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CLINICAL & BASIC RESEARCH

Identifying Risk Factors for Healthcare-Associated Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii* in a Neonatal Intensive Care Unit

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تحديد عوامل الخطورة للاصابة بالعدوى المرتبطة بالرعاية الصحية التي تسببها بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم في وحدة العناية المركزة لحديثي الولادة

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ABSTRACT: ***Objectives:*** *Acinetobacter baumannii* is a causative pathogen of various healthcare-associated infections (HAIs) and is particularly prevalent in high-risk hospital settings. This study aimed to determine risk factors associated with HAIs caused by carbapenem-resistant *A. baumannii* (CRAB) in a neonatal intensive care unit (NICU). ***Methods:*** This prospective study was performed between January 2013 and June 2014 among NICU patients at the Mansoura University Children's Hospital, Mansoura, Egypt. Neonates who developed HAIs due to CRAB were assigned to a case group, while those infected with carbapenem-sensitive *A. baumannii* (CSAB) were assigned to a control group. ***Results:*** Among the 124 neonates who developed *A. baumannii*-caused HAIs during the study period, 91 (73.4%) were caused by CRAB and 33 (26.6%) were caused by CSAB. Prematurity, premature rupture of the membranes (PROM), a previous stay in another hospital, prolonged NICU stay, the presence of invasive devices, previous exposure to carbapenems or aminoglycosides and prolonged antibiotic therapy before infection were significantly associated with CRAB-caused HAIs. A multivariate logistic regression analysis identified prematurity (adjusted odds ratio [aOR] = 25.3; P <0.01), mechanical ventilation (aOR = 18.9; P <0.01) and the previous use of carbapenems (aOR = 124.7; P <0.01) or aminoglycosides (aOR = 22.6; P = 0.04) to be independent risk factors for CRAB infections. ***Conclusion:*** Various risk factors were significantly associated with CRAB-caused HAIs among the studied NICU patients.

Keywords: Healthcare Associated Infections; Antimicrobial Drug Resistance; Carbapenem Antibiotics; Acinetobacter baumannii; Neonatal Intensive Care Units; Egypt.

الملخص: الهدف: تعتبر بكتيريا أسينيتوباكتر بوماني أحد مسببات العدوى المرتبطة بالرعاية الصحية. و حيث أنها تتواجد بشكل خاص في مناطق الرعاية الصحية ذات الخطورة العالية فقد هدفت هذه الدراسة الى تحديد عوامل الخطورة للاصابة بالعدوى المرتبطة بالرعاية الصحية التي تسببها بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم في وحدة العناية المركزة لحديثي الولادة. **الطريقة:** أجريت هذه الدراسة الاستطلاعية بين يناير 2013 ويونيو 2014 في وحدة العناية المركزة لحديثي الولادة بمستشفى الأطفال الجامعى، المنصورة، مصر. تم ادراج المرضى المصابين بالعدوى المرتبطة بالرعاية الصحية الناتجة عن بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم في مجموعة الدراسة في حين تم ادراج المرضى المصابين بالعدوى المرتبطة بالرعاية الصحية الناتجة عن بكتيريا أسينيتوباكتر بوماني الحساسة للكاربابنيم في المجموعة الضابطة. **النتائج:** تم رصد 124 مريضا مصابا بالعدوى المرتبطة بالرعاية الصحية الناتجة عن بكتيريا أسينيتوباكتر بوماني خلال فترة الدراسة. و قد كان عدد المرضى المصابين بالعدوى المرتبطة بالرعاية الصحية الناتجة عن بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم هو 91 مريضا (73.4%) بينما كان عدد المرضى المصابين بالعدوى المرتبطة بالرعاية الصحية الناتجة عن بكتيريا أسينيتوباكتر بوماني الحساسة للكاربابنيم هو 33 مريضا (26.6%). وقد شملت عوامل الخطورة للاصابة بالعدوى المرتبطة بالرعاية الصحية التي تسببها بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم كل من الأطفال الخدج، والتمزق المبكر للأغشية المحيطة بالجنين، والاقامة في مستشفى آخر، والإقامة لفترات طويلة في وحدة العناية المركزة لحديثي الولادة، ووجود أجهزة اجتياحية، والتعرض السابق للكاربابنيم أو أمينوغليكوزيدس والعلاج بالمضادات الحيوية لفترات طويلة قبل الاصابة بالعدوى. وقد بين الانحدار اللوجستي متعدد المتغيرات أن كل من الأطفال الخدج (نسبة الأرجحية المعدلة (aOR) = 25.3؛ P <0.01)، والتهوية الميكانيكية ((نسبة الأرجحية المعدلة (aOR) = 18.9؛ P <0.01) والاستخدام السابق للكاربابنيم (نسبة الأرجحية المعدلة (aOR) = 124.7؛ P <0.01) أو أمينوغليكوزيدز (نسبة الأرجحية المعدلة (aOR) = 22.6؛ P = 0.04) يمثلون عوامل خطورة مستقلة للإصابة بالعدوى المرتبطة بالرعاية الصحية التي تسببها بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم. **الخلاصة:** لقد تبين أنه يوجد عدة عوامل خطورة مرتبطة بالإصابة بالعدوى المتعلقة بالرعاية الصحية التي تسببها بكتيريا أسينيتوباكتر بوماني المقاومة للكاربابنيم في وحدة العناية المركزة لحديثي الولادة.

الكلمات المفتاحية: العدوى المرتبطة بالرعاية الصحية؛ الميكروبات المقاومة للمضادات الحيوية؛ مضادات الكاربابنيم؛ بكتيريا أسينيتوباكتر بوماني؛ وحدة العناية المركزة لحديثي الولادة؛ مصر.

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Advances in Knowledge

- *The current study identified significant risk factors associated with healthcare-associated infections (HAIs) caused by carbapenem-resistant Acinetobacter baumannii (CRAB) among patients in a neonatal intensive care unit (NICU) in Egypt.*
- *Significant risk factors included prematurity, premature rupture of the membranes, a previous stay in another hospital, prolonged NICU stay, the presence of an invasive device (i.e. an umbilical catheter, urinary catheter or mechanical ventilator), previous exposure to carbapenems or aminoglycosides and prolonged antibiotic therapy prior to the infection.*

Application to Patient Care

- *The findings of this study may be utilised by NICU staff to decrease risk factors associated with carbapenem resistance among Egyptian neonates.*

Healthcare-associated infections (HAIs) are infections contracted in various healthcare settings and are well known to increase morbidity, mortality, length of hospital stay and the cost of medical care.[1] Intensive care units (ICUs), including neonatal ICUs (NICUs), constitute high-risk areas for HAIs as admitted patients are usually critically ill and commonly undergo invasive procedures.[2] *Acinetobacter baumannii* is a major causative pathogen of various HAIs, such as bloodstream infections and pneumonia, particularly in high-risk settings such as ICUs. Unfortunately, recent studies have reported a steady increase in the prevalence of carbapenem-resistant *A. baumannii* (CRAB) strains isolated from patients with HAIs.[3–5] This study therefore aimed to determine risk factors for the development of CRAB-caused HAIs among patients in a NICU in Egypt.

Methods

This prospective single-centre study was conducted between January 2013 and June 2014 in the NICU of the Mansoura University Children's Hospital, Mansoura, Egypt. All patients who developed *A. baumannii*-caused HAIs of any type following their admission to the NICU were included in the study. The identification of *A. baumannii* strains was performed using colony morphology, microscopic examination and biochemical tests. The API® 20 NE identification system (bioMérieux Inc, St. Louis, Missouri, USA) was used to confirm the diagnosis of an *A. baumannii*-caused infection. Patients who developed HAIs with *A. baumannii* isolates showing resistance to imipenem or meropenem were assigned to a case group while those with isolates sensitive to imipenem and meropenem were assigned to a control group. The sensitivity patterns of the isolated *A. baumannii* strains were detected using the disc diffusion method. All results were interpreted using the guidelines of the Clinical and Laboratory Standards Institute.[6]

Surveillance procedures conducted for patients with different types of HAIs were performed according to the definitions, elements and criteria of the Centers for Disease Control and Prevention.[7] Infections developing during the first two calendar days of hospital stay were deemed to have been present upon admission, while infections developing on or after the third calendar day of hospital stay were considered HAIs. Information regarding the HAI was collected by reviewing the patients' medical records and their clinical and laboratory findings. Possible risk factors were documented for each patient, including prematurity (<37 gestational weeks); low birth weight (<2,500 g); premature rupture of the membranes; age; gender; previous stay in another hospital; length of NICU stay prior to infection; the presence of an invasive device; duration of antibiotic therapy before the HAI; and previous antibiotic exposure. The latter risk factor was considered present only in cases wherein systemic antibiotics were administered for a minimum of 24 hours within the 14-day period prior to the isolation of the *A. baumannii* strain. In terms of patient outcome, HAI-related mortality was defined as death within 30 days of developing the infection.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), Version 22.0 (IBM Corp, Armonk, New York, USA). Nonparametric demographic and clinical parameters were compared using the Mann-Whitney U test and presented as medians and ranges. Categorical variables were compared using the Chi-squared test and presented as percentages. A multivariate analysis was performed using binary logistic regression to assess independent risk factors for CRAB-caused HAIs. Differences were considered statistically significant at $P \leq 0.05$.

Table 1: Healthcare-associated infections caused by carbapenem-resistant or -sensitive *Acinetobacter baumannii* in a neonatal intensive care unit in Egypt (N = 124)

Type of infection	n (%)	
	CRAB (n = 91)	CSAB (n = 33)
Blood stream	65 (71.4)	22 (66.7)
Pneumonia	17 (18.7)	7 (21.2)
Urinary tract	7 (7.7)	3 (9.1)
Other	2 (2.2)	1 (3)

CRAB = carbapenem-resistant Acinetobacter baumannii; CSAB = carbapenem-sensitive A. baumannii.

Table 2: Risk factors associated with healthcare-associated infections caused by carbapenem-resistant or -sensitive *Acinetobacter baumannii* in a neonatal intensive care unit in Egypt (N = 124)

Risk factor	Univariate analysis, n (%)			Multivariate analysis	
	CRAB (n = 91)	CSAB (n = 33)	*P* value	aOR (95% CI)	*P* value
Postnatal age in days					
<7	45 (49.5)	18 (54.5)	0.65		
≥7	46 (50.5)	15 (45.5)	0.35		
Male gender	39 (42.9)	16 (48.5)	0.78		
Prematurity	54 (59.3)	8 (24.2)	0.03*	25.3 (8.4–784.8)	<0.01*
LBW	29 (31.9)	10 (30.3)	0.88		
PROM	42 (46.2)	5 (15.2)	0.01*		
PSAH	17 (18.7)	2 (6.1)	0.03*		
Median length of stay in the NICU prior to HAI (range)	10 (6.4–15.2)	4 (2.6–7.9)	0.04*		
Presence of an invasive device					
Umbilical catheter	70 (76.9)	11 (33.3)	0.04*		
PPCL	10 (11)	5 (15.2)	0.85		
Urinary catheter	66 (72.5)	7 (21.2)	<0.01*		
MV	72 (79.1)	9 (27.3)	<0.01*	18.9 (3.5–1,135.1)	<0.01*
Previous antibiotic exposure					
Carbapenems	55 (60.4)	5 (15.2)	<0.01*	124.7 (45.2–588.1)	<0.01*
Cephalosporins	24 (26.4)	6 (18.2)	0.07		
Aminoglycosides	42 (46.2)	4 (12.1)	0.02*	22.6 (1.1–864.9)	0.04*
Vancomycin	30 (33)	12 (36.4)	0.79		
Median duration of antibiotic therapy before HAI in days (range)	8 (5.7–10.4)	2 (1.2–4.6)	<0.05*		

CRAB = carbapenem-resistant Acinetobacter baumannii; CSAB = carbapenem-sensitive A. baumannii; aOR = adjusted odds ratio; CI = confidence interval; LBW = low birth weight; PROM = premature rupture of the membranes; PSAH = previous stay in another hospital; NICU = neonatal intensive care unit; HAI = healthcare-associated infection; PPCL = peripheral percutaneous central line; MV = mechanical ventilator.

**Considered statistically significant at P ≤0.05.*

This study received ethical approval from the Institutional Review Board of the Faculty of Medicine, Mansoura University (#R/17.10.10). Informed consent was obtained from a parent or guardian of all of the patients included in the study.

Results

During the study period, 124 neonates in the NICU developed HAIs caused by *A. baumannii*. Of these, 91 infections (73.4%) were caused by CRAB and 33 (26.6%) were caused by carbapenem-sensitive *A. baumannii* (CSAB). In both groups, bloodstream infections were most common [Table 1]. There was no statistically significant difference between the groups in terms of sites of infection. Prematurity, premature rupture of the membranes, a previous stay in another hospital and prolonged NICU stay prior to infection were identified as significant risk factors for CRAB-caused HAIs (*P* <0.05 each). Moreover, the presence of an umbilical catheter, urinary catheter or mechanical ventilator, previous exposure to carbapenems or aminoglycosides and prolonged antibiotic therapy were also significant risk factors (*P* <0.05 each). Prematurity (adjusted odds ratio [aOR] = 25.3; *P* <0.01), mechanical ventilation (aOR = 18.9; *P* <0.01) and the previous use of carbapenems (aOR = 124.7; *P* <0.01) or aminoglycosides (aOR = 22.6; *P* = 0.04) were independent risk factors for CRAB infections [Table 2].

A total of 70 (76.9%) patients with CRAB infections and eight (24.2%) patients with CSAB infections died; this difference in mortality rate between the two groups was statistically significant (*P* = 0.01). Significant mortality-related risk factors among patients with

Table 3: Mortality-related risk factors among patients with health-care-associated infections caused by carbapenem-resistant or -sensitive *Acinetobacter baumannii* in a neonatal intensive care unit in Egypt (N = 124)

Variable	Univariate analysis, n (%)			Multivariate analysis	
	CRAB (n = 70)	CSAB (n = 8)	*P* value	aOR (95% CI)	*P* value
Postnatal age in days					
<7	32 (45.7)	3 (37.5)	0.38		
≥7	38 (54.3)	5 (62.5)	0.61		
Male gender	34 (48.6)	4 (50)	0.80		
Prematurity	33 (47.1)	3 (37.5)	0.21		
LBW	25 (35.7)	3 (37.5)	0.89		
PROM	32 (45.7)	4 (50)	0.42		
PSAH	10 (14.3)	1 (12.5)	0.67		
Median length of NICU stay prior to HAI (range)	12 (8.3–15.2)	5.4 (3.6–7.9)	0.02*		
Presence of an invasive device					
Umbilical catheter	55 (78.6)	1 (12.5)	<0.01*		
PPCL	8 (11.4)	1 (12.5)	0.82		
Urinary catheter	54 (77.1)	6 (75)	0.87		
MV	57 (81.4)	2 (25)	0.02*	17.2 (2.1–129.2)	0.04*
Previous antibiotic exposure					
Carbapenems	53 (75.7)	1 (12.5)	<0.01*	79.1 (32.7–278.9)	<0.01*
Cephalosporins	18 (25.7)	2 (25)	0.94		
Aminoglycosides	20 (28.6)	2 (25)	0.76		
Vancomycin	25 (35.7)	3 (37.5)	0.65		
Median days of antibiotic therapy before HAI in days (range)	5.1 (3.8–8.7)	3.2 (2.1–3.5)	0.09		

CRAB = carbapenem-resistant Acinetobacter baumannii; CSAB = carbapenem-sensitive A. baumannii; aOR = adjusted odds ratio; CI = confidence interval; LBW = low birth weight; PROM = premature rupture of the membranes; PSAH = previous stay in another hospital; NICU = neonatal intensive care unit; HAI = healthcare-associated infection; PPCL = peripheral percutaneous central line; MV = mechanical ventilator.

**Considered statistically significant at P ≤0.05.*

CRAB infections included prolonged NICU stay, the presence of an umbilical catheter or mechanical ventilator and the previous administration of carbapenems (*P* <0.02 each). Independent risk factors for mortality were mechanical ventilation (aOR = 17.2; *P* = 0.04) and the previous use of carbapenems (aOR = 79.1; *P* <0.01) [Table 3]. Isolates from both the CRAB and CSAB groups demonstrated high resistance rates to all antimicrobials except for tigecycline, with no significant differences between the two groups [Table 4].

Discussion

The ability to survive in a hospital environment has resulted in a high incidence of HAIs attributed to *A. baumannii*; furthermore, the organism rapidly develops resistance to a broad range of antibiotic classes.[8] Previous research has indicated that the incidence of *A. baumannii*-resistant strains is increasing all over the world.[3–5] According to surveillance data in the USA, carbapenem resistance increased from 5.2% to 40.8% between 1999 and 2010.[9] Similarly, in Europe, surveillance data from 2012 indicated that 68.8% of *A. baumannii* strains isolated from ICUs were resistant to carbapenems.[10] These findings support those of the present study which indicated a high rate of carbapenem resistance in the studied Egyptian NICU.

In terms of invasive procedures, mechanical ventilation was the only independent risk factor for CRAB-caused HAIs in the current study. Previous studies have reported similar findings.[11,12] Mechanical ventilation is indicated for neonates in cases of respiratory distress,

Table 4: Antimicrobial resistance of carbapenem-resistant and -sensitive *Acinetobacter baumannii* isolates in a neonatal intensive care unit in Egypt (N = 124)

Antimicrobial	n (%)		*P* value
	CRAB (n = 91)	CSAB (n = 33)	
Amoxicillin and clavulanic acid (30 µg/mL)	85 (93.4)	27 (81.8)	0.85
Piperacillin-tazobactam (110 µg/mL)	80 (87.9)	25 (75.8)	0.68
Cefotaxime (30 µg/mL)	91 (100)	33 (100)	>0.99
Cefepime (30 µg/mL)	71 (78)	26 (78.8)	0.98
Gentamicin (10 µg/mL)	78 (85.7)	27 (81.8)	0.87
Amikacin (30 µg/mL)	87 (95.6)	29 (87.9)	0.69
Ciprofloxacin (5 µg/mL)*	86 (94.5)	27 (81.8)	0.85
Tigecycline (15 µg/mL)	9 (9.9)	4 (12.1)	0.58

*CRAB = carbapenem-resistant Acinetobacter baumannii; CSAB = carbapenem-sensitive A. baumannii. *Not recommended for use in neonates.*

hypoxaemia or hypercapnia; however, organisms present in the hospital environment frequently attach to the ventilator tube and form a biofilm which is associated with an increased risk of antibiotic resistance.[13] Furthermore, ventilated critically-ill neonates often undergo endotracheal intubation which can interrupt immunity barriers.[14] Therefore, the incidence of HAIs may potentially be reduced by encouraging the use of noninvasive ventilation among neonates, such as nasal continuous positive pressure ventilation.[15]

In the current study, a previous stay in another hospital and prolonged NICU stay prior to infection were found to constitute significant risk factors for subsequent CRAB infections. This may be attributable to prolonged exposure to organisms present in the hospital environment and the extended use of antibiotics that aid in the development of antimicrobial resistance.[11,12] Rosa *et al.* reported that exposure to a contaminated hospital environment increased the risk of acquisition of CRAB isolates.[16] Baran *et al.* indicated that patients admitted to the ICU had a three-fold higher risk of CRAB infections.[17] Playford *et al.* also observed an association between prolonged ICU stay and CRAB infection.[18] Unfortunately, the nature of multidrug-resistant microorganisms, including *A. baumannii*, in ICUs is endemic. In addition, the likelihood of antimicrobial therapy increases with the duration of ICU stay, thus leading to the colonisation of resistant strains of bacteria.

Previous exposure to carbapenems was another independent risk factor for HAIs caused by CRAB in the present study. Sheng *et al.* also noted that patients with CRAB infections were significantly more likely to have been exposed to carbapenems.[19] Such findings emphasise the need for the judicious use of carbapenem antibiotics, which should remain a last resort in the treatment of serious infections so as to control the development of carbapenem-resistant microbes. As with carbapenems, previous exposure to aminoglycosides was another independent risk factor for CRAB infections in the current study. Chen *et al.* also observed prior exposure to aminoglycosides such as amikacin to be a risk factor for CRAB.[20] Treating physicians should therefore consider these findings before prescribing aminoglycosides to ICU patients.

In the current study, CRAB isolates showed high resistance rates to other antibiotics. Similar findings were reported by Falagas *et al.* among pandrug-resistant *A. baumannii* infection cases.[21] Infections caused by multidrug-resistant pathogens have many adverse outcomes, including prolonged hospital stay, higher treatment costs and increased mortality rates.[22] The treatment of patients suffering from infections caused by such strains is challenging. Adequate knowledge of local *A. baumannii* resistance patterns is a fundamental element to a successful therapeutic approach.[23] In terms of mortality, the presence of an umbilical catheter or mechanical ventilator, prolonged stay in the NICU and the previous administration of carbapenems resulted in significantly increased mortality among patients with HAIs caused by CRAB. Similar results were reported by Djordjevic *et al.* among adult patients admitted to a medical-surgical ICU.[24]

This study is subject to certain limitations. Generally, NICUs in developing countries such as Egypt usually have low staff-to-patient ratios, often resulting in a lack of essential infection control precautions like thorough hand hygiene and aseptic procedures. Under these conditions, resistant bacteria can more easily spread between patients, resulting in more colonised and infected cases compared to adequately staffed units. In addition, the low number of patients in the control group in comparison to the case group resulted in a wide confidence interval, weakening the findings of the present study.

Conclusion

This study found that prematurity, premature rupture of the membranes, a previous stay in another hospital, prolonged NICU stay, the presence of an invasive device, previous exposure to carbapenems or aminoglycosides and prolonged antibiotic therapy were signif-

icantly associated with CRAB-caused HAIs in an NICU in Egypt. Moreover, prematurity, mechanical ventilation and previous exposure to carbapenems or aminoglycosides were independent risk factors for the development of HAIs caused by CRAB.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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