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Research Article

Ventilator associated pneumonia caused by extensive-drug resistant *Acinetobacter* species: Colistin is the remaining choice

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KEYWORDS

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Abstract *Introduction:* Ventilator-associated pneumonia [VAP] is associated with increased morbidity and mortality especially when caused by extensive drug resistant [XDR] pathogens. Till now, little is known regarding the exact pathogenesis of XDR Acinetobacter baumannii [XDR-AB] infection. The aim of the present study was to identify prevalence and risk factors for VAP caused by XDR-AB in our intensive care unit, and to test the susceptibility pattern of tigecycline, carbapenems, and Colistin among the isolates.

Methods: A prospective cohort study was conducted to enroll patients who developed VAP over 18-month period. All possible risk factors were documented as well as patient outcome. Susceptibility testing for the isolates was performed using inhibitory concentrations [MICs] determined by Epsilometer tests (E-tests) to Carbapenems, Tigecycline, and Colistin.

Results: Among 544 consecutive patients admitted to our ICU during 18 months, Forty-seven patients developed VAP. The prevalence of XDR-AB was 63.8% (30 patients). No specific factor was associated with increase of the risk of acquisition of AB-VAP in our cohort either by univariate or by multivariate analysis. Carbapenems showed poor activity against all isolates [MIC range 10–128 mg/L]. Tigecycline showed good activity against only 15 isolates [MIC range 0.25–2 mg/L]. Colistin demonstrated potent in vitro activity against all isolates of AB [MIC range 0.016–1 mg/L].

Conclusions: XDR AB-VAP is endemic in our ICU without a definite factor associated with increased risk of infection. Given that almost half of the strains are also resistant to tigecycline, colistin appears to be an appropriate first-line antimicrobial drug in critically ill patients developing VAP based on invitro results.

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1. Introduction

Ventilator-associated pneumonia [VAP] is associated with prolonged mechanical ventilation, increased intensive care unit [ICU] length of stay, and substantially increased mortality [1]. Furthermore, the risk of mortality associated with VAP increased when VAP is caused by one of multidrug-resistant (MDR) pathogens [2].

Acinetobacter species [*Acinetobacter* spp.] is a non-fermentative, aerobic, gram-negative coccobacilli, non-lactose-fermenting and oxidase negative microorganism. Multiple mechanisms have been implicated in the resistance of *Acinetobacter* spp. and it is considered one of the most virulent MDR pathogens. *Acinetobacter* has been isolated in food and inanimate objects and may colonize humans and survive on dry or moist environment [3–5].

Carbapenems were considered for many years the mainstay of therapy of VAP caused by *Acinetobacter* spp. [6]. However, recent outbreaks of carbapenem-resistant Acinetobacter infection have raised the interest in colistin, an 'old' antibiotics introduced in 1959 and was abandoned in the 1970s after introduction of aminoglycosides [7,8]. However, the ability of colistin to penetrate the lung tissue is a debatable issue and moreover, it demonstrated dose-dependent neurotoxicity and nephrotoxicity [9]. On the other hand, tigecycline is a newer relatively safe broad spectrum tetracycline and displays inhibitory activity against *Acinetobacter* spp. [10].

We previously reported the prevalence of extensive drug resistant gram negative bacilli in our institution [11]; in this study, we sought to conduct a prospective cohort study to identify primarily the prevalence of VAP caused by extensive drug resistant [XDR] *Acinetobacter* spp. and secondarily to test the susceptibility pattern of tigecycline, carbapenems, and colistin against VAP caused by *Acinetobacter* spp. as well as the possible risk factors.

2. Methods

A cross sectional observational study was performed in Cairo University hospitals surgical ICU admitting trauma and emergency postoperative patients over 18-month period. All consecutive patients who were clinically suspected of having developed VAP after 48 h of mechanical ventilation [MV] in our ICU were included.

Patients were assumed to have VAP when new, persistent infiltrate was seen on chest X-rays and at least two of the following were observed: a body temperature below 36 °C or above 38 °C; a white blood cell count lower than 4000/mm^3 or higher than 11,000/mm^3; and macroscopically purulent tracheal aspirate [12]. Tracheal aspirate was classified as purulent or nonpurulent after visual inspection by the clinical treatment team.

Once VAP was suspected, tracheal aspirate for quantitative culture was obtained [Day 0], before antimicrobial treatment was started (for patients not on current antimicrobial therapy). Blood cultures were obtained for patients with suspected bacteremia.

2.1. Bacteriological analysis

Tracheobronchial secretions were aseptically collected, following specimen collection guidelines, after tracheal instillation of 10 ml saline. The specimens were sent to the laboratory and cultivated within 1 h of collection. A dilution of the tracheal aspirate was prepared and inoculated with a calibrated loop on chocolate, blood and MacConkey agar. After overnight incubation in appropriate conditions, the plates were interpreted according to quantification of growth [13]. Qualitative cultures were considered positive when the growth of 10^5 colony-forming units cfu/ml or more is observed.

All non-fermentative, oxidase-negative, catalase-positive, strictly aerobic, motionless, Gram-negative coccobacilli were considered belonging to Acinetobacter genus. [Phenotype identification was completed with API 20 NEsystem, Biomérieux, France].

Susceptibility testing was performed using inhibitory concentrations [MICs] determined by Epsilometer tests [E-tests; AB.Biodisk, Sweden] for the following antibiotics: tigecycline, colistin, and Imipenem.

Extensive drug resistance was defined as resistance to all classes of antimicrobial agents except for one or two classes. Modifications to the empirical therapy were based on the results of tracheal aspirate cultures and blood cultures.

The severity of presenting illness was assessed by an Acute Physiology and Chronic Health Evaluation II [APACHE II] score calculated within 24 h of ICU admission. Other data collection included smoking status; history of congestive heart failure; history of malignancy; immunosuppression; albumin level; use of H2 antagonists; proton pump inhibitor use; corticosteroid use; and the need for dialysis, cause of ICU admission, reoperation, use of blood product, central venous catheterization, urinary tract catheterization duration of mechanical ventilation, and duration of stay in the ICU before VAP.

3. Statistical analysis

To assess risk factor status, two groups of patients were considered. AB-VAP: patients who developed VAP with *Acinetobacter* spp., and Non AB-VAP: patients who developed VAP with other pathogens. All the pre-operative variables and post-operative events were compared between the two groups using univariate and multivariate analyses. Student's *t*-test or the Mann–Whitney *U*-test was used for quantitative data and Pearson's chi-square or Fisher's exact test for categorical data. Differences were considered statistically significant when the p value is <0.2. Data were shown as mean ± SD or as median and range or as percentages. All variables significant in univariate analysis were analyzed by a multiple regression logistic model. The forward stepwise logistic strategy was applied, and variables were included in the model if the log likelihood ratio chi-square test was significant. SPSS version 15.0 for Windows [SPSS, Inc., Chicago, IL, USA] was used for statistical analyses.

4. Results

Among 544 consecutive patients admitted to our ICU during 18 months, total number of mechanically ventilated patients was 243. Forty-seven patients [19.3%] developed VAP. The prevalence of *Acinetobacter* spp. was 30 [63.8%].

Demographic and baseline data were comparable among both groups [Table 1]. There is no specific factor associated

Table 1 Demographic data. Data are described as mean ± SD, median (quartiles).

	AB-VAP patients (n = 30)	Non-AB-VAP patients (17)	P value
Age (years)	39 ± 22	43 ± 20	0.5
Gender (male/female)	19/11	12/5	0.7
APACHE II	18(15–22)	17(15–22)	0.8
SOFA on admission	6(3–8)	5(2–8)	0.5

Table 2 Risk factors for acquisition of VAP. Data are presented as mean ± standard deviation and number (frequency).

	AB-VAP patients (n = 30)	Non-AB-VAP patients (n = 17)	P value
Diabetes	6(20%)	5(29.4%)	0.4
Blood transfusion {number of patients (%)}	10(33.3%)	5(29.4%)	0.7
Sepsis	7(23.3%)	7(41.2%)	0.2
Serum Albumin (gm/dl)	2.5(2.2–3.1)	2.3(2.3–2.6)	0.6
Previous antimicrobial therapy	12(40.0%)	8(47.1%)	0.63
Previous mechanical ventilation	6(20.7%)	5(29.4%)	0.5
Duration of ventilation before infection	6 ± 4	4 ± 4	0.1
TPN	3(10%)	1(5.9%)	0.3
H2 blockers	26(86.7%)	15(88.2%)	0.87
Proton pump inhibitors	4(13.3%)	3(17.6%)	1.0
Steroids	15(50%)	7(41%)	0.6
Patients with previously inserted central line	27(90%)	13(76.5%)	0.3
Previous surgery	11(36.7%)	9(52.9%)	0.27
Patients with history of repeated operation	7(23.3%)	4(23.5%)	0.9
Hemodialysis	6(20%)	1(5.9%)	0.24

with the increase of the risk of acquisition of AB-VAP in our cohort either by univariate or by multivariate analysis [Tables 2 and 3]. Length of hospital stay was 9 ± 4 days in the AB-VAP versus 7 ± 4 days in the non-AB-VAP group [P = 0.1]. Overall the in-hospital mortality was 25 [53.2%]. Moreover, the incidence of mortality for patients in AB-VAP group was 16 [53.3%] and this was not different from mortality in the non-AB-VAP group of 9 [52.9%] [p = 0.75] [Table 4].

Carbapenems showed poor activity against all *Acinetobacter* spp. [MIC range 10–128 mg/L]. Tigecycline showed good activity against 15 isolates [MIC range 0.25–2 mg/L], moderate activity against 10 isolates [MIC range 2.5–4 mg/L], and poor activity against 5 isolates of *Acinetobacter* spp. [MIC range 10–12 mg/L].

Colistin demonstrated potent in vitro activity against all isolates of *Acinetobacter* spp. [MIC range 0.016–1 mg/L].

Table 3 Multivariate analysis factor predicting AB-VAP.

		Odds ratio	95% CI	P value
APACHE II	< 20	1	(0.2–4)	0.09
	> 20	1.08	(0.2–4)	0.09
Dialysis	Yes	1	(0.6–3.7)	0.4
	No	0.8	(0.6–3.7)	0.4
Diabetes	Yes	1	(0.4–12)	0.4
	No	2.1	(0.4–12)	0.4
Transfusion	Yes	1	(0.2–5)	0.9
	No	0.9	(0.2–5)	0.9
TPN	Yes	1	(0.8–14)	0.9
	No	1.5	(0.8–14)	0.9
Reoperation	Yes	1	(0.75–5)	0.76
	No	1.2	(0.75–5)	0.76

Table 4 Patients outcome. Data are presented as median (IQR), and number (frequency).

	AB-VAP patients (n = 30)	Non-AB-VAP patients (n = 17)	P value
Ventilation days	7(6–11)	11(7–16)	0.2
Length of ICU stay	15(11–34)	20(15–40)	0.2
Mortality	16(53.3%)	9(52.9%)	0.75

5. Discussion

The main finding of the study described herein, was that the prevalence of ventilator associated pneumonia induced by XDR-resistance *Acinetobacter* spp. was high in our critical care unit approaching 2/3 of all isolated species.

Consistent with our finding, several authors have shown that *Acinetobacter* spp. is the most prevalent multidrug resistant pathogens in patients with VAP [14–17]. A previous study in our unit addressed the prevalence of extensive drug resistant gram negative bacilli; however, the antimicrobial resistance to carbapenems in *Acinetobacter* spp. was lower than that in our findings and this is most probably due to increased use of carbapenems in our unit last year [11].

Previous use of antibiotics, central venous catheter, urinary catheter, hemodialysis, nasogastric tube, trauma, malignancy, previous septic shock, and the duration of hospital stay was previously reported to be independent risk factors for *Acinetobacter* infection [18–20]. In the present study we did not find any factor associated with increased risk of VAP caused by *Acinetobacter* spp. Furthermore, VAP caused by *Acinetobacter* was not associated with increased risk of mortality. One way to explain this result was that, most of patients developed VAP in our study were infected with MDR pathogens and we believe that most of the aforementioned factors are independent risks for multidrug resistant in general and not for specific pathogens.

In the study described herein, 100% of isolated *Acinetobacter* spp. were resistant to carbapenems. In line with our results, several studies have reported that carbapenem resistance of

Acinetobacter spp. isolated from patient suffering from VAP ranged from 55% to 81% [21,22].

On the other hand, colistin demonstrated potent in vitro activity against all *Acinetobacter* isolates in our cohort. Similar to this finding, several authors have shown that colistin maintained significant in vitro activity against *Acinetobacter* spp. and the colistin-resistant *Acinetobacter* isolates were recovered from patients who had been pre treated with Colistin [23–25]. Colistin was not available at our institution till few months before the beginning of our study; even after it was available it was not prescribed except for patients with cultures susceptible only for it. Thus, colistin in vitro activity is well preserved.

In the current study, we can consider that the activity of tigecycline was inadequate against XDR-*Acinetobacter* spp. given that, only 50% of the isolated carbapenem resistant *Acinetobacter* spp. showed good susceptibility to this agent. Consistent with our finding, inadequate activity of tigecycline against carbapenem-resistant *Acinetobacter* spp. has been demonstrated in several studies [26,27]. However, other studies reported adequate activity which is defined as 90% susceptibility of the total number of *Acinetobacter* isolates to tigecycline [28,29]. Tigecycline is rarely used in our hospital that makes the fact of having resistant strains a matter of interest. The mechanism of carbapenem resistance is quite different from resistance to tigecycline making the concept of cross resistance between the two agents unlikely to occur. A possible explanation is that clinical strains of *Acinetobacter* spp. under study possess several mechanisms (possibly interrelated) that enable them to develop resistance to various antimicrobial drugs.

Several debatable issues have been recently raised regarding the use of tigecycline for treatment of *Acinetobacter* spp. First of all, there is no universally accepted interpretation of MIC breakpoint. The Food and Drug Administration [FDA]-approved MIC breakpoints for susceptibility and resistance are $\leqslant -2$ and $\geqslant -8$ mg/L, respectively, whereas the corresponding European Committee on Antimicrobial Susceptibility Testing EUCAST breakpoints are $\leqslant -1$ and $\geqslant 2$ mg/L respectively [30]. Secondly, tigecycline has been approved for the treatment of complicated intra-abdominal infections, complicated skin and soft tissue infections, and its role in VAP is questionable and more recently, the FDA determined that tigecycline resulted in increased mortality risk, especially in hospital-acquired pneumonia, compared with other antibiotics [31,32].

The increasing pattern of antimicrobial resistance among our patients, as well as patients in other parts of the world, including tigecycline is an alarming threat that made colistin to be the last effective drug in VAP. This increased pattern of antimicrobial resistance needs aggressive implementation of infection control measures as well as antibiotic stewardship to avoid reaching a pre-antibiotic Era.

6. Conclusion

Our study has shown that extensive drug resistant *Acinetobacter* spp. VAP is endemic in our ICU without a definite factor associated with increased risk of infection. Given that almost half of the strains are also resistant to tigecycline, colistin appears to be an appropriate first-line antimicrobial drug in critically ill patients developing VAP. Our results are based only on invitro findings and need to be confirmed in the clinical setting in future studies.

7. Conflict of interests

The authors declare that there are no conflict of interests.

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