Observational Study

Medicine®

OPEN

Treatment outcomes of patients with non-bacteremic pneumonia caused by extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex isolates

Is there any benefit of adding tigecycline to aerosolized colistimethate sodium?

Shio-Shin Jean, MD[a,b,*], Tai-Chin Hsieh, MD[c,d], Wen-Sen Lee, MD[d,e], Po-Ren Hsueh, MD[f], Chin-Wan Hsu, MD[a,b], Carlos Lam, MD[a,b]

Abstract

Few therapeutic options exist for various infections caused by extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* (XDR-Acb) complex isolates, including pneumonia. This study investigated the clinical efficacy between aerosolized colistimethate sodium (AS-CMS, 2 million units thrice a day) treatment alone or in combination with standard-dose tigecycline (TGC) in patients with non-bacteremic pneumonia due to XDR-Acb, and explored the factors influencing patients' 30-day mortality.

A 1:1 case (n = 106; receiving TGC plus AS-CMS) control (receiving AS-CMS alone with matching scores) observational study was conducted among adult patients with non-bacteremic XDR-Acb complex pneumonia in a Taiwanese medical center from January 2014 through December 2016. The clinically relevant data were retrospectively recorded. The primary endpoint was 30-day case fatality. Secondary endpoints investigated that if the co-morbidities, XDR-*A. baumannii* as a pneumonic pathogen, therapy-related factors, or airway colonization with colistin-resistant Acb negatively influenced the 14-day clinical condition of enrolled patients.

A higher 30-day mortality rate was noted among the group receiving combination therapy (34.0% vs 22.6%; $P = .17$). The ≥7-day AS-CMS therapy successfully eradicated > 90% of airway XDR-Acb isolates. Nevertheless, follow-up sputum specimens from 10 (6.4% [10/156]) patients were colonized with colistin-resistant Acb isolates. After the conditional factors were adjusted by multivariate logistic analysis, the only factor independently predicting the 30-day case-fatality was the failure of treating XDR-Acb pneumonia at 14 days (adjusted odds ratio [aOR] = 38.2; 95% confidence interval [CI] = 9.96–142.29; $P < .001$). Cox proportional regression analysis found that chronic obstructive pulmonary disease (COPD) (adjusted hazard ratio [aHR] = 2.08; 95% CI = 1.05–4.10; $P = .035$), chronic renal failure (aHR = 3.00; 95% CI = 1.52–5.90; $P = .002$), non-invasive ventilation use (aHR = 2.68; 95% CI = 1.37–5.25; $P = .004$), and lack of TGC therapy (aHR = 0.52; 95% CI = 0.27–1.00; $P = .049$) adversely influenced the 14-day clinical outcomes. Conversely, the emergence of colistin-resistant Acb isolates in the follow-up sputum samples was not statistically significantly associated with curing or improving XDR-Acb pneumonia.

In conclusion, aggressive pulmonary hygiene care, the addition of TGC, and corticosteroid dose tapering were beneficial in improving the 14-day patients' outcomes.

Abbreviations: aHR = adjusted hazard ratio, aOR= adjusted odds ratio, APACHE = Acute Physiology and Chronic Health Evaluation, AS = aerosolized, CCI = Charlson co-morbidity index, CI = confidence interval, CMS = colistimethate sodium, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, GNB = Gram-negative bacteria, ICU = intensive care unit, IV =

Editor: Mehmet Bakir.

S-SJ and T-CH are co-first authors.

This study was supported by the Department of Medical Education and Research, Wan Fang hospital.

The authors report no conflicts of interest.

[a] Department of Emergency, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [b] Department of Emergency Medicine, Departments of Emergency and Intensive Care Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, [c] Division of General Medicine and Infectious disease, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, [d] Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, [e] Division of Infectious Disease, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, [f] Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan.

[*] Correspondence: Shio-Shin Jean, Department of Emergency, School of Medicine, College of Medicine, Taipei Medical University, No. 250, Wu-Xing Street, Xin-Yi District, Taipei 11031, Taiwan (e-mail: jeanshioshin168@gmail.com).

Medicine (2018) 97:39(e12278)

Received: 6 June 2018 / Accepted: 15 August 2018

http://dx.doi.org/10.1097/MD.0000000000012278

intravenous, LPF = low power field, MDR = multidrug-resistant, MIC = minimum inhibitory concentration, NIV = non-invasive ventilation, SIRS = systemic inflammatory response syndrome, TGC = tigecycline, VAP = ventilator-associated pneumonia, XDR-Acb complex = extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii*.

Keywords: *acinetobacter calcoaceticus-acinetobacter baumannii* complex, aerosolized colistimethate sodium, combination therapy, pneumonia, tigecycline

1. Introduction

In the last decade, extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex isolates (XDR-Acb complex, mainly *A. baumannii*) have emerged as important nosocomial pathogens globally.[1–3] In 2017, the World Health Organization ranked *A. baumannii* among the first catalog of antibiotic-resistant "critical priority pathogens" because the healthcare-acquired *A. baumannii* strains pose a tremendous threat to human health. Additionally, among the diverse XDR-Acb septicemia, hospital-acquired pneumonia especially showed high case-fatality rates.[1,3,4]

Of the many presently available antimicrobials, the most active agents against XDR-Acb in vitro are polymyxin B or colistin, and tigecycline (TGC).[2,3,5,6] Colistimethate sodium (CMS), a prodrug hydrolyzed after intravenous (IV) administration, is converted into several derivatives, including the active drug colistin.[7] However, the colistin concentration in lung tissue is low when it is administered intravenously in mice and humans.[8,9] Aerosolized CMS (AS-CMS) was prescribed as either an adjuvant drug[10–12] or monotherapy[13] for XDR-Acb pneumonia with clinically variable successful rates. Nevertheless, a survey on the use of CMS in treating patients with microbiologically documented ventilator-associated pneumonia (VAP) addressed that AS-CMS therapy was the only independent predictor of clinical cure in patients with VAP.[14]

In 2009, high non-susceptible rates (> 70%) to anti-pseudomonal carbapenem agents were observed among Taiwanese clinical *A. baumannii* isolates.[15] Previously in vitro investigations showed that some combination schemes have potential in vitro efficacy against XDR-*A. baumannii* isolates,[16,17] including imipenem or meropenem plus sulbactam or colistin, rifampin plus colistin, and TGC in conjunction with colistin. However, the emergence of Taiwanese XDR-*A. baumannii* strains showing high-degree resistance to imipenem-sulbactam has been noted since 1999,[18] and the IV formulation of rifampin is not available in Taiwan. In addition, regarding treatment against XDR-*A. baumannii* pneumonia in Taiwan, carbapenem plus colistin was shown not to significantly decrease the 14-day patients' mortality rate as compared to TGC plus CMS by statistical analysis ($P = .61$) during 2010 to 2013.[19] After cautious consideration of the pharmacokinetic data of TGC and AS-CMS,[8,9,20] some clinicians in Taiwan prescribed AS-CMS in combination with TGC to effectively treat XDR-Acb pneumonia as suggested in previous studies.[21,22] Compared with AS-CMS alone, however, no clinical studies evaluated the clinical efficacy of this combination therapy on XDR-Acb complex pneumonia. Moreover, data on short-term clinical outcomes of patients with XDR-*Acinetobacter* pneumonia are lacking. Therefore, we conducted this randomized study to compare the 14-day clinical outcomes and 30-day case-fatality rates in patients with non-bacteremic XDR-Acb pneumonia treated with either AS-CMS alone or in combination with TGC.

2. Materials and methods

2.1. Hospital settings and ethical review

This retrospective case-control study was conducted at Wan Fang hospital, a 750-bed medical center in Taipei, Taiwan. This investigation was approved by the Institutional Review Board of Wan Fang hospital, Taipei Medical University (TMU-JIRB-201604038). As this study is retrospective observational in nature, the need for patients' informed consent was waived.

2.2. Definition of the inclusion and exclusion criteria

From 2014 January to 2016 December, following failure of responding to the preceding ≥3-day antibiotic therapy, the adult (≥ 18 years of age) in-hospital patients who were diagnosed as XDR-Acb pneumonia with clinical manifestations of sepsis or septic shock (definitions are seen as follows), and were subsequently treated with AS-CMS (colimycin, TTY Biopharm, Taipei, Taiwan) alone or AS-CMS plus TGC (Pfizer, New York, NY) were consecutively considered as the potential candidates for enrollment in this investigation. The medical records of enrolled patients were reviewed in detail. The definitions of systemic inflammatory response syndrome (SIRS) as well as sepsis or septic shock were stated elsewhere.[23] In this study, only the first episode of XDR-Acb pneumonia for the septic patients was enrolled into investigation. Septic shock is defined as sepsis with persisting hypotension despite appropriate fluid resuscitation in association with hypoperfusion abnormalities (altered mental status, oliguria, or lactic acidosis, etc.), requiring at least 1 vasopressor to maintain the mean blood pressure ≥ 65 mm Hg.[23] XDR-Acb pneumonia was defined as new infiltrates or consolidation on radiographic evidence, as well as the consistent sputum Gram stain finding (> 25 leukocytes/low power field [LPF], < 10 epithelial cells/LPF, and numerous gram-negative pleomorphic coccobacilli seen by high power field of smear) and culture of tracheal aspirate growing heavy XDR-Acb complex (the microbiological definition is seen as follows).[4,12] Using the propensity matching score, we selected the control group patients who received AS-CMS alone based on age (± 5 years) and Acute Physiology and Chronic Health Evaluation (APACHE) II score (± 4 points) by the computers. An AS-CMS dose of 2 million international units thrice per day was used, and a TGC loading dose of 100 mg and 50 mg every 12 hours was administered. To simplify the patients' assessment, patients with XDR-Acb complex bacteremia, who had infection (s) other than XDR-Acb complex pneumonia, who previously received therapy of any formulation of CMS or TGC, or concomitantly received antibiotic (s) other than TGC and AS-CMS were excluded from the study.

2.3. Data collection and definitions

The collected data included demographic characteristics, underlying co-morbidities, Charlson co-morbidity index (CCI), presence of shock as well as most severe points of APACHE II

score within 24 hours of XDR-Acb pneumonia emergence, use of non-invasive ventilation (NIV), and necessity of care at the intensive care units (ICU) of the enrolled patients. As patients with septic shock had higher case-fatality rates than those without shock,[23] we also compared the difference in survival rate between these 2 septic subgroups with XDR-Acb pneumonia. The definition of immunosuppressive status was defined as those receiving chemotherapy, radiotherapy, or immunomodulatory drugs within 6 months of cancer treatment.[4] Prolonged use of high-dose corticosteroid (≥ 15 mg prednisolone dose equivalent daily for ≥ 14 days) was defined as suggested elsewhere.[4] Furthermore, we recorded the intervals (days) between the emergence of XDR-Acb pneumonia and start of therapy by AS-CMS alone or AS-CMS plus TGC, and durations of AS-CMS therapy in enrolled patients. Moreover, we investigated the follow-up microbiological data of sputum if available within 3 weeks of XDR-Acb pneumonia episodes, complications plausibly relevant to AS-CMS or TGC therapy, and the causes of patients' mortality if they are able to be judged with reasonable evidence. Acute renal failure (ARF) was defined according to the Kidney Disease-Improving Global Outcomes Clinical Practice Guidelines. The primary endpoint of this study was 30-day case fatality, thereby searching for the independent predictors of 30-day mortality. Additionally, secondary endpoints measured if the co-morbidities, XDR-*A. baumannii* as pneumonic pathogen, physiological severity, therapy-related factors, or airway colonization with colistin-resistant Acb had a significant impact on the 14-day clinical condition among the enrolled patients receiving therapy with in vitro appropriate antibiotic (s).

2.4. Microbiological testing

The identification of Acb complex isolates, antimicrobial susceptibility testing were performed using the Becton Dickinson Phoenix TM Automated Microbiology System (Becton Dickinson, East Rutherford, NJ). Genospecies of *A. baumannii* strains were validated according to the intergenic spacer region of 16S-23S ribosomal RNA gene, as previously described.[24] The susceptibility data against routinely tested antibiotics were interpreted according to the minimum inhibitory concentration (MIC) breakpoints recommended by the Clinical and Laboratory Standards Institute 2014.[25] The definition of XDR phenotype of tested Acb complex isolates, use of the Etest (AB BIODISK, Solna, Sweden) for determining the susceptibility (on the freshly made Mueller-Hinton agar) to TGC, and broth microdilution method for determining the MICs of colistin against the Acb complex isolates under evaluation were as stated elsewhere.[4,12,22]

2.5. Definitions of the patients' outcomes, and follow-up sputum microbiological survey

We classified the clinical outcomes of enrolled patients ≥ 3 days after starting appropriate antibiotic therapy as treatment against XDR-Acb pneumonia: cured, if all of the following 3 criteria were met on the last day of a given regimen use: free from all SIRS criteria regardless of sepsis or septic shock,[23] chest x-ray showing improvements in infiltrative lesions, and resolution of organ dysfunction; improved, if 2 of the above 3 criteria were achieved; and failed, if 1 or none of the above 3 criteria were achieved.[4,12] Eradication was defined as no XDR-Acb isolates recovered from follow-up sputum cultures if available after a ≥ 3-day appropriate antibiotic therapy. The follow-up sputum culture growing colistin-resistant Acb isolates was also recorded.

2.6. Statistical analyses

Group percentages were calculated for categorical variables and differences were assessed using Pearson chi-square or Fisher's exact test. Continuous variables were assessed using Student's *t* test or Wilcoxon rank-sum test depending on the normality of distributions. Using the backward conditional method, all biologically plausible variables with $P < .15$ in the univariate analysis were used in the multivariate logistic regression model to search for independent predictors (corresponding adjusted odds ratio [aOR] and 95% confidence interval [CI]) of the 30-day case-fatality among the enrolled patients. The Kaplan–Meier survival estimate was used to demonstrate the difference in survival within 30 days between the therapy groups. Furthermore, to determine if the co-morbidities, XDR-*A. baumannii* as pneumonic pathogen, physiological severity, therapy-related factors, airway colonization with colistin-resistant Acb, or the 14-day clinical failure outcome were independent predictors of 30-day mortality, Cox proportional regression analysis was used to investigate the associated variables with $P < .15$ in the univariate analyses if any, and estimate their strengths accordingly. Two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Science Version 23 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Selection of patients, and preceding antibiotic regimens before therapy of AS-CMS alone or TGC plus AS-CMS

From January 1st, 2014 through December 31th, 2016, the process of all XDR-Acb pneumonia patients who received AS-CMS plus TGC therapy (n = 106, selected consecutively as the index cases) and the control cases with non-bacteremic XDR-Acb pneumonia (n = 106, selected by the computers) who received AS-CMS alone are illustrated in Figure 1. Before AS-CMS alone or TGC plus AS-CMS therapy were initiated for the enrolled XDR-Acb pneumonia patients, the majority (56.1%) of them received a single anti-pseudomonal carbapenem agent plus isepamicin, followed by piperacillin-tazobactam or ciprofloxacin in combination with gentamicin or amikacin (24.5% and 17.0%, respectively).

3.2. Patient characteristics, therapy-related complications, causes of death, and microbiological results of follow-up sputum samples

The demographic features, the CCI, presence of septic shock, the APACHE II score points, oxygen support equipment, and patients' need for ICU care are shown in Table 1. Patients with septic shock accounted for 23.1% of all enrolled XDR-Acb pneumonia cases. Except for diabetes mellitus, no statistically significant differences were detected in most variables between the 2 treatment groups. Notably, during the treatment, bronchospasm developed in 4 patients with chronic obstructive pulmonary disease (COPD). For the 4 COPD cases, further bronchospasm was successfully prevented by administering concomitant bronchodilators during AS-CMS therapy. No AS-CMS-related neurotoxicity was observed in our study. Regarding the causes of 30-day mortality among 60 fatal cases, 24 (40%) fatalities were due to refractory ARF (hemodialysis was suggested and refused by the patients), 23 (38.3%) were due to progression into severe adult respiratory distress syndrome, while 13 (21.7%)

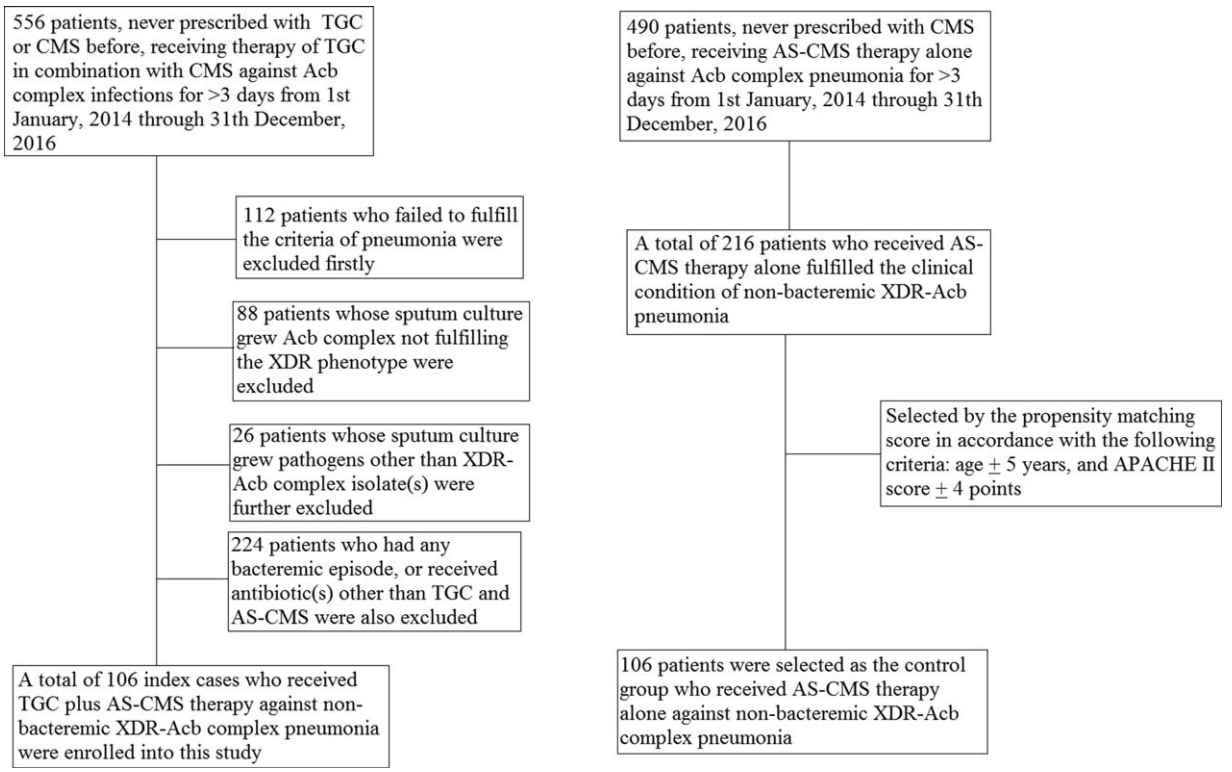

Figure 1. Processes of selecting index cases (n = 106) who received tigecycline plus aerosolized colistimethate sodium (AS-CMS), as well as control cases (n = 106) who received AS-CMS therapy alone as treatment for non-bacteremic extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex pneumonia. TGC, tigecycline. AS-CMS, aerosolized colistimethate sodium. XDR-Acb, extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii*.

were related to acute coronary syndrome or fulminant gastrointestinal hemorrhage. Of the 212 implicated pneumonic XDR-Acb complex isolates, 142 (67.0%) were validated as XDR-*A. baumannii* isolates. In addition, of the 156 patients with available follow-up sputum culture results, 4 (4.9% [4/82]) from the subset who received AS-CMS alone and 6 (8.1% [6/74]) from the other subset who received AS-CMS plus TGC exhibited the colistin-resistant Acb isolates cultured from the follow-up sputum samples ($P = .41$).

3.3. Therapy-associated microbiological results and clinical outcomes

The 30-day mortality rates of the group who received AS-CMS plus TGC and the group who received AS-CMS alone were 34.0% and 22.6%, respectively ($P = .17$). Of note, after in vitro treatment with the appropriate antibiotic (s), the 30-day case-fatality rate for the XDR-Acb pneumonia subgroup of septic shock was higher than that of sepsis without shock subgroup (34.7% [17/49] vs 26.4% [43/163], respectively), but their difference was not statistically significant (aOR = 1.346; 95% CI = 0.811–2.234; $P = .280$). The duration of AS-CMS use ranged from 3 to 29 days (mean ± standard deviation [SD], 12.2 ± 6.0). The 7-day AS-CMS therapy (regardless of concomitant TGC use) successfully eradicated > 90% (98/108) of the airway XDR-Acb isolates. Nevertheless, no difference existed in the duration (5 [4–6] days for combination therapy subset vs 5 [3–6] days for AS-CMS alone subset; $P = .82$) and percentages (68.3% [56/82] vs 70.3% [52/74]; OR = 0.91, 95% CI = 0.35–2.39, $P = 1.00$) of eradicating the airway XDR-Acb isolates between the 2 therapy groups. The cumulative survival curves between the 2 patient groups are illustrated in Figure 2.

3.4. Factors associated with 30-day mortality and 14-day treatment outcomes in patients with XDR-Acb complex pneumonia

Variables indicating the differences in the 30-day case-fatality rate of 212 patients with XDR-Acb pneumonia are shown in Table 2. Univariate statistical analysis showed the group of fatal cases did not exhibit a significantly higher percentage of shock than the survivor group among patients with XDR-Acb pneumonia ($P = .26$). In the multivariate logistic analysis, after the conditional factors were adjusted, the only independent predictor of 30-day case fatality was the 14-day clinical failure of curing/improving XDR-Acb pneumonia (aOR = 38.2; 95% CI = 9.96–142.29; $P < .001$). This finding was also true in 156 patients with clear bacteriological results if available follow-up sputum samples were considered (aOR = 22.1; 95% CI = 5.66–86.11; $P < .001$). The adjusted hazard ratios (aHRs) for the 30-day mortality among patients with 14-day failed outcomes, stratified by APACHE II score > 16, > 20, and > 25 were 0.99 (95% CI = 0.53–1.83; $P = .97$), 1.32 (95% CI = 0.69–2.51; $P = .41$), and 1.91 (95% CI = 0.88–4.14; $P = .10$), respectively. Furthermore, univariate analyses revealed that COPD, chronic renal failure (CRF), prolonged use of high-dose corticosteroid, APACHE II score > 25 points, NIV use, and no TGC therapy adversely affected the rate of clinical cure or improvement in patients with XDR-Acb pneumonia.

Table 1

Comparisons of demographic features, underlying co-morbidities, and associated parameters of initial clinical severity among patients with extensively drug-resistant *Acinetobacter calcoaceticus-A baumannii* complex pneumonia who received tigecycline plus aerosolized colistimethate sodium or aerosolized colistimethate sodium alone by univariate analyses.

Characteristics	Treatment groups (case no.)		Odds ratio	95% confidence interval	*P* value
	TGC plus aerosolized CMS (n = 106)	Aerosolized CMS alone (n = 106)			
Demographics					
Gender, male	70 (66.0%)	70 (66.0%)	1.000	0.761, 1.314	1.000
Age (years) range; median (IQR)	51–100; 82 (77–86)	51–97; 83 (75–87)			.76
Age > 65 years	102 (96.2%)	100 (94.3%)	1.020	0.937, 1.110	1.000
BMI, range; mean (± SD)	11.2–28.0; 20.7 (± 3.7)	13.6–31.4; 20.4 (± 4.2)			.704
BMI > 25.0	10 (9.4)	14 (13.2)	0.714	0.242, 2.109	.761
Underling co-morbidities					
Charlson co-morbidity index score, range; median (IQR)	0–9; 2 (2–4)	0–11; 2 (1–3)			.356
COPD	20 (18.9)	36 (34.0)	0.452	0.185, 1.104	.122
Bronchiectasis	0 (0)	2 (1.9)	1.019	0.982, 1.058	1.000
Old pulmonary tuberculosis	8 (7.5)	10 (9.4)	0.800	0.227, 2.816	1.000
Pulmonary fibrosis	2 (1.9)	0 (0)	0.981	0.945, 1.018	1.000
CAD	36 (34.0)	24 (22.6)	1.757	0.745, 4.146	.281
CHF	44 (41.5)	44 (41.5)	1.000	0.462, 2.166	1.000
Neurology diseases	54 (50.9)	68 (64.2)	0.580	0.267, 1.263	.238
Malignancy	24 (22.6)	12 (11.3)	2.293	0.790, 6.656	.195
Diabetes mellitus	62 (58.5)	38 (35.8)	2.522	1.152, 5.519	.032
Chronic renal failure	26 (24.5)	20 (18.9)	1.398	0.551, 3.542	.638
Hepatic cirrhosis	2 (1.9)	6 (5.7)	0.321	0.032, 3.185	.618
Immunosuppressive status	2 (1.9)	2 (1.9)	1.000	0.061, 16.417	1.000
Receipt of long-term high-dose steroid therapy	42 (39.6)	40 (37.7)	1.084	0.495, 2.367	1.000
Clinical severity, associated parameters					
Septic shock	27 (25.5)	22 (20.8)	1.227	0.749, 2.012	.515
APACHE II score, range; median (IQR)	6–41; 16 (12–23)	6–39; 16 (13–21)			
APACHE II ≥ 17	48 (45.3)	44 (41.5)	1.166	0.541, 2.516	.845
APACHE II ≥ 21	34 (32.1)	28 (26.4)	1.315	0.568, 3.047	.670
NIV use	22 (20.8)	26 (24.5)	0.806	0.324, 2.007	.817
Invasive ventilation	38 (35.8)	34 (32.1)	1.183	0.529, 2.647	.838
Indicated for ICU care	42 (39.6)	38 (35.8)	1.174	0.535, 2.578	.841
Acinetobacter baumannii validated as an implicated pneumonic pathogen	69 (65.1)	73 (68.9)	0.843	0.475, 1.495	.661

APACHE II score = Acute Physiological and Chronic Health Evaluation II score, BMI = body mass index, CAD = coronary artery disease, CHF = congestive heart failure, CMS = colistimethate sodium, COPD = chronic obstructive pulmonary disorder, HD = hemodialysis, ICU = intensive care unit, NIV = non-invasive ventilation, PD = peritoneal dialysis, SD = standard deviation, TGC = tigecycline, XDR-Acb complex = extensively drug-resistant *Acinetobacter calcoaceticus-A. baumannii* complex isolates.

As shown in Table 3, Cox regression analysis showed that the factors that strongly adversely impacted curing or improving XDR-Acb pneumonia among all 212 enrolled patients included COPD, CRF, NIV use, and no TGC therapy, while prolonged high-dose corticosteroid use showed borderline statistical significance (aHR = 1.82; 95% CI = 0.92–3.61; *P* = .085). Conversely, high (> 25) APACHE II score and emergence of colistin-resistant Acb isolates (n = 10) in follow-up sputum samples was not statistically significantly associated with curing or improving XDR-Acb pneumonia on day 14.

4. Discussion

In our study, we found that addition of TGC failed to improve the 30-day case-fatality rate of patients with non-bacteremic XDR-Acb pneumonia. Nevertheless, in significant contrast with other surveys that focused on the multidrug-resistant (MDR)-*A. baumannii*-associated mortality,[3,19,26] addition of TGC to AS-CMS resulted in improved short-term outcomes in these patients compared with AS-CMS therapy alone. AS-CMS is less toxic in humans than in rats[27] as compared to IV CMS therapy due to the low systemic availability.[9,28] Notably, the 30-day case-fatality rate of the group that received AS-CMS alone (22.6%) was higher than that (0%) of the group in a VAP (mostly caused by MDR-*Pseudomonas aeruginosa*) study.[10] Contrastingly, 1 Taiwanese survey on XDR-*A. baumannii* bacteremia revealed that a high case-fatality rate (7/16 [43.8%]) was observed in the pneumonia patient subgroup who received IV CMS plus TGC.[19] This result is similar to that (53%) of the Thailand study.[3] These results suggested that AS-CMS therapy alone might have a clinically modest efficacy in the treatment of patients with non-bacteremic XDR-Acb pneumonia in Taiwan.

Against the 40 non-clonal carbapenem-resistant *A. baumannii* strains collected from patients with VAP, which showed high susceptibility rates to TGC (85%) and colistin (97.5%), Cikman et al observed that a high proportion (62.5% and 80%, respectively) of these strains exhibited antagonistic effects (assessed using the in vitro fractional inhibitory concentration index ≥ 4 and ≥ 2, respectively) against TGC plus colistin.[29] These results, however, showed a remarkable difference from the other in vitro studies.[22,30] Additionally, Burkhardt et al found that extremely low TGC concentrations (0.01–0.02 μg/mL) were

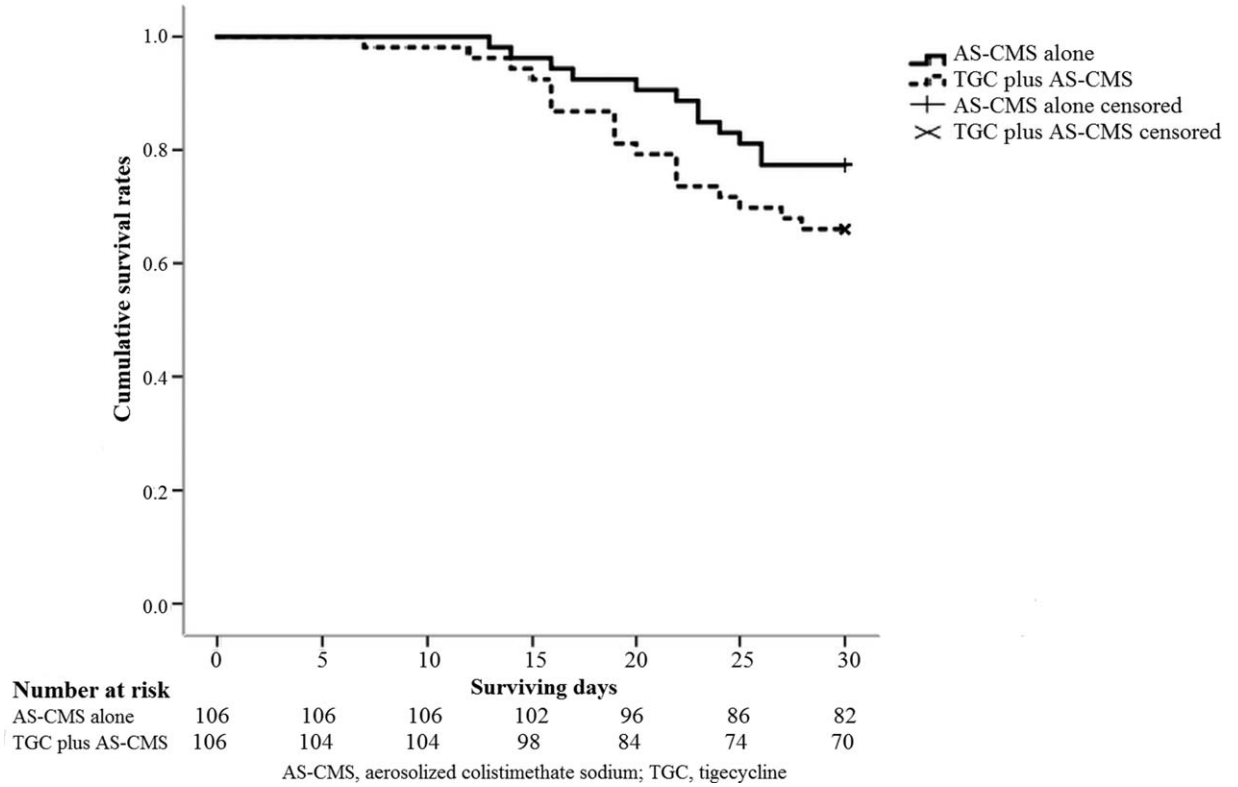

Figure 2. Kaplan-Meier survival analysis comparing the 30-day cumulative survival curves between the two groups of patients with non-bacteremic extensively drug-resistant *Acinetobacter calcoaceticus-A. baumannii* complex pneumonia who received either aerosolized colistimethate sodium plus tigecycline (dotted line) or aerosolized colistimethate sodium therapy alone (solid line).

detected in the epithelial lining fluid of patients who received a standard-dose TGC therapy,[31] markedly contrasting the high TGC concentrations (78-fold plasma concentration) in the alveoli.[20] Although a poor efficacy of adjunctive TGC to IV CMS was reported decreasing the mortality rates of patients with XDR-*A. baumannii* pneumonia,[19] Lee et al observed that the earlier (within 2 days) initiation of standard-dose TGC plus IV CMS in few patients with imipenem-resistant *A. baumannii* bacteremia significantly improved patient outcomes.[32] Moreover, in a rat model of pneumonia, administering TGC plus CMS in the peritoneal muscles was verified to provide a greater significant decrease in XDR-*A. baumannii* counts within alveoli than colistin or TGC alone.[21] Despite these conflicting data, Felton et al emphasized that the drug concentrations in the lung parenchyma are related to the therapeutic efficacy when treating established invasive infections.[33] This important viewpoint corresponds to the results of our study, which found that the addition of TGC to AS-CMS improved the 14-day clinical condition of non-bacteremic XDR-Acb pneumonia.

A sufficient colistin concentration in the lung tissue was detected in the ventilated piglets with pneumonia after AS-CMS therapy.[8] Additionally, humans achieve high pulmonary area-under-the-concentration of colistin (ranging 18.9–73.1 μg·h/mL) and high maximum pulmonary colistin concentrations (mean ± SD, 6.00 ± 3.45 μg/mL) during an AS-CMS dosing (with 2 million units) interval.[9] Nevertheless, we observed that 10 (6.4%) colistin-resistant Acb isolates were cultured from sputum samples (from 156 patients) after an appropriate antibiotic therapy. During a review of the PubMed databases, 2 articles revealed that the airways of a large number (> 12%) of patients were colonized with colistin-resistant *A. baumannii* or other gram-negative bacteria (GNB) isolates after adjunctive AS-CMS therapy.[28,34] After CMS exposure, Li et al observed that some heteroresistant subpopulations of *A. baumannii* can grow in the presence of up to 10 μg/mL of colistin.[29] These strains are not virtually detected during initial MIC measurement using commercial automated systems or disc diffusion susceptibility testing.[35] These reasons plausibly explain why the subsequent emergence of colistin-resistant Acb isolates within airway is not necessarily associated with the 14-day unfavorable outcome in the treatment of XDR-Acb pneumonia.

Despite the limitation (focusing on patients receiving therapy of AS-CMS alone or TGC plus AS-CMS) set at the initial stage of study design existed, some important factors negatively influencing the outcomes of patients with non-bacteremic XDR-Acb pneumonia were still found. In this study, after appropriate antibiotic therapy, the 14-day clinical failure about treatment of XDR-Acb pneumonia independently predicted the 30-day mortality. Numerous virulence factors (including outer membrane protein A, lipopolysaccharide capsule, pili, and others) are observed in *A. baumannii*,[36] which accounted for about two-thirds (67.0%) of all pneumonic Acb complex isolates in this survey. However, apart from septic shock, the *A. baumannii* as implicated pneumonic pathogen was also not an independent predictor of 14-day treatment failure, which was directly associated with 30-day mortality of the enrolled patients. The latter finding is similar to the other study regarding the Taiwanese Acb complex bacteremia.[31] In addition, as seen in many investigations, the underlying co-morbidities undoubtedly exert adverse effects on the survival of patients with XDR-Acb

Table 2

Comparison of demographic features, underlying co-morbidities, initial clinical severity and respiratory support maneuvers before therapy, and post-therapy conditions among patients with extensively drug-resistant *Acinetobacter calcoaceticus-A. baumannii* complex pneumonia who died within 30 days of therapy (n = 60) or did not (n = 152) as indicated in the univariate analyses.

Characteristics	Day 30 outcomes (case no.)		Odds ratio	95% confidence interval	*P* value
	30-day fatal cases (n = 60)	30-day non-fatal cases (n = 152)			
Demographics					
Gender, male	42 (70.0)	98 (64.5)	1.286	0.517, 3.198	.654
Age (years), range; median (IQR)	51–93; 82 (72–88)	51–100; 83 (77–86)			.972
Age > 65 years	52 (86.7)	144 (94.7)	0.361	0.084, 1.550	.218
BMI, range; mean (± SD)	11.2–26.6; 20.66 (± 3.49)	13.3–31.4; 20.51 (± 4.13)		−1.433, 1.740	.847
BMI > 25.0	4 (6.7)	20 (13.2)	0.471	0.097, 2.292	.502
Underling co-morbidities					
Charlson co-morbidity index score, range; median (IQR)	0–8; 3 (2–4)	0–11; 2 (1–3)			.426
COPD	26 (43.3)	30 (19.7)	3.110	1.243, 7.779	.026
Bronchiectasis	0 (0)	2 (1.3)	1.013	0.987, 1.040	1.000
Old pulmonary tuberculosis	6 (10)	12 (7.9)	1.296	0.302, 5.556	.710
Pulmonary fibrosis	0 (0)	2 (1.3)	1.013	0.987, 1.040	1.000
CAD	18 (30)	42 (27.6)	1.122	0.443, 2.841	.814
vCHF	26 (43.3)	62 (40.8)	1.110	0.472, 2.610	.830
Neurology diseases	30 (50)	92 (60.5)	0.652	0.279, 1.527	.385
Malignancy	12 (20)	24 (15.8)	1.333	0.450, 3.952	.579
Diabetes mellitus	28 (46.7)	72 (47.4)	0.972	0.417, 2.268	1.000
Chronic renal failure	20 (33.3)	26 (17.1)	2.423	0.922, 6.365	.114
Receipt of chronic HD or PD therapy	4 (6.7)	2 (1.3)	5.357	0.467, 61.425	.192
Hepatic cirrhosis	0 (0)	8 (5.3)	1.056	1.001, 1.113	.575
Immunosuppressive status	0 (0)	4 (2.6)	1.027	0.990, 1.066	1.000
Receipt of long-term high-dose steroid therapy	34 (56.7)	48 (31.6)	2.833	1.188, 6.757	.026
Clinical severity, associated parameters and supportive maneuvers					
Septic shock	17 (28.3)	32 (21.1)	1.346	0.811, 2.234	.257
APACHE II score, range; median (IQR)	8–41; 16 (13–26)	6–40; 16 (11–21)			.244
APACHE II ≥ 17	26 (43.3)	66 (43.4)	0.996	0.425, 2.338	1.000
APACHE II ≥ 21	22 (36.7)	40 (26.3)	1.621	0.658, 3.992	.345
APACHE II ≥ 26	14 (23.3)	14 (9.2)	3.000	0.951, 9.465	.064
NIV use	24 (40)	24 (15.8)	3.556	1.367, 9.248	.011
Invasive ventilation	20 (33.3)	52 (34.2)	0.962	0.393, 2.353	1.000
Indicated for ICU care	28 (46.7)	52 (34.2)	1.683	0.712, 3.975	.270
Acinetobacter baumannii validated as an implicated pneumonic pathogen	38 (63.3)	104 (68.4)	0.797	0.426, 1.492	.518
Post-treatment courses, outcomes					
Use of TGC	36 (60)	70 (46.1)	1.757	0.745, 4.146	.281
Days of starting antibiotic (s) after pneumonia happened. Range; median (IQR)	1–20; 4 (3–6)	2–30; 4 (3–6)			.820
Patients who received appropriate antibiotic (s) within 3 days after pneumonia happened	42 (70)	100 (65.8)	1.560	0.587, 4.148	.478
Durations (days) of aerosolized CMS use; Range; mean (± SD)	3–23; 11.73 (± 5.94)	3–29; 12.39 (± 6.05)		-3.243, 1.921	.610
Durations ≤ 8 days	22 (36.7)	50 (32.9)	1.181	0.488, 2.857	.820
Durations ≤ 10 days	24 (40)	64 (42.1)	0.917	0.388, 2.168	1.000
Acute renal failure	8 (13.3)	16 (10.5)	1.308	0.363, 4.715	.737
No eradication of airway XDR-Acb isolates*	20/48 (41.7)	28/108 (25.9)	2.041	0.740, 5.268	.191
Colistin-resistant Acb isolates cultured from follow-up sputum*	6/48 (12.5)	4/108 (3.7)	3.714	0.578, 23.849	.144
Clinically not cured, or not improved condition on post-therapy day 14	54 (90)	28 (18.4)	39.857	10.580, 150.147	<.001

APACHE II score = Acute Physiological and Chronic Health Evaluation II score, BMI = body mass index, CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disorder, HD = hemodialysis, ICU = intensive care unit, IQR = interquartile range, NIV = non-invasive ventilation, PD = peritoneal dialysis, SD = standard deviation, TGC = tigecycline, XDR-Acb complex = extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex isolates.

* A total of 156 patients (including 48 fatal and 108 non-fatal patients on day 30) with clear microbiological data of the follow-up sputum specimens.

pneumonia or septicemia to a considerable degree.[3,4,19,31] CRF and ≥ 2-week high-dose corticosteroid use, both were deemed factors superimposing hosts into the immunocompromised status[3,4] and were shown to negatively affect the rate of clinical cure or improvement in patients with XDR-Acb pneumonia. In our survey, recipients of prolonged corticosteroid therapy accounted for 57.1% (32/56) of the COPD patients. These results differ from those of a previous study.[3] The results of our study reveal that tapering corticosteroid maintenance dose might be beneficial in improving the short-term clinical outcomes of XDR-Acb pneumonia patients. Furthermore, our study also highlights the significance of aggressive pulmonary hygiene care (not by NIV use) in treating XDR-Acb pneumonia effectively.

Although we performed the comprehensive analyses to search for the significant predictors regarding the 30-day mortality and 14-day treatment failure outcomes of patients

Table 3

Cox proportional regression analysis of predictors for the condition of a 14-day not clinically curing or improving pneumonia among 212 patients with extensively drug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex pneumonia.

Variables	Clinically not cured, or not improved (n = 82)	Clinically cured or improved (n = 130)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
COPD	30 (36.6)	26 (20.0)	1.90 (1.00–3.59)	0.049	2.08 (1.05–4.10)	.035
Chronic renal failure	30 (36.6)	16 (12.3)	2.80 (1.48–5.31)	0.002	5.90 (1.52–5.90)	.002
Receipt of long-term high-dose steroid therapy	46 (56.1)	36 (27.7)	2.39 (1.29–4.45)	0.006	1.82 (0.92–3.61)	.085
APACHE II score >25 points	16 (19.5)	12 (9.2)	1.91 (0.88–4.14)	0.102	0.97 (0.42–2.24)	.942
NIV use	28 (34.1)	20 (15.4)	2.16 (1.13–4.12)	0.020	2.68 (1.37–5.25)	.004
Use of TGC	48 (58.5)	58 (44.6)	1.61 (0.87–3.00)	0.133	1.92 (1.00–3.68)	.049
No eradication of airway XDR-Acb isolates*	28/68 (41.2)	20/88 (22.7)	1.92 (0.97, 3.80)	0.063	1.30 (0.57–2.97)	.535
Colistin-resistant Acb isolates cultured from follow-up respiratory secretion*	8/68 (11.8)	2/88 (2.3)	2.35 (0.82–6.69)	0.111	2.01 (0.64–6.33)	.231

APACHE II = Acute Physiologic and Chronic Health Evaluation II, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, NIV = non-invasive ventilation, TGC = tigecycline.
* For 156 patients with clear in vitro bacteriological results of follow-up sputum specimens after ≥ 3-day therapy with in vitro appropriate antibiotic (s).

with non-bacteremic XDR-Acb, this survey had limitations. The possibility of clonal XDR-Acb dissemination was not excluded by the pulsotype study.

5. Conclusions

In conclusion, in patients with non-bacteremic XDR-Acb pneumonia, regimen of AS-CMS alone showed moderate efficacy. No 30-day survival benefit was observed after adding TGC to AS-CMS in the treatment of XDR-Acb complex pneumonia. Nevertheless, the addition of TGC, aggressive chest care (probably achieved by intubation or tracheostomy use), and decrease in maintenance corticosteroid dose were beneficial in improving the 14-day clinical outcomes of patients with XDR-Acb pneumonia after receiving in vitro appropriate antibiotic therapy. In addition, some co-morbidities in fact adversely influenced the treatment outcomes of these patients to a considerable degree as well.

Acknowledgments

We thank all of the staff (CH Wang and others) of microbiological department of Wan Fang Hospital in assisting in determining the susceptibility data as well as molecular tests of the implicated pneumonic Acb isolates.

Author contributions

Conceptualization: Shio-Shin Jean, Tai-Chin Hsieh, Wen-Sen Lee.
Data curation: Shio-Shin Jean, Tai-Chin Hsieh, Wen-Sen Lee, Po-Ren Hsueh.
Formal analysis: Shio-Shin Jean, Tai-Chin Hsieh, Chin-Wan Hsu, Wen-Sen Lee, Carlos Lam.
Funding acquisition: Tai-Chin Hsieh, Wen-Sen Lee, Chin-Wan Hsu.
Investigation: Shio-Shin Jean, Tai-Chin Hsieh, Chin-Wan Hsu, Wen-Sen Lee, Carlos Lam.
Methodology: Shio-Shin Jean, Tai-Chin Hsieh, Po-Ren Hsueh.
Project administration: Shio-Shin Jean, Tai-Chin Hsieh, Wen-Sen Lee, Carlos Lam.
Resources: Shio-Shin Jean, Po-Ren Hsueh, Tai-Chin Hsieh, Wen-Sen Lee, Chin-Wan Hsu.
Software: Carlos Lam, Shio-Shin Jean, Tai-Chin Hsieh.
Supervision: Shio-Shin Jean, Tai-Chin Hsieh, Wen-Sen Lee, Po-Ren Hsueh.
Validation: Shio-Shin Jean, Tai-Chin Hsieh, Wen-Sen Lee, Po-Ren Hsueh, Chin-Wan Hsu.
Writing – original draft: Shio-Shin Jean, Tai-Chin Hsieh, Chin-Wan Hsu, Wen-Sen Lee, Carlos Lam.
Writing – review & editing: Shio-Shin Jean, Tai-Chin Hsieh, Wen-Sen Lee, Po-Ren Hsueh, Chin-Wan Hsu, Carlos Lam.

References

[1] Kuo SC, Chang SC, Wang HY, et al. Emergence of extensively drug-resistant Acinetobacter baumannii complex over 10 years: nationwide data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program. BMC Infect Dis 2012;12:200.
[2] Viehman JA, Nguyen MH, Doi Y. Treatment options for carbapenem-resistant and extensively drug-resistant Acinetobacter baumannii infections. Drugs 2014;74:1315–33.
[3] Khawcharoenporn T, Pruetpongpun N, Tiamsak P, et al. Colistin-based treatment for extensively drug-resistant Acinetobacter baumannii pneumonia. Int J Antimicrob Agents 2014;43:378–82.
[4] Jean SS, Hsieh TC, Hsu CW, et al. Comparison of the clinical efficacy between tigecycline plus extended-infusion imipenem and sulbactam plus imipenem against ventilator-associated pneumonia with pneumonic extensively drug-resistant Acinetobacter baumannii bacteremia, and correlation of clinical efficacy with in vitro synergy tests. J Microbiol Immunol Infect 2016;49:924–33.
[5] Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005;40:1333–41.
[6] Karageorgopoulos DE, Kelesidis T, Kelesidis I, et al. Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) Acinetobacter infections: a review of the scientific evidence. J Antimicrob Chemother 2008;62:45–55.
[7] Li J, Coulthard K, Milne R, et al. Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. J Antimicrob Chemother 2003;52:987–92.
[8] Lu Q, Girardi C, Zhang M, et al. Nebulized and intravenous colistin in experimental pneumonia caused by Pseudomonas aeruginosa. Intensive Care Med 2010;36:1147–55.
[9] Yapa SWS, Li J, Patel K, et al. Pulmonary and systemic pharmacokinetics of inhaled and intravenous colistin methanesulfonate in cystic fibrosis patients: targeting advantage of inhalational administration. Antimicrob Agents Chemother 2014;58:2570–9.
[10] Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of Pseudomonas aeruginosa and Acinetobacter baumannii ventilator-associated pneumonia. Respir Care 2012;57:1226–33.

[11] Kalin G, Alp E, Coskun R, et al. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia: do we really need this treatment? J Infect Chemother 2012;18:872–7.
[12] Hsieh TC, Chen FL, Ou TY, et al. Role of aerosolized colistin methanesulfonate therapy for extensively-drug-resistant Acinetobacter baumannii complex pneumonia and airway colonization. J Microbiol Immunol Infect 2016;49:523–30.
[13] Choi HK, Kim YK, Kim HY, et al. Inhaled colistin for treatment of pneumonia due to colistin-only-susceptible Acinetobacter baumannii. Yonsei Med J 2014;55:118–25.
[14] Korbila IP, Michalopoulos A, Rafailidis PI, et al. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. Clin Microbiol Infect 2010;16:1230–6.
[15] Jean SS, Hsueh PR, Lee WS, et al. Carbapenem susceptibilities and non-susceptibility concordance to different carbapenems amongst clinically important gram-negative bacteria isolated from intensive care units in Taiwan: results from the Surveillance of Multicentre Antimicrobial Resistance in Taiwan (SMART) in 2009. Int J Antimicrob Agents 2013;41:457–62.
[16] Perez F, Hujer AM, Hujer KM, et al. Global challenge of multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2007;51:3471–84.
[17] Principe L, D'Arezzo S, Capone A, et al. In vitro activity of tigecycline in combination with various antimicrobials against multidrug resistant Acinetobacter baumannii. Ann Clin Microbiol Antimicrob 2009;8:18.
[18] Hsueh PR, Teng LJ, Chen CY, et al. Pandrug-resistant Acinetobacter baumannii causing nosocomial infections in a university hospital, Taiwan. Emerg Infect Dis 2002;8:827–32.
[19] Cheng A, Chuang YC, Sun HY, et al. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant Acinetobacter baumannii bacteremia: a multicenter prospective observational study. Crit Care Med 2015;43:1194–204.
[20] Peterson LR. A review of tigecycline–the first glycylcycline. Int J Antimicrob Agents 2008;32:S215–22.
[21] Mutlu Yilmaz E, Sunbul M, Aksoy A, et al. Efficacy of tigecycline/colistin combination in a pneumonia model caused by extensively drug-resistant Acinetobacter baumannii. Int J Antimicrob Agents 2012; 40:332–6.
[22] Dizbay M, Tozlu DK, Cirak MY, et al. In vitro synergistic activity of tigecycline and colistin against XDR-Acinetobacter baumannii. J Antibiot (Tokyo) 2010;63:51–3.
[23] Davies MG, Hagen PO. Systemic inflammatory response syndrome. Br J Surg 1997;84:920–35.
[24] Chuang YC, Sheng WH, Li SY, et al. Influence of genospecies of Acinetobacter baumannii complex on clinical outcomes of patients with Acinetobacter bacteremia. Clin Infect Dis 2011;52:352–60.
[25] Clinical and Laboratory Standards InstitutePerformance standards for antimicrobial susceptibility testing: twenty-fourth informational supplement M100-S24. CLSI, Wayne, PA:2014.
[26] Liang CA, Lin YC, Lu PL, et al. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant Acinetobacter baumannii. Clin Microbiol Infect 2017;24: 908.e1–7.
[27] Marchand S, Gobin P, Brillault J, et al. Aerosol therapy with colistin methanesulfonate: a biopharmaceutical issue illustrated in rats. Antimicrob Agents Chemother 2010;54:3702–7.
[28] Kuo SC, Lee YT, Yang SP, et al. Eradication of multidrug-resistant Acinetobacter baumannii from the respiratory tract with inhaled colistin methanesulfonate: a matched case-control study. Clin Microbiol Infect 2012;18:870–6.
[29] Cikman A, Gulhan B, Aydin M, et al. In vitro activity of colistin in combination with tigecycline against carbapenem-resistant Acinetobacter baumannii strains isolated from patients with ventilator-associated pneumonia. Int J Med Sci 2015;12:695–700.
[30] Sheng WH, Wang JT, Li SY, et al. Comparative in vitro antimicrobial susceptibilities and synergistic activities of antimicrobial combinations against carbapenem-resistant Acinetobacter species: Acinetobacter baumannii versus Acinetobacter genospecies 3 and 13TU. Diagn Microbiol Infect Dis 2011;70:380–6.
[31] Lee YC, Huang YT, Tan CK, et al. Acinetobacter baumannii and Acinetobacter genospecies 13TU and 3 bacteraemia: comparison of clinical features, prognostic factors and outcomes. J Antimicrob Chemother 2011;66:1839–46.
[32] Lee HY, Chen CL, Wu SR, et al. Risk factors and outcome analysis of Acinetobacter baumannii complex bacteremia in critical patients. Crit Care Med 2014;42:1081–8.
[33] Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev 2014;27:68–88.
[34] Abdellatif S, Trifi A, Daly F, et al. Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial. Ann Intensive Care 2016;6:26.
[35] Li J, Rayner CR, Nation RL, et al. Heteroresistance to colistin in multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2006;50:2946–50.
[36] Richards AM, Abu Kwaik Y, Lamont RJ. Code blue: Acinetobacter baumannii, a nosocomial pathogen with a role in the oral cavity. Mol Oral Microbiol 2015;30:2–15.