MDR *P. aeruginosa* isolates among cases was only reported in two cases.

Significant factors in bivariate analysis were included in the binary logistic regression model using both univariate and multivariate analysis. In univariate analysis, the factors of congenital heart disease and NICU/PICU stay duration were identified as significant factors. Adjusting for setting, age and gender of patients, the multivariate analysis reported sepsis 6.44 (95% CI: 1.39-29.7, P < 0.05), congenital heart diseases 6.89 (95% CI: 1.62-29.3, P < 0.01), malnutrition 3.64 (95% CI: 1.02-13.2, P < 0.05) and surgery history 4.02 (95% CI: 1.02-15.7, P < 0.05) as significant factors (Table 4).

Table 1: Basic characteristics of participants.

Variable	Cases n=31	Control n=62	P-value
Setting			
PICU	9(29.0)	18(29.0)	
NICU	22(71.0)	44(71.0)	0.992
Age			
0-1 month	22(71.7)	45(72.6)	
1-12 months	5(16.1)	4(6.5)	
1-5 years	3(9.7)	5(8.1)	
5-10 years	1(3.2)	7(11.3)	
10-14 years	-	1(1.6)	0.419
Gender			
Female	15(48.4)	31(50.0)	
Male	16(51.6)	31(50.0)	0.883

Table 2: Univariate analysis of risk factors for *Pseudomonas aeruginosa* infection or colonization in the NICU and PICU between cases and controls.

Variable	Control n=62	Cases n=31	P-value	Unadjusted OR	CI 95%
RD syndrome					
No	45(72.6)	13(41.9)	0.004	3.66	
Yes	17(27.4)	18(58.1)			1.48-9.06
Asthma					
No	59(95.2)	30(96.8)	0.718	0.66	
Yes	3(4.8)	1(3.2)			0.06-6.56
Pneumonia					
No	54(87.1)	24(77.4)	0.232	1.97	
Yes	8(12.9)	7(22.6)			064-6.05
Sepsis					
No	52(83.9)	16(51.6)	0.001	4.88	
Yes	10(16.1)	15(48.4)			1.83-12.9
Premature					
>37 weeks	35(56.5)	6(19.4)	0.002	-	
36-34	8(12.9)	3(9.7)			
33-32	3(4.8)	5(16.1)			
31-28	5(8.1)	3(9.7)			
<28 weeks	1(1.6)	4(12.9)			
NA	10(16.1)	10(32.3)			
Low birth wt					
>4000	3(4.8)	2(6.5)	0.002	-	
4000-2500	27(43.5)	3(9.7)			
2499-1500	11(17.7)	5(16.1)			
1499-1000	4(6.5)	6(19.4)			
<1000	2(3.2)	6(19.4)			
NA	15(24.2)	9(29.0)			
Heart disease					
No	55(88.8)	13(41.9)	0.001	10.88	
Yes	7(11.3)	18(58.1)			3.76-10.5
Malnutrition					
No	48(77.4)	15(48.4)	0.005	3.66	
Yes	14(22.6)	16(51.6)			1.45-9.19
Hematological					
No	50(80.6)	27(87.1)	0.437	0.62	
Yes	12(19.4)	4(12.9)			0.18-2.10
Malignancy					
No	58(93.5)	27(87.1)	0.296	2.15	
Yes	4(6.5)	4(12.9)			0.49-9.24
Nephrological					
No	59(95.2)	29(93.5)	0.745	1.36	
Yes	3(4.8)	2(6.5)			0.22-8.57
Urological					
No	60(96.8)	28(90.3)	0.193	3.21	
Yes	2(3.2)	3(9.7)			0.51-20.3
Neurological					
No	50(80.6)	18(58.1)	0.021	3.01	
Yes	12(19.4)	13(41.9)			1.16-7.79
Stay duration					
1-15 days	42(67.7)	9(29.0)	0.001	5.13	
15-30 days	20(32.3)	22(71.0)			2.00-13.2
History Hosp					
No	43(69.4)	24(77.4)	0.414	0.66	
Yes	19(30.6)	7(22.6)			0.24-1.79
Previous antibio					
No	20(32.3)	12(38.7)	0.537	0.75	
Yes	42(67.7)	19(61.3)			0.31-1.85

Previous surgery					
No	53(85.5)	16(51.6)	0.001	5.52	2.03-14.9
Yes	9(14.5)	15(48.4)			
Peripheral line					
No	21(33.9)	12(38.7)	0.646	0.881	0.33-1.98
Yes	41(66.1)	19(61.3)			
Central line					
No	48(77.4)	18(58.1)	0.053	2.47	0.98-6.27
Yes	14(22.6)	13(41.9)			
Folly					
No	56(90.3)	30(96.8)	0.266	0.31	0.04-2.70
Yes	6(9.7)	1(3.2)			
Feeding tubes					
No	35(56.5)	14(45.2)	0.304	1.57	0.66-3.75
Yes	27(43.5)	17(54.8)			
Ventilation					
No	27(43.5)	13(41.9)	0.882	1.06	0.44-2.55
Yes	35(56.5)	18(58.1)			
Chest tube					
No	58(93.5)	30(96.8)	0.516	0.48	0.05-4.52
Yes	4(6.5)	1(3.2)			
Endotracheal					
No	47(75.8)	26(83.9)	0.372	0.6	0.20-1.85
Yes	15(24.2)	5(16.1)			

Table 3: Susceptibility results of various antimicrobial drugs used in the treatment of Pseudomonas among cases.

Antimicrobial drug	Sensitive	Resistance	Not reported
Ceftazidime	24 (77%)	6 (19%)	1 (3%)
Cefepime	4 (13%)	6 (19%)	21 (68)
Tazocin	22 (71%)	8 (26%)	1 (3%)
Ciprofloxacin	26 (84%)	4 (13%)	1 (3%)
Imipenem	10 (32%)	5 (16%)	16 (52%)
Meropenem	11 (35%)	3 (10%)	17 (55%)
Gentamicin	27 (87%)	3 (10%)	1 (3%)

Table 4: Univariate and multivariate binary logistic regression model of factors associated with the disease.

	Univariate analysis		Multivariate analysis	
Factor	**OR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**
Respiratory	1.06 (0.54-2.05)	0.866	2.44 (0.53-11.2)	0.251
Sepsis	1.50 (0.67-3.33)	0.321	6.44 (1.39-29.7)	0.017*
Congenital Heart disease	2.57 (1.07-6.15)	0.034*	6.89 (1.62-29.3)	0.009**
Malnutrition	1.14 (0.56-2.34)	0.715	3.64 (1.02-13.2)	0.048*
neurological diseases	1.08 (0.49-2.37)	0.842	0.17 (0.01-2.84)	0.217
NICU/PICU duration	0.21 (0.10-0.44)	0.001**	0.34 (0.09-1.25)	0.106
Surgery history	1.67 (0.73-3.80)	0.226	4.02 (1.02-15.7)	0.046*
Central line	0.93 (0.44-1.97)	0.847	0.45 (0.09-2.04)	0.299

*Significant at 5%, **Significant at 1%, AOR: adjusted for setting, age and gender

4. Discussion

This study investigated several variables to determine the association of these factors and the risk of *P. aeruginosa.* Based on the statistical analysis, prematurity and low birth weight were found to be of statistical significance. A similar finding was reported in Bartels et al. as their study claimed it can be explained by immature immunity and these infants often require invasive medical procedures like mechanical ventilation and intravenous lines, which can serve as entry points for pathogens[19].

Another important factor was length of stay, as staying longer would expose the neonates to higher chances of acquiring the infection. According to Rao YB et al. in south China, a multi-center study investigating the risk factors of imipenem-resistant *Pseudomonas aeruginosa* infection in NICUs, a univariate analysis reported an association between imipenem resistance infection and increased length of stay[17].

However, in a study performed to estimate the prevalence of infections in NICU, both prematurity and low birth weight did not report statistical significance[23]. As per this study, higher rates of infection with MDR *P. aeruginosa* were identified in cases with sepsis and patients with peripheral line. This finding is supported by multiple studies including Scamardo MS et al as they reported line related infection was proved to be the most frequent reported infection by a percentage of 82[22].

After adjusting for setting, age and gender of patients, the analysis in our study revealed that sepsis, congenital heart diseases, malnutrition and surgery history were all independently associated with an increased likelihood of Pseudomonas infection or colonization.

The strong association observed between sepsis and Pseudomonas infection is consistent with existing literature. Sepsis represents a state of systemic inflammation and immune dysregulation, rendering patients more susceptible to opportunistic infections, including those caused by *Pseudomonas aeruginosa.* Sepsis-related immunosuppression, characterized by diminished cytokine responses and increased lymphocyte apoptosis, is believed to be a major contributing factor to this increased susceptibility[24].

Our finding that congenital heart diseases (CHD) and history of surgery significantly increase the risk of Pseudomonas infection or colonization. Children with CHD often undergo invasive procedures, including central line insertions and surgeries. A study on nosocomial infections in newborns with congenital heart disease following cardiac surgery identified several significant risk factors, which include prolonged hospital stays, chest drain use, extended central venous catheterization and mechanical ventilation, multiple transfusions and repeat surgery[25], which further can support our finding.

In our research, malnutrition was found to be an additional independent risk factor for Pseudomonas infection. The host's immune system can be seriously weakened by nutritional deficits, which can affect humoral and cellular immunity. Patients who are malnourished may produce less immunoglobulins, have impaired neutrophil phagocytic activity and have weakened cell-mediated immunity, all of which increase their vulnerability to infections[26]. Due to the severity of their illnesses, patients in the NICU/PICU often experience worsening nutritional problems, resulting in a vicious cycle of impaired immunity and increased vulnerability to infections[27].

5. Conclusion

Nosocomial infections remain one of the major causes

of morbidity and mortality in neonates in the NICU, with *P. aeruginosa* being one of the common pathogens of such infections. Further research with larger sample sizes and across different healthcare settings is warranted to validate these research findings and to explore other potential risk factors for *P. aeruginosa* infection and colonization in pediatric populations which will offers better understanding of the infection rates and better approach in the management of the infection and the prevention of complications.

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