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?

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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 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] = 3.82; 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 = intravenous, MD = medical doctor, OR = odds ratio, PaO2/FiO2 = ratio of arterial oxygen tension to airway oxygen fraction, XDR = extensively drug-resistant, CA-MS = carbapenemase-producing, Acb = Acinetobacter baumannii, TGC = 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. 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.

Of the many presently available antimicrobials, the most active agents against XDR-Acb in vitro are polymyxin B or colistin, and tigecycline (TGC). Colistimethate sodium (CMS), a prodrug hydrolyzed after intravenous (IV) administration, is converted into several derivatives, including the active drug colistin. However, the colistin concentration in lung tissue is low when it is administered intravenously in mice and humans. Aerosolized CMS (AS-CMS) was prescribed as either an adjuvant drug or monotherapy 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.

In 2009, high non-susceptible rates (> 70%) to anti-pseudomonal carbapenem agents were observed among Taiwanese clinical A. baumannii isolates. Previously in vitro investigations showed that some combination schemes have potential in vitro efficacy against XDR-A. baumannii isolates, including imipenem or meropenem plus sulfactam 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-sulfactam has been noted since 1999, 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 during 2010 to 2013. After cautious consideration of the pharmacokinetic data of TGC and AS-CMS, some clinicians in Taiwan prescribed AS-CMS in combination with TGC to effectively treat XDR-Acb pneumonia as suggested in previous studies. 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 baumannii 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. 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 persistent 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.

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 (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 100mg and 50mg every 12 hours was administered.
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,\textsuperscript{23,24} 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.\textsuperscript{19} Prolonged use of high-dose corticosteroid (≥ 15 mg prednisolone dose equivalent daily for ≥ 14 days) was defined as suggested elsewhere.\textsuperscript{13} 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-\textit{A. baumannii} as pneumatic pathogens, 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 \textit{A. baumannii} strains were validated according to the intergenic spacer region of 16S-23S ribosomal RNA gene, as previously described.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{23,24} 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.\textsuperscript{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-\textit{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%)
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-\textit{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 = 0.39–2.39, \(P = 1.00\)) 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 = 0.33–1.83; \(P = .97\)), 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.

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**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 \textit{Acinetobacter calcoaceticus-Acinetobacter baumannii} complex pneumonia. TGC, tigecycline. AS-CMS, aerosolized colistimethate sodium. XDR-Acb, extensively drug-resistant \textit{Acinetobacter calcoaceticus-Acinetobacter baumannii}.
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; \( P = 0.085 \)). 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,\(^{13,19,26} \) 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\(^{27,28} \) 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-\( P. \) aeruginosa) study.\(^{10} \) Contrarily, a 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.\(^{5} \) 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 \( \geq 4 \) and \( \geq 2 \), respectively) against TGC plus colistin.\(^{29} \)

### Table 1

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

| Characteristics | TGC plus aerosolized CMS (\( n = 106 \)) | Aerosolized CMS alone (\( n = 106 \)) | Odds ratio | 95% confidence interval | \( P \) value |
|-----------------|----------------------------------------|---------------------------------------|------------|------------------------|------------|
| Demographics    |                                        |                                       |            |                        |            |
| Gender, male    | 70 (66.0%)                             | 70 (66.0%)                            | 1.000      | 0.761, 1.314           | 1.000      |
| Age (years)     | 51–100; 82 (77–88)                     | 51–97; 83 (75–87)                     | 0.76       |                        |            |
| 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) | 0.704 |                      |            |
| BMI > 25.0      | 10 (9.4%)                              | 14 (13.2%)                            | 0.714      | 0.242, 2.109           | 0.761      |
| Underlying co-morbidities |                                |                                       |            |                        |            |
| Charlson co-morbidity index score, range; median (IQR) | 0–9; 2 (2–4) | 0–11; 2 (1–3) | 0.396 |                      |            |
| COPD            | 20 (18.9%)                             | 36 (34.0%)                            | 0.452      | 0.185, 1.104           | 0.122      |
| Bronchiectasis  | 0 (0)                                  | 2 (1.9%)                              | 1.019      | 0.982, 1.056           | 1.000      |
| Old pulmonary tuberculosis | 8 (7.5%) | 10 (9.4%) | 0.981 | 0.945, 1.018           | 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           | 0.281      |
| 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           | 0.238      |
| Malignancy      | 24 (22.6%)                             | 12 (11.3%)                            | 2.293      | 0.790, 6.656           | 0.195      |
| Diabetes mellitus | 62 (58.5%) | 36 (33.8%) | 2.522 | 1.152, 5.519           | 0.032      |
| Chronic renal failure | 26 (24.5%) | 20 (18.9%) | 1.398 | 0.551, 3.542           | 0.638      |
| Hepatic cirrhosis | 2 (1.9%) | 6 (5.7%) | 0.321 | 0.032, 3.185           | 0.618      |
| 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           | 0.515      |
| APACHE II score, range; median (IQR) | 6–41; 16 (12–23) | 6–39; 16 (13–21) | 1.166 | 0.541, 2.516           | 0.845      |
| APACHE II \( \geq 17 \) | 48 (45.3%) | 44 (41.5%) | 1.166 | 0.541, 2.516           | 0.845      |
| APACHE II \( \geq 21 \) | 34 (32.1%) | 28 (26.4%) | 1.315 | 0.568, 3.047           | 0.670      |
| NIV use         | 22 (20.8%)                             | 24 (22.6%)                            | 0.806      | 0.324, 2.007           | 0.817      |
| Invasive ventilation | 38 (35.8%) | 34 (32.1%) | 1.183 | 0.529, 2.647           | 0.838      |
| Indicated for ICU care | 42 (39.6%) | 38 (35.8%) | 1.174 | 0.535, 2.578           | 0.841      |
| Acinetobacter baumannii validated as an implicated pneumonic pathogen | 68 (65.1%) | 73 (68.9%) | 0.843 | 0.475, 1.495           | 0.661      |

**Note:** APACHE II score = Acute Physiological and Chronic Health Evaluation II score; BMI = body mass index; CAD = coronary artery disease; CRF = 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 = extensively drug-resistant Acinetobacter calcoaceticus-A. baumannii complex isolates.
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-\textit{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 \textit{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-\textit{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.[35] Additionally, humans achieve high pulmonary area-under-the-concentration of colistin (ranging 18.9–73.1 \mu g/mL) and high maximum pulmonary colistin concentrations (mean ± SD, 6.00 ± 3.45 \mu g/mL) during an AS-CMS dosing (with 2 million units) interval.[39] 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 \textit{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 \textit{A. baumannii} can grow in the presence of up to 10 \mu g/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 \textit{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 \textit{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
pneumonia or sepsis to a considerable degree.\textsuperscript{1,3,4,19,31} CRF and \( \geq 2 \)-week high-dose corticosteroid use, both were deemed factors superimposing hosts into the immunocompromised status\textsuperscript{1,3,4} 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.\textsuperscript{31} 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 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 | 30-day fatal cases (n=60) | 30-day non-fatal cases (n=152) | Odds ratio | 95% confidence interval | P value |
|------------------|--------------------------|--------------------------------|------------|-------------------------|---------|
| Demographics | | | | | |
| Gender, male | 42 (70.0) | 98 (64.5) | 1.286 | 0.517, 3.198 | .654 |
| Age (years), range; median (IQR) | 51–83; 82 (72–88) | 51–100; 83 (77–86) | | | .972 |
| BMI, range; mean (± SD) | 11.2–26.6; 20.66 (± 3.49) | 13.3–31.4; 20.51 (± 4.13) | | | |
| Age > 65 years | 52 (86.7) | 144 (94.7) | 1.346 | 1.013, 1.704 | .039 |
| BMI > 25.0 | 4 (6.7) | 20 (13.2) | | | |
| Underlying 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) | 1.206 | 0.930, 5.566 | .170 |
| 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 |
| Neurology diseases | 30 (50) | 92 (60.5) | 3.537 | 0.467, 61.425 | .192 |
| 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 | .900 |
| Chronic renal failure | 19 (31.7) | 20 (13.1) | 3.423 | 0.922, 12.635 | .114 |
| Receipt of chronic HD or PD therapy | 4 (6.7) | 2 (1.3) | | | |
| 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 | 0.611, 2.343 | .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, 3.902 | .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) | 0.707 | 0.426, 1.492 | .518 |
| Post-treatment courses, outcomes | | | | | |
| Use of TGC | 36 (60) | 70 (46.1) | 1.757 | 0.745, 4.146 | .281 |
| Odds of clinical cure or improvement on post-therapy day 14 | 42 (70) | 100 (65.8) | 1.560 | 0.587, 4.148 | .478 |
| Patients who received appropriate antibiotic(s) within 3 days after pneumonia happened | | | | | |
| Durations (days) of aerosolized CMS use; Range; mean (± SD) | 3–23; 11.73 (± 5.94) | 3–29; 12.39 (± 6.05) | | | .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, 7.415 | .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*-*A. baumannii* complex isolates.

\textsuperscript{1} 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.
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.

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