Epidemiological Aspects and Main Determinants of Prognosis in Children with *Acinetobacter* Infections Admitted to Intensive Care Units at Aliasghar Children's Hospital, Tehran, Iran

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Abstract

Background: There is not enough information about the prevalence of *Acinetobacter* infection as well as its risk factors, especially in neonatal intensive care units. The present research aimed at conducting a five-year study on *Acinetobacter* infection and its main factors in neonatal and pediatric intensive care units in Iran.

Methods: This cross-sectional survey was conducted on 89 children with positive culture for hospital-acquired Acinetobacter, admitted to intensive care units of Aliasghar Children's Hospital in Tehran, between 2010 and 2015. Besides, 97 patients with similar baseline characteristics without *Acinetobacter* positivity were enrolled as the control group. Epidemiological information and clinical data were collected by reviewing the hospital recorded files.

Results: In the group with positive *Acinetobacter* culture, complete and partial improvement was observed in 62.9% and 11.2%, respectively, while 25.8% died due to treatment failure. In this regard, complete and partial improvement in the control group was revealed in 85.6% and 11.3% with an overall death rate of 3.1%, indicating significantly higher failure rate in the case group (P = 0.001). To determine the main factors for in-hospital death, all variables with a significant association with positive culture in univariate analysis (considering P < 0.2) were entered in a backward multivariable logistic regression model. In this regard, venous access (OR = 7.80, 95% CI: 1.06 to 57.19, P = 0.043), carbapenem use (OR = 27.03, 95% CI: 1.93 to 377.780, P = 0.014), and ampicillin use (OR = 0.12, 95% CI: 0.019 to 0.739, P = 0.022) were shown as the main determinants for *Acinetobacter*-related death.

Conclusions: Although the study was not a prognostic study and determination of the main determinants of prognosis in children with *Acinetobacter* infections was not possible yet it seems that the mortality rate due to *Acinetobacter* infection in the population was about 25.8% in the global range reported in the literature. The main factors for *Acinetobacter* infection-related death are central venous catheters related to TPN, carbapenem use, and ampicillin use.

Keywords: Acinetobacter, Children, Iran, Course

1. Background

Neonates, who are admitted to intensive care units are at high risk for various types of Infections, such as *Acinetobacter* infection (1). *Acinetobacter* species are the most important pathogens associated with hospital-acquired infections and can be accounted for up to 20% of infections in ICUs worldwide (2). This infection was initially identified within the first decade of the twentieth century and is now accepted as a pathogen responsible for opportunistic infections of the skin, bloodstream, urinary tract, and other soft tissues (3). The overall preponderance of *Acinetobacter* infection varies in different geographical areas as well as in different clinical settings due to differences in its related identified risk factors, the difference in hospital-based managerial and controlling approaches, and also the rate of resistance against various antibiotics (4). The common risk factors discovered for *Acinetobacter* infections include cigarette and alcohol use, diabetes mellitus, chronic pulmonary disorders, prolonged hospitalization, surgeries, central venous catheter insertion, mechanical ventilation, intravenous feeding, and the use of broad-spectrum antibiotics (5, 6). The respiratory system is the most com-

mon location for colonization of *Acinetobacter* because of high transient colonization of the bacteria in the throat, besides colonization in patients with tracheostomy (7). In this regard, *Acinetobacter* is the most important reason for tracheal bronchiolitis and pneumonia in hospitalized children (8). High rates of in-hospital mortality due to *Acinetobacter* are reported in children admitted to intensive care units (9). In other words, neonatal pneumonia, sepsis, colonization in traumatic ulcers, and also cellulitis caused by intravenous catheters in such patients are the main etiologies for in-hospital death in this age subgroups (10). Another scenario is the resistance of *Acinetobacter* to different common antibiotics. The resistance mechanisms for these bacteria include enzymatic degradation of drugs, target modifications, multidrug efflux pumps, and permeability defects (11, 12). Unfortunately, high resistance rate of *Acinetobacter* to various antibiotics, especially in developing countries, has been reported. According to a recent systematic review from Iran (13), there has been an upward trend in the prevalence rate of resistance of *Acinetobacter* to different antibiotics, where between 2001 and 2011, the resistance rate to penicillin changed from 63.9% to 93.4%, to imipenem changed from 51.1% to 76.5%, to trimethoprim sulfamethoxazole changed from 76.6% to 99.0%, and to aminoglycosides changed from 58.4% to 95.0%. This high resistance to antibiotics makes controlling infection more difficult, specifically among children. In this regard, there is not enough information about the prevalence of these bacteria as well as the risk factors, especially in neonatal intensive care units. The present research aimed at to studying the five-year outbreak of *Acinetobacter* infections and its main determinants in neonatal and pediatric intensive care units.

2. Methods

This cross-sectional study was conducted on 89 children with positive culture for hospital-acquired *Acinetobacter* (according to NNIS methods), admitted to intensive care units of Aliasghar Children's Hospital of Tehran between 2010 and 2015. The patients without manifestations related to *Acinetobacter* infection, in spite of positive culture for these bacteria, were excluded from the study. All collected information was approved by the hospital committee for infection control. After completing epidemiological information by reviewing the hospital recorded files, the data on probable main determinants of infection were obtained, including invasive procedures (central vein catheterization, intubation, chest tube insertion, nasogastric tube insertion, or urinary catheterization), surgical interventions, the use of mechanical ventilation, respi-

ratory tract suction, the use of antibiotics, underlying disorders, the length of hospital stay, especially at intensive care units, primary diagnosis requiring critical care, biochemical parameters, the treatment protocols, and the disease prognosis. Those patients with similar baseline characteristics (same age and gender), who had been admitted during the same period of cases yet without *Acinetobacter* positivity were considered as the control group.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than five were observed. Quantitative variables were also compared with t test or Mann U test. For the statistical analysis, the SPSS statistical software version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P-values of 0.05 or less were considered statistically significant.

3. Results

In total, 89 patients with positive *Acinetobacter* infection and 97 individuals as controls during the same admission period in the same wards were included in the study. There was no difference in male gender (51.7% in the case group and 54.6% in the control group, P = 0.68) and also in age subgroups (age range of one to two years: 84.3% and 90.7%, age range of two to five years: 7.9% and 1.0% and age range higher than five years: 7.9% and 8.2%, respectively, P = 0.07). In the case group, the sources of bacterial culture included respiratory pathways in 73.0%, urine sample in 6.7%, and blood sample in 20.2%. No considerable difference was found across the two case and control groups in clinical features and respiratory distress was found in 61.4% and 49.5%, sepsis in 2.3% and 9.3%, seizure in 6.8% and 5.2%, vomiting in 12.5% and 13.4%, fever in 8.0% and 4.1%, and bowel obstruction in 1.1% and 1.0%, respectively (P = 0.14). In the group with positive *Acinetobacter* culture, complete and partial improvement was seen in 62.9% and 11.2%, respectively while 25.8% died due to treatment failure. In this regard, complete and partial improvement in the control group was revealed in 85.6% and 11.3% with an overall death rate of 3.1%, indicating significantly higher failure rate in the case group (P = 0.001). Regarding laboratory parameters (Table 1), except for serum HS-CRP that was significantly higher in the case than in the control group, the mean for other parameters, including serum albumin level, serum creatinine, serum glucose level, serum hemoglobin level, and white blood cell count was similar

between the two groups. With respect to underlying determinants in case and control groups, more frequent central venous catheterization (58.7% versus 24.7%, P < 0.001), intubation (82.0% versus 27.8%, P < 0.001), nasogastric tube (28.1% versus 4.1%, P < 0.001), central venous catheters related TPN (25.8% versus 9.3%, P < 0.001), underlying disorder (69.7% versus 4.5%, P < 0.001), gastrointestinal anomalies (21.3% versus 6.2%, P < 0.001), history of seizure (21.3% versus 5.2%, P < 0.001), and history of surgery within hospitalization (55.1% versus 18.6%, P < 0.001) was found in the former group. Similarly, the use of some antibiotics, including vancomycin (79.8% versus 37.1%, P < 0.001), aminoglycoside (69.7% versus 51.5%, P < 0.001), carbapenem (55.1% versus 22.7%, P < 0.001), cephalosporin (50.6% versus 18.6%, P < 0.001), ranitidine (63.6% versus 21.6%, P < 0.001), corticosteroids (4.5% versus 0.0%, P = 0.038), and packed cells higher than 4 units (46.0% versus 16.5%, P < 0.001) was significantly higher in the case group as compared to the control group. Also, compared to the control group, the case group underwent more mechanical ventilation (86.5% versus 21.6%, P < 0.001) and suction (85.4% versus 35.1%, P < 0.001). However, no difference was found in other conditions, such as chest tube insertion, respiratory anomalies, having tracheoesophageal fistula, prematurity, neurological disorders, metabolic disorders, renal insufficiency, immunodeficiency, using macrolides or ampicillin, and also history of trauma or coma. As shown in Table 2, the mean number of days at risk, hospitalization at the NICU or PICU, use of antibiotics, intubation, having venous catheter or chest tube, and having central venous catheters related TPN was significantly higher in those with positive *Acinetobacter* culture when compared to the control group.

To determine the main indicators for in-hospital death, all variables with a significant association with positive culture in univariate analysis (considering P < 0.2) were entered in a backward multivariable logistic regression model. In this regard, central venous catheter-related TPN (OR = 7.80, 95% CI: 1.06 - 57.19, P = 0.043), carbapenem use (OR = 27.03, 95% CI: 1.93 - 377.780, P = 0.014), and ampicillin use (OR = 0.12, 95% CI: 0.019 - 0.739, P = 0.022) were the main determinants of *Acinetobacter*-related death.

4. Discussion

In the recent years, *Acinetobacter* has had increasing resistance to a broad range of antibiotics. Among different clinical settings in each hospital, intensive care units are the most common areas affected by *Acinetobacter* infections, due to requiring mechanical ventilation or venous catheterization, prolonged stay, patients receiving various

antimicrobials and immunodeficiency conditions. This issue is especially important among neonates and children because of the greater likelihood of infection-related mortality and morbidity. In the current study, a mortality rate of 25.8% was reported that was a considerably high among infants with *Acinetobacter* infection. In a study by Kapoor et al. [9] on an Indian sample, a mortality rate of 28.2% was found. Previous studies have reported mortality ranging from 17% to 63% [14-17]. Mortality rates were higher (50%) in surgical patients, which may be due to the prolonged ventilator support required by these patients and the post-operative broad-spectrum use of antibiotics. In the current observation, several risk factors were identified to increase the risk of *Acinetobacter* infection and its related mortality and morbidity. In this regard and using multivariable regression models with the presence of confounders, the main indicators for ICU deaths among children with *Acinetobacter* infection included central venous catheter-related TPN and using carbapenem or ampicillin. In fact, both inserting central venous catheters for feeding and also administration of some antibiotics could be considered as major factors predicting poorer outcome due to *Acinetobacter* infection. Similarly, in some studies, known risk factors for similar infections included invasive procedures and the use of broad-spectrum antimicrobials [18]. Consistent with the mentioned studies, the current research found that use of central venous catheters, especially for feeding, and use of broad-spectrum antibiotics were significant risk factors. However, use of urinary catheters and intercostal drainage tubes were not statistically associated with *Acinetobacter* infection as shown by others [19]. As a main point, *Acinetobacter* has the ability to survive for long periods on inanimate surfaces in the patient's vicinity, thereby providing a constant source of infection [20]. A longer PICU stay is associated with greater exposure and hence this has been reported as a risk factor in other studies [21, 22]. This study could not determine underlying disorders, such as respiratory anomalies, tracheoesophageal fistula, prematurity, neurological disorders, metabolic disorders, renal insufficiency, immunodeficiency, or history of trauma or coma as the main determinants of poor outcome of *Acinetobacter* infection or its occurrence. Previous studies have shown that risk factors associated independently with poor prognosis include severity of the underlying disease, pneumonia, inappropriate antimicrobial treatment, recent surgery, mechanical ventilation, acute renal failure, septic shock, and DIC [23, 24]. Also, although prolonged ventilation, venous catheterization, and prolonged ICU stay were potential risk factors for *Acinetobacter* infection and its prognosis, the current researchers could not reveal such findings. In other words, as indicated by

Table 1. Laboratory Parameters of Patients with and Without Acinetobacter Infection

Marker	Case Group	Control Group	P-Value
Serum albumin	0.048 ± 0.455	0.001 ± 0.001	0.32
Creatinine	0.640 ± 0.510	0.629 ± 0.599	0.89
HS-CRP	12.710 ± 26.301	1.266 ± 3.683	< 0.001
Serum glucose	68.844 ± 54.759	58.331 ± 112.540	0.42
Serum hemoglobin	12.119 ± 10.706	11.522 ± 3.429	0.60
WBC count	5511.77 ± 5496.889	5379.60 ± 4918.979	0.86

Table 2. Duration of Different Conditions in Patients with and Without Acinetobacter Infection

Marker	Case Group	Control Group	P-Value
Days at risk	10.73 ± 18.14	3.90 ± 5.96	< 0.001
Days for PICU stay	17.66 ± 36.05	3.83 ± 8.03	0.001
Days for NICU stay	18.63 ± 18.14	11.70 ± 12.25	0.004
Days for antibiotic use	16.16 ± 29.15	11.16 ± 9.89	< 0.001
Days between admission to antibiotic use	0.02 ± 0.22	0.26 ± 1.13	0.06
Days for intubation	13.97 ± 9.54	7.17 ± 5.34	0.020
Days for venous catheterization	9.40 ± 12.01	3.10 ± 7.48	0.020
Days for chest tube	2.40 ± 9.63	0.02 ± 3.27	0.040
Days for venous feeding	7.67 ± 13.27	3.00 ± 4.03	0.050

Reddy et al., traumatic brain injury, prolonged PICU duration of stay, and mechanical ventilation were the main correlates for death in these patients, however, there was no association with increased mortality as reported elsewhere (25, 26). The difference in risk profile for *Acinetobacter* infection and its prognosis is related to the difference in the study type, inclusion criteria, underlying diseases, and severity of disorders requiring admission to ICUs and also the rate of anti-microbial resistance. In this regard, it seems that the prevalence rate of *Acinetobacter* infection, its-related mortality and morbidity and also its main risk factors may be unique for each population. Adherence to infection control practices is very important if these resistant infections are to be controlled (27).

4.1. Conclusion

Overall, the mortality rate due to *Acinetobacter* infection in the population of the current study was about 25.8% in the global range reported in the literature. The main indicators for *Acinetobacter* infection-related death were central venous catheters related TPN, carbapenem use and ampicillin use, thus, greater efforts should be made for better control of CV line hygiene when they are used for total parenteral nutrition, and antibiotic stewardship principles must be respected if these infections are to be decreased in pediatric intensive care (28).

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