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NOSOCOMIAL IMIPENEM-RESISTANT *ACINETOBACTER BAUMANNII* INFECTIONS IN INTENSIVE CARE UNITS: INCIDENCE AND RISK FACTORS ASSESSMENT

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ABSTRACT

Imipenem-resistant *Acinetobacter baumannii* (*A. baumannii*) (IRAB) has emerged as a challenging nosocomial pathogen particularly in intensive care units (ICUs). Studying the risk factors associated with IRAB infection is of paramount importance for appropriate control of IRAB spread. The aim of this study was to assess the incidence rate and possible risk factors associated with nosocomial IRAB infections in ICUs. A prospective cohort study was carried out in surgical and emergency ICUs of a tertiary care hospital in Egypt. All patients who developed nosocomial *A. baumannii* infection from the start of January 2014 to the end of December 2015 were included. Isolates were identified as *A. baumannii* using API 20NE and E-test was used to define IRAB. Out of 146 *A. baumannii* isolates, 11 were found to be IRAB (7.5% incidence rate), of them 72.7% (8/11) were found to be multidrug resistant (MDR). Univariate analysis demonstrated that hospital stay before ICU admission [Relative risk (RR) 3.51, 95% confidence interval (CI) 1.0-12.7, P= 0.04)], longer ICU stay (P= 0.005), exposure to emergent surgery (RR 17.5, CI 7.39-41.4, P= 0.000), the presence of central venous catheter (RR 3.26, CI 1.0-10.6, P= 0.04) and previous carbapenem use (RR 4.05, CI 1.12-14.6, P =0.02) were significant risk factors for IRAB infection. In conclusion, a relatively high IRAB incidence was recorded in ICUs of our hospital. Hospital stay before ICU admission, longer ICU stay, exposure to emergent surgery, the presence of central venous catheter and previous carbapenem use were significant risk factors for IRAB infection. Rationale use of carbapenems in ICUs should be considered.

Key words: Imipenem-resistant, *Acinetobacter baumannii*, Intensive care units

LES INFECTIONS *ACINETOBACTER BAUMANNII*NOSOCOMIALES RESISTANTS A L'IMIPENEME DANS LES UNITES DE SOINS INTENSIFS: L'INCIDENCE ET LES FACTEURS DE RISQUE EVALUATION.

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RESUME

***Acinebacter Baumannii* (*A. baumannii)* résistant à l'imipenème (IRAB) a émergé comme une pathogène difficile en particulier dans les unités de soins intensifs (USI). L'étude des facteurs de risque associe à l'infection IRAB est d'une importance capitale pour le contrôle de la propagation de l'IRAB. Le but de cette étude était d'évaluer le taux d'incidence et les facteurs de risque possibles associesà des infections nosocomiales d'IRAB dans les USI. Une étude de cohorte prospective a été menée dans une USI chirurgicale et d'urgence d'un hôpital de soins tertiaire en Egypte. Tous les patients qui ont développé l'infection *A. baumannii* depuis le début de janvier 2014 jusqu'à la fin de décembre 2015 ont été inclus. Les isolats ont été identifiés comme *A. baumannii* en utilisant API 20NE et E – test a été utilisé pour définir l'IRAB. Sur 146 isolats d'*A. baumannii*, 11 ont été trouvés d'être IRAB (7,5% taux d'incidence), d'entre eux, 72,7% (8/11) ont été trouvés multi résistantes (MDR). Analyse univariée a montré que l'hospitalisation avant l'admission USI [Risque relative (RR)3,51, 95% intervalle de confiance (CI) 1,0-12,7, P=0.04)], long séjour à USI (P=0.0005), l'exposition à la chirurgie d'urgence (RR 17,5 CI 7,39-41.4, P= 0,000), la présence d'un cathéter veineux central (RR 3,26, CI 1,0-10,6 P=0.04) et l'usage de carbapenemprécédente (RR 4,05 CI 1,12-14.6 P=0,02) étaient des facteurs de risque importants d'infection IRAB. En conclusion, un incident relativement élevé d'IRAB a été enregistréà USI de notre hôpital. Séjour à l'hôpital avant l'admission à l'unité de soins intensifs, long séjour à USI, l'exposition à la chirurgie d'urgence, la présence d'un cathéter veineux central, et l'utilisation de carbapenemprécédenteétaient des facteurs de risque important pour l'infection d'IRAB. L'utilisation rationnelle des carbapanemes en USI devrait êtreconsidéré.**

Mots clés : Résistant àImipenème, *Acinebacterbaumannii*unité des soins intensifs.

INTRODUCTION

Acinetobacter spp., in particular *Acinetobacter baumannii* (*A. baumannii*), are opportunistic pathogens frequently involved in nosocomial infections. These occur mostly in intensivecare units (ICUs). These infections can range from urinary tract infections (UTI) to pneumonia and septicemia (1). The ability of these bacteria to survive for long periods on dry

inanimate surfaces as well as their ability to persist on human skin can potentiate the risk of cross-contamination in hospital settings resulting in endemic and/or epidemic outbreaks of infection (2,3). This could result in secondary morbidity particularly in patients with serious underlying diseases, but whether these infections have an attributable mortality, is controversial (4).

Isolates of *A. baumannii* are well known for their antibiotic resistance and multidrug-resistant (MDR) strainshave emerged globally (5). Carbapenems are often considered the antibiotics of last choice for treating infections caused by *A. baumannii*. Unfortunately, carbapenem-resistant *A. baumannii*(CRAB) has become a worldwide issue (6). Moreover, these isolates are often MDR, which constitutes a great challenge to the treating physician, who finds himself facing an untreatable organism.

In spite of the extreme difficulty recorded in controlling CRAB in hospital settings, successful trials have been reported previously (7,8). This indicates that the strict implementation of infection control measures, rationale use of antimicrobials according to a sound policy, regular antimicrobial resistance surveillances, as well as risk factor assessment, may help control or contain the threat of this challenging organism.

This work aimed to assess the incidence and possible risk factors associated with nosocomial infections caused by imipenem-resistant *A. baumannii* (IRAB) in ICUs of a tertiary care hospital in Egypt.

MATERIALS AND METHODS

Study population and Case definition

A prospective cohort study was conducted in the emergency and the surgical ICUs of Zagazig University Hospitals, a tertiary care hospital in the eastern governorate of Egypt. Patients who had *A. baumannii* infections from the start of January 2014 to the end of December 2015 were included in the study. Only the initial *A. baumannii* isolate from each patient was included. The clinical significance (colonization or infection) of each *A. baumannii* isolate was assessed according to Centre for Disease Control (CDC) criteria (9,10). For patients with an indwelling bladder catheter, UTI was diagnosed with detection of pyuria(10 leukocytes/mm^3), growth of $\geq 10^5$ CFU/ml bacteria (with no more than two species) in urine culture, and the presence of clinical signs of infection (fever 38˚C, leukocytosis, abnormal macroscopic appearance of urine, presence of urinary nitrites). In mechanically ventilated patients, pneumonia was diagnosed by the presence of a new or progressive infiltrate in chest X-ray with the presence of purulent endotracheal aspirates, supported by a growth of $\geq 10^5$ CFU/ml bacteria in a quantitative culture of deep endotracheal aspirate. For non-ventilated patients, the diagnosis of pneumonia was made when patients had a compatible chest X-ray and purulent sputum, with Gram stain and sputum culture yielding a pathogenic microorganism. Surgical site infection (SSI) was diagnosed by the presence of purulent discharge and presence of suggestive clinical signs (incision site pain, tenderness, localized swelling, redness or heat, spontaneous opening of the incision) supported by microbiologic results of specimen analysis. Diagnosis of sepsis was made by the presence of positive blood cultures and sepsis criteria. Patients colonized with *A. baumannii* as well as patients from whom *A. baumannii* isolates had been recovered within 48 h of admission to ICU were excluded. Data were recorded on individual forms for each patient. The form included age, gender, diagnosis, length of hospital stay before ICU admission (if any), length of ICU stay, comorbidity (diabetes mellitus, renal insufficiency, dialysis, hepatic failure, malignancy, immunosuppression, neutropenia, chronic lung disease, malnutrition and anoxic encephalopathy), emergent surgical operations, ventilator support, physical examination findings, hematological and biochemical test results, antibiotics given to the patient, culture and antimicrobial susceptibility test results, and time between admission to ICU and isolation of the first positive *A. baumannii* culture. Carbapenem uptake during 14 days (for at least 24 h) prior to isolation of the *A. baumannii* was considered (11).For all included patients, written or verbal informed consent was obtained from the patients themselves, or their guardians. Patients were assigned as IRAB cases if they had imipenem-resistant *A. baumannii* infections and as ISAB cases if they had imipenem-sensitive *A. baumannii* infections.

Microbiologic examination

This was carried out at the Microbiology and Immunology Department, Faculty of Medicine, Zagazig University.Identification of isolates as *A. baumannii* was performed using API 20NE (Bio-Mérieux, Marcy L´Etoile, France). The minimum inhibitory concentration (MIC) of the identified isolates for imipenem was determined using E-test (Bio-Mérieux, Marcy L´Etoile, France) according to the manufacturer's instructions. Isolateswereassigned as IRAB if theyhad MIC values ≥ 8 µg/ml, while those with MIC values <8 µg/ml were assigned as ISAB (12). In addition, all identified isolates were tested against the following antibiotics; amikacin,

gentamicin, aztreonam, cefipime, ceftazidime, ciprofloxacin, levofloxacin, piperacillin—tazobactam, trimethoprim—sulfamethoxazole, tigecycline and colistin by disc diffusion method. All discs were supplied from Bioanalyse (TibbiMalzemelerSanayiveTicaret Ltd. Sti., Turkey) except tigecycline was from Oxoid, England. Isolates were identified as being MDR if resistance to at least one agent in more than three antimicrobial categories was detected (13).

Statistical analysis

Potential risk factors were analyzed by univariate analysis. Independent Student's t-test, Chi-square test and Fisher's exact tests were used when appropriate to compare proportions. A P value of <0.05 was considered statistically significant.

RESULTS

One hundred and forty-six non-repeated *A. baumannii* were isolated from an equal number of patients during the study period. IRAB was isolated from 11 (7.5%) patients while 135 isolates (92.5%) were ISAB. The isolation frequency of both IRAB and ISAB from different nosocomial infections is presented in **Table 1**. Lower respiratory tract infection (LRTI) and SSI represented the main infections from which IRAB were isolated (36.4% isolation frequency for each), followed by UTI (18.2%) and then blood stream infection (9.1 %). No significant difference was found between IRAB and ISAB regarding the type of infection **(Table 1)**.

TABLE 1: ISOLATION FREQUENCY OF IMIPENEM-RESISTANT *A. BAUMANNII* (IRAB) AND IMIPENEM-SENSITIVE *A. BAUMANNII* (ISAB) FROM DIFFERENT NOSOCOMIAL INFECTIONS

Type of infection	IRAB (n = 11) No. (%)	ISAB (n = 135) No. (%)	Total (n = 146) No. (%)	P
Surgical site infection (SSI)	4 (36.4)	45 (33.3)	49 (33.56)	0.8
Urinary tract infection (UTI)	2 (18.2)	41 (30.4)	43 (29.5)	0.4
Lower respiratory tract infection (LRTI)	4 (36.4)	29 (21.5)	33 (22.6)	0.3
Blood stream infection	1 (9.1)	20 (14.8)	21 (14.4)	0.6

The susceptibility profiles of IRAB and ISAB isolates to the tested antimicrobials in disc diffusion method are presented in **Table 2**. All IRAB isolates were susceptible to colistin, followed by tigecycline (81.8%), while they were all resistant to cefepime. Multidrug resistance was detected in 72.7% of IRAB isolates (8/11).

Univariate analysis of different factors associated with IRAB infection (Table 3) demonstrated that five factors were recognized significant in IRAB infection. These included; hospital stay before ICU admission (RR 3.51, CI 1.0-12.7, P= 0.04), longer ICU stay (21.5±6.1 day with IRAB, compared to 16.1±5.6 day with ISAB, P= 0.005), exposure to emergent surgery (RR 17.5, CI 7.39-41.4, P= 0.000), the presence of central venous catheter (RR 3.26, CI 1.0-10.6, P= 0.04) and previous carbapenem use (RR 4.05, 1.12-14.6 CI, P=0.02).

TABLE 2: ANTIMICROBIAL SUSCEPTIBILITY RATES OF IMIPENEM-RESISTANT *A. BAUMANNII* (IRAB) AND IMIPENEM-SENSITIVE *A. BAUMANNII* (ISAB) ISOLATES TO THE TESTED ANTIMICROBIALS IN DISC DIFFUSION TEST

Antimicrobial	IRAB (n=11) No. (%)	ISAB (n=135) No. (%)	P
Amikacin	2 (18.2)	72 (53.3)	0.24
Gentamycin	1 (9.09)	64 (47.4)	0.01*
Aztreonam	2 (18.2)	78 (57.8)	0.01*
Cefipime	0 (0.0)	17 (12.6)	-------
Ceftazidime	4 (36.4)	87 (64.4)	0.06
Ciprofloxacin	3 (27.3)	92 (68.1)	0.006**
Levofloxacin	6 (54.54)	113 (83.7)	0.16
Piperacillin-tazobactam	5 (45.5)	97 (71.85)	0.06
Trimethoprim-Sulfamethoxazole	2 (18.2)	77 (57)	0.12
Tigecycline	9 (81.8)	127 (94.1)	0.12
Colistin	11 (100)	135 (100)	-------

*significant, **highly significant

TABLE 3: UNIVARIATE ANALYSIS OF RISK FACTORS FOR IMIPENEM-RESISTANT *A.BAUMANNII* (IRAB) INFECTIONS

Risk factors	IRAB (n = 11)	ISAB (n = 135)	RR (95% CI)	P
Mean age in years ±SD	49 ± 11.2	46 ± 10.1		0.4
Gender Males (n=74) Females (n=72)	 6 (8.1) 5 (6.9)	 68 (91.9) 67 (93.1)	 1.17 (0.37-3.66)	 0.8
Presence of comorbidity Yes (n=59) No (n=87)	 5 (8.5) 6 (6.9)	 54 (91.5) 81 (93.1)	 1.2 (0.4-3.8)	0.7
Hospital stay before ICU admission Yes (n=63) No (n=83)	 8 (12.7) 3 (3.6)	 55 (87.3) 80 (96.4)	 3.51 (1.0-12.7)	 0.04*
Mean length of ICU stay in days ± SD	21.5 ± 6.1	16.1 ± 5.6		0.005**
Emergent Surgery Yes (n=45) No (n=101)	 6 (13.3)	 39 (86.7)	 17.5 (7.39-41.4)	0.000**

	5 (5.0)	96 (95.0)		
Total parenteral nutrition				
Yes (n=45)	**6 (13.4)**	**39 (86.6)**	**2.69 (0.87-8.37)**	
No (n=101)	**5 (5.0)**	**96 (95.0)**		**0.1**
Enteral nutrition				
Yes (n=21)	**2 (9.5)**	**19 (90.5)**	**1.32 (0.31-5.7)**	
No (n=125)	**9 (7.2)**	**116 (92.8)**		**0.7**
Endotracheal tube				
Yes (n=43)	**5 (11.6)**	**38 (88.3)**	**2.0 (0.64-6.19)**	
No (n=103)	**6 (5.8)**	**97 (94.1)**		**0.3**
Central venous catheter (CVC)				
Yes (n=51)	**7 (13.7)**	**44 (86.2)**	**3.26 (1.0-10.6)**	
No (95)	**4 (4.2)**	**91 (95.7)**		**0.04***
Urinary catheter				
Yes (n=90)	**9 (10.0)**	**81 (90)**	**2.8 (0.62-12.5)**	
No (n=56)	**2 (3.6)**	**54 (96.4)**		**0.2**
Surgical drain				
Yes (n=13)	**2 (15.4)**	**11 (84.6)**	**2.27 (0.55-9.43)**	
No (n=133)	**9 (6.8)**	**124 (93.2)**		**0.3**
Arterial line				**0.3**
Yes (n=45)	**5 (11.1)**	**40 (88.9)**	**1.87 (0.6-5.81)**	
No (101)	**6 (6.0)**	**95 (94.0)**		
Nasogastric tube				
Yes (n=46)	**5 (10.9)**	**41 (89.1)**	**1.81 (0.58-5.63)**	
No (n=100)	**6 (6.0)**	**94 (94.0)**		**0.3**
Previous carbapenems use				
Yes (n=58)	**8 (13.8)**	**50 (86.2)**	**4.05 (1.12-14.6)**	
No (n=88)	**3 (3.4)**	**85 (96.6)**		**0.02***

RR; Relative risk, CI; Confidence interval,*significant, **highly significant

DISCUSSION

In this work,146 *A.baumannii* were isolated from an equal number of patients during the study period. IRAB was isolated from 11 patients accounting for 7.5% isolation frequency. In USA and Canada, the incidence of imipenem resistance in *Acinetobacter* spp. ranged from 6-8%. Higher levels were recorded in Latin America and Europe (10% and 16%, respectively) (14,15,16). In Asian countries, the prevalence ranged from 2% to 26% (17,18). Marked increase in CRAB incidence was reported in a previous study from South Africa (19).Variable results were reported from Arabian countries, where the incidence of CRAB ranged from 5.4% in Kingdom Saudi Arabia (20) to 37.2% in Kuwait (21) to as high as 58% in Manama (22). In a previous Egyptian study, a very high incidence was recorded in an ICU of a university hospital in Upper Egypt (71.4%) (23). These discrepant results may be contributed to the different study designs where one center evaluation was performed in some

studies (23), whereas, other studies were nation-wide (18).

In our study, the highest isolation frequency of IRAB was from LRTI and SSI (36.4% each), followed by UTI (18.2%) and then blood stream infection (9.1%). A number of previous studies have reported LRTI as the main infection yielding IRAB (11,18,19,24). A similar finding was also reported previously in Egypt (23). This was not unexpected, as previous studies demonstrated that as much as two-thirds of hospitalized patients have their respiratory tract colonized with *A. baumannii* (25) and that infection by MDR *A. baumannii* is strongly correlated to this initial colonization (26), particularly when excessive manipulations are encountered as in ICU environment.

Among the obtained IRAB isolates, 72.7% were found to be MDR being resistant to three or more different classes of antimicrobials. This is supported by a previous study where most of the examined CRAB isolates were found to be resistant to all tested antimicrobials (27). On the other hand, all IRAB isolates were found susceptible to colistin and 81.8% were susceptible to tigecycline. This comes in accordance with what was reported in South Africa concerning the susceptibility pattern of CRAB (19).

Accumulating evidence suggested that *A. baumannii* isolates are difficult to eradicate in hospital settings as they rapidly adapt to the hospital environment and become endemic with a remarkable ability to contaminate hospital equipment and to be transmitted via contact and even airborne methods. This constitutes a great threat to patients as well as to their physicians particularly with mostly an untreatable organism such as IRAB (28). This makes the study of the factors that could be associated with the acquisition of such an organism of paramount importance as it could help control its spread.

Previous studies had assigned different risk factors to be significantly associated with IRAB acquisition. These included; prolonged hospital stay, prolonged ICU stay, exposure to and duration of different invasive procedures, exposure to emergent surgical procedure, the presence in a unit accommodating patients infected with IRAB and previous exposure to broad-spectrum antimicrobials particularly carbapenems (11,18,24). Our study revealed that longer duration of ICU stay (21.5±6.1 with IRAB compared to 16.1±5.6 with ISAB infection, P=0.005), hospital stay before ICU admission (P=0.04), exposure to emergent surgery (P=0.000) and exposure to CVC (P= 0.04) were significantly associated with IRAB acquisition. Our results are supported by previous studies that demonstrated the same results (11,29,30). Prior exposure to antimicrobials has been recognized as being, by far, the most important risk factor for developing of multi-drug resistance in *A. baumannii* (31). This was evident with IRAB where exposure to broad-spectrum antibiotics particularly third generation cephalosporins (32), fluoroquinolones (33) and carbapenems (11) were all significant risk factors for IRAB acquisition. Our result comes to confirm these observations where previous carbapenem use was significantly associated with IRAB infection (P=0.02). This highlights the importance of implementing strict antimicrobial policies in health care facilities. Further studies that assess the level of hygiene and the compliance to infection control measures as other risk factors are warranted.

CONCLUSION

In conclusion, the spread of antibiotic resistance among clinically important Gram-negative bacilli seems to be an unstoppable problem. This study demonstrated that the incidence of IRAB in ICUs of our hospital is relatively high. Longer ICU stay, hospital stay prior to ICU admission, usage of CVC, exposure to emergent surgery and prior use of carbapenems were all significant risk factors for IRAB infection. Restricted use of carbapenems in the ICUs of our hospital should be considered. Implementation of infection control measures may help to control the danger of this challenging organism.

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