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ORIGINAL ARTICLE

Clinical Manifestations and Risk Factors Influencing Eradication of Extensive Multidrug-resistant *Acinetobacter baumannii* from the Respiratory Tract

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Purpose: Extensive multidrug-resistant *Acinetobacter baumannii* (XDRAB) has increasingly emerged as one of the most difficult bacteria to treat in the healthcare setting. In this study, we intended to evaluate the factors affecting eradicating XDRAB from the respiratory tract, clinical manifestations, and treatment outcomes.

Methods: We retrospectively reviewed the medical records of patients who had XDRAB isolated from the respiratory tract in our medical center from January 1, 2012 to February 28, 2013.

Results: In total, 87 patients were included in this study. Eradication was achieved in 69 patients (79.3%). The factors that negatively affect eradication of XDRAB by aerosolized colistin therapy for two weeks included: (1) receiving noninvasive mechanical ventilation; (2) being infected/colonized during residency in long-term care facilities; and (3) receiving combination therapy with intravenous tigecycline. The 30-day mortality in patients with versus without eradication was 26.1% versus 55.6%, respectively ($p < 0.05$), and the in-hospital mortality rate (40.6% vs. 66.7%, $p < 0.05$), were significantly lower in the eradication group than the noneradication group. Steroid use was associated with significantly higher overall mortality (32% vs. 61%, $p < 0.05$) in both high and low dose groups.

Conclusion: XDRAB eradication from the respiratory tract is associated with improved clinical outcomes. Clinicians should be aware of the possible negative effect of combination therapy with aerosolized colistin and tigecycline for eradicating XDRAB.

1. Introduction

Acinetobacter baumannii has emerged as an important cause of nosocomial infections and is associated with high mortality.[1] Many nosocomial strains are extensively multidrug-resistant, and have limited antibiotic choices clinically, thus extensive multidrug-resistant *A. baumannii* (XDRAB) has become an important issue for infection control.

Bacterial colonization of the airway is a major risk factor for developing nosocomial pneumonia.[2] Eradicating XDRAB from the respiratory tract may prevent development of nosocomial pneumonia, and have successful treatment, resulting in improving mortality and clinical outcome. In the literature, few reports exist that describe the efficacy of aerosolized colistin for eradicating XDRAB from the respiratory tract. Therefore in this study we evaluated the outcomes and risk factors of patients with XDRAB infections and colonization in our medical center.

2. Methods

This retrospective study was conducted at Wan Fang Medical Center, a teaching hospital of Taipei Medical University. We reviewed the medical records of patients with XDRAB isolated from the respiratory tract between January 1, 2012 and February 28, 2013.

2.1. Data collection and definitions

Clinical data or laboratory parameters were collected using a standard form, in which definitions in this study were predefined.

Conflicts of interest: None.

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We collected information on demographic characteristics, underlying conditions, acute physiology, chronic health evaluation II (APACHE II) score within 48 hours, the status of XDRAB isolation and associated antibiotic use, as well as clinical outcomes of those patients.

2.2. Microbiological testing

We performed antimicrobial susceptibility tests using both the disk diffusion method and the Becton Dickinson Phoenix Automated Microbiology System (Franklin Lakes, New Jersey, USA). The breakpoints were those defined by the Clinical and Laboratory Standards Institute.[3] According to the European breakpoints published by the European Committee on Antimicrobial Susceptibility Testing for *Acinetobacter* species, A. *baumannii* is defined as susceptible to colistin if its minimal inhibitory concentration (MIC) is less than or equal to 2 mg/L, and defined as resistant to colistin if its MIC is greater than 2 mg/L.[4]. XDRAB is defined as *A. baumannii* which is sensitive only to one or two categories of the following antibiotics: antipseudomonas penicillin + beta lactamase inhibitors, antipseudomonas carbapenems, antipseudomonas fluoroquinolones, third or fourth generation cephalosporins, trimethoprim/sulfamethoxazole, polymyxins and tetracyclines see also (www.eucast.org/fileadmin/src/media/PDFs/EUCAST).[5]

2.3. Inclusion and exclusion criteria

We included only adult patients who were older than 20 years of age, and who had at least one set of monomicrobial growth of XDRAB isolated from the respiratory tract secretion, and who had available subsequent respiratory secretion culture results collected every 3–7 days until 14 days after the index day. We excluded the patients without any available data on subsequent cultures of the respiratory secretion within 14 days after the index day.

2.4. Definitions of outcomes

In this study, eradication was defined as achieved if no XDRAB was recovered from subsequent cultures in 14 days after initiating aerosolized colistin therapy. Persistent isolation of XDRAB was considered if the XDRAB continued to be isolated during colistin aerosol therapy or recurrent infection of XDRAB within 14 days after complete therapy.

We also classified clinical outcomes in this study as being: (1) cured (having resolution of presenting symptoms and signs of infection by the end of treatment); (2) improved (having partial resolution of presenting symptoms and signs or infection), and (3) failed (having no improvement, persistence or worsening of presenting symptoms and/or signs of XDRAB infection.) The 30-day mortality was defined as crude mortality at 30 days after the index day.

2.5. Statistical analysis

We compared categorical and continuous variables using the χ^2 or Fisher exact test and the independent *t* test, respectively. A *p* value of less than 0.05 was considered significant and the two-tailed test was adopted for all probabilities. All significant variables of univariate analysis were put into multivariate logistic regression analysis to calculate odds ratio. All statistical analysis was performed using the Statistical Package for Social Science version 21 (SPSS Inc., Chicago, IL, USA).

3. Results

During the study period, XDRAB was isolated from total 147 patients. Of those patients, 27 were excluded because *A. baumannii* (AB) isolates cultured from their respiratory secretions did not fulfill the criteria of XDRAB. Subsequent sputum cultures were not available in 33 patients. Thus, we included only 87 patients in analysis.

Table 1 describes the demographic data, clinical features, comorbidities, microbiology of XDRAB isolates, and the clinical outcomes. All the patients received aerosolized colistin as specific treatment. Eradication of XDRAB was achieved in 69/87 patients (79.3%). Table 2 shows multivariate analysis of factors associated with failure to eradication of XDRAB. We found three significant influential factors related with failure to eradicate XDRAB. Table 3 lists multivariate analysis of factors associated with increased 30-day mortality.

4. Discussion

XDRAB is one of the most notorious and challenging nosocomial pathogens for healthcare institutions worldwide. The organism's ability to survive and to persist for long periods under various environmental conditions poses great challenges for hospital infection control.[6,7] This bacteria's ability to be resistant to various antibiotics in a relatively short time was alarming,[8–11] because of the limited choice of antibiotics for treating XDRAB available to clinicians.

The findings in our study (Table 2) revealed that eradication of XDRAB was less likely to be achieved in patients who were

Table 1 Demographic data, clinical features, underlying comorbidities, and clinical outcomes in noneradicated and eradicated patients

Characteristics of patients	Noneradicated ($N = 18$) *n* (%)	Eradicated ($N = 69$) *n* (%)
Male	13 (72)	46 (67)
Age (*n* ± SD years)	80.67 ± 12.1	80.3 ± 10.5
Underlying comorbidity		
Lung disease	6 (33)	19 (28)
Heart disease	6 (33)	27 (29)
Neurological disease	13 (72)	42 (67)
Malignancy	3 (17)	10 (15)
Diabetes mellitus	8 (44)	32 (46)
Chronic renal insufficiency	3 (17)	15 (22)
APACHEII score	17.22 (SD ± 8.8)	18.03 (SD ± 6.8)
Previous steroid use	9 (50)	27 (39.1)
Chemotherapy	0 (0)	2 (2.9)
NIV use*	8 (44.4)	14 (20.3)
Invasive ventilator use	3 (16.7)	26 (37.7)
Origin of isolates		
Healthcare associated*	8 (44)	13(19)
Nosocomial (intensive care unit)	5 (28)	36 (52)
Nosocomial (ward)	6 (33)	20 (29)
With concomitant tigecycline use*	12 (67)	27 (39)
Outcomes		
Thirty-day mortality*	10 (56)	18 (26)
In-hospital mortality*	12 (67)	28 (41)
Recurrent colonization	6 (33)	21 (30)
Development of colistin resistant†	5 (28)	0 (0)
Clinical outcomes		
Cured†	0 (0)	18 (26)
Improved†	5 (28)	26 (38)
Failed	13 (72)	25 (36)
Duration of hospital stay (*n* ± SD days)	51.5 ± 23.51	46 ± 26.43

Eradication was defined as achieved if no XDRAB was recovered from subsequent cultures in 14 days after initiating aerosolized colistin therapy.
*$p < 0.05$.
†$p < 0.001$.
APACHEII = Acute Physiology and Chronic Health Evaluation score; NIV = noninvasive mechanical ventilation; SD = standard deviation.

Table 2 Multivariate analysis of factors associated with failure to eradication of XDRAB

Influencing factors	Noneradicated ($N = 18$) n (%)	Eradicated ($N = 69$) n (%)	Odds ratio	(95% CI)
Use of noninvasive mechanical ventilation*	8 (44)	14 (20)	0.247	0.073–0.836
Healthcare associated origin*	8 (44)	13 (19)	0.273	0.082–0.911
Use of tigecycline*	12 (67)	27 (39)	0.321	0.091–0.958

*$p < 0.05$.
CI = confidence interval; OR = odds ratio; XDRAB = extensive multidrug-resistant *Acinetobacter baumannii*.

receiving combination inhalation colistin and tigecycline therapy (67% vs. 39%, OR: 0.321; 95% CI: 0.09–0.958, $p < 0.05$). Tigecycline and colistin are currently the two most commonly used antibiotics in treating XDRAB.[5,6] Tigecycline and colistin act on bacteria with different mechanisms of action. Tigecycline[11] inhibits protein synthesis, whereas colistin acts on the outer cell membrane of bacteria. Also, tigecycline[11] is bacteriostatic in nature, whereas colistin is bactericidal. Therefore, a potential phenomenon exists for either antagonism or synergy. Several investigators have examined the activity of tigecycline in combination with different drugs against *A. baumannii in vitro* which showed inconsistent results.[12–16] Schafer et al[17] have evaluated tigecycline in combination with nebulized or intravenous colistin and/or carbapenems for the treatment of ventilator-associated pneumonia (VAP), and/or bacteremia caused by XDRAB. Clinical cure has been achieved in 9/9 patients (100%) treated with tigecycline combined with imipenem, in 4/7 patients (57%) treated with tigecycline combined with colistin, and in 3/4 patients (75%) treated with a combination of the three drugs.[17] In that study, the lowest clinical success rate has been seen in patients who received tigecycline and colistin combination therapy.

The concentration of tigecycline in epithelial lining fluid and respiratory secretions after intravenous infusion of standard doses of tigecycline (50 mg every 12 hours) are very low.[18] Albur et al[19] found that at low concentrations of tigecycline and colistin, both antibiotics show an antagonistic effect when these drugs have been used in combination against New Delhi metallo-betalactamase 1-producing Enterobacteriaceae. Similar antagonism existed between colistin and tigeclycine at low concentrations as possible when these combined antibiotics were used for XDRAB respiratory tract infection or colonization. Thus, failure to eradicate XDRAB is found in combinations of colistin and tigecycline therapy.

As shown in Table 2, the use of noninvasive mechanical ventilation (NIV) was also significantly associated with failure to eradicate XDRAB (44% vs. 20%, OR: 0.247; 95% CI: 0.037–0.836, $p < 0.05$). Aspiration is one of common complications of noninvasive mechanical ventilation.[20] Recurrent aspiration of oropharygeal secretions in these patients who are NIV-dependent may be responsible for failure to eradication.

Table 3 Multivariate analysis of factors associated with increased 30-day mortality

Influencing factors	Surviving patients ($N = 69$) n (%)	30-day mortality ($N = 28$) n (%)	Odds ratio	95% CI
Structural lung disease	10 (17)	15 (54)	3.026	0.99–9.27
History of previous steroid use*	19 (32)	17 (61)	5.784	1.96–17.1
Eradication of pathogen*	51 (86)	18 (64)	0.230	0.66–0.801
Acute kidney injury*	10 (17)	10 (36)	4.182	1.24–14.09

*$p < 0.05$.
CI = confidence interval.

Eradication of XDRAB is more difficult in patients who are residents in nursing homes. XDRAB can colonize multiple body sites and can also survive in the environment.[8,21] Nursing home residents from whom XDRAB was isolated from respiratory secretions may be colonized with XDRAB on other body parts. This may result in failure to eradicate XDRAB.

As shown in Table 3, we found that in our present study, 30-day mortality (32% vs. 61%, $p < 0.05$) was significantly higher in patients where XDRAB was not eradicated. Bacterial colonization of the airway is a risk for developing nosocomial pneumonia. Eradicating XDRAB colonization from the respiratory tract can decrease development of nosocomial pneumonia, resulting in improving mortality and clinical outcome.

We also found that steroid use was significantly associated with increased both the 30-day mortality ($p < 0.05$) and in hospital mortality ($p < 0.01$), irrespective of microbiology eradication status in both group (data not shown). Steroid use has been associated with increasing mortality in XDRAB infected patients in a previous study.[21,22] In our study (Table 3), steroid was routinely used for patients with chronic obstructive pulmonary disease, which was also found to be significantly associated with increased 30-day mortality in our study (OR: 5.784, 95% CI: 1.957–17.1, $p < 0.05$). Long-term steroid use, ≥20 mg/day prednisolone or equivalent corticosteroid for more than 7 days within 4 weeks was associated with increased mortality in patients with XDRAB infection or colonization.

4.1. Limitations of the study

The readers are warned against over-interpreting our study results because this study has three major limitations. First, it is a retrospective study using a relatively small number of patients. Second, we had excluded the patients who had no subsequent sputum cultures which might have impacted on outcomes of the study group. Third, we did not categorize patients with XDRAB pneumonia as opposed to colonization, which might cause bias in patients' outcomes.

4.2. Study summary

In summary, XDRAB eradication from the respiratory tract is associated with improved clinical outcomes. Clinicians should be aware of the possible negative effect of combination therapy with aerosolized colistin and tigecycline especially with additional steroid therapy for eradicating XDRAB.

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