Efficacy and Safety Profile Comparison of Colistin and Tigecycline on the Extensively Drug Resistant Acinetobacter baumannii

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Colistin and tigecycline are the only therapeutic options for extensively drug resistant Acinetobacter baumannii (XDR-AB), but there is little comparative study. This retrospective observation study evaluated two-colistin and tigecycline-antibiotics profiles like treatment success rate, negative conversion rate, the length of hospital stay, intensive care unit (ICU) stay and antibiotics use, mortality rate during hospital stay and adverse event rate, based on the medical record of XDR-AB positive patients who were treated at least 5d with those intravenous antibiotics. Treatment success rate of colistin (n=39) and tigecycline (n=16) were not different: 48.7% and 43.8%, respectively (p=0.737), though negative conversion rate was significantly higher in the colistin group: 46.2% against 12.5% (p=0.049). There was no statistically significant difference in mortality rate between two groups during hospital stay (43.6% vs. 56.3%, p=0.393). There were no significant differences in the following parameters: the median length of hospital stay (46.0 d vs. 72.5 d), the median length of intensive care units stay (26.0 d vs. 27.0 d), the median length of antibiotics use (15.0 d vs. 13.0 d). The colistin group showed serum creatinine elevation (defined as elevation more than 2.0 mg/dL and 50% increase from the baseline) as 43.6% when compared with 12.5% of the tigecycline group (p=0.028). As a therapeutic option of XDR-AB, colistin showed significantly better negative conversion rate than tigecycline with more frequent nephrotoxic prevalence, and treatment success rate and mortality rate were not different from both antibiotics groups.

Key words extensively drug resistant (XDR); Acinetobacter baumannii; colistin; tigecycline

Acinetobacter baumannii is aerobic Gram negative cocco-bacillus, which is a problematic cause of opportunistic infection in the immunocompromised patient population.1,2 As it is one of the commonly increasing hospital infection sources worldwide,3 A. baumannii is also an important rising threat in our intensive care units (ICUs), resulting ventilator associated pneumonia or blood stream infection by extensively drug resistant A. baumannii (XDR-AB).

In our hospital (tertiary care, academic hospital), A. baumannii accounts for 53% (74 cases) in 2008 and 62% (209 cases) in 2009, among carbapenem resistant Gram negative bacterial infection. While in ICUs, carbapenem susceptibility has decreased from 46–51% in 2008 to 23–24% in 2009. As a result, colistin known as a therapeutic antibiotic showing 98% sensitivity4 to A. baumannii got a great attention. Colistin, which has been used as a topical agent due to serious adverse events like nephrotoxicity after the introduction in 19595,6 gets new attention as an effective antibiotics nowadays because multidrug resistant Pseudomonas, Acinetobacter spp. infection emerges.7 Though the expected neurotoxicity and nephrotoxicity was not high compared with the previous reports,8 it will be still appropriate to do close monitoring and dose modification in the patients with decreased renal function because nephrotoxicity is still the most frequent adverse events.

In 2009, there was a shortage of colistin worldwide and tigecycline was used in our hospital against carbapenem resistant A. baumannii infection, even though there were mostly in-vitro data,9 and clinical experience was limited. Considering the fact that both of these drugs—colistin and tigecycline—are the only therapeutic options for the XDR-AB infection8 and there are not sufficient comparative data between them though there were clinical studies for each drug in small patient population. Therefore, we compared the efficacy and safety of these two antibiotics in the XDR-AB infected patients in order to explore the clinical application of tigecycline in our clinical drug decision.

METHODS

Population This retrospective study included all the patients who were given colistin (colistimethate sodium) or tigecycline for more than 5 consecutive days intravenously, among A. baumannii isolated patients with all other antibiotics resistant, except colistin and minocycline in antibiotics susceptibility test results. Tigecycline patients were collected usually between 2009 September and 2010 January and colistin patients were collected from 2010 February to 2010 August in Seoul St. Mary’s Hospital of Catholic Medical College of Catholic University in Korea. This patient population can be considered as carbapenem resistant, XDR-AB infected patient population only susceptible to colistin or minocycline (in our hospital, minocycline sensitivity result used for the tigecycline because tigecycline is derivate of minocycline). Antibiotics susceptibility tests of cultured bacteria were done by the microwell dilution method, using Vitek 2 (Biomerieux, France) and interpreted using Clinical and Laboratory Standard Institute (CLSI) guideline. Minimum inhibitory concentration (MIC) ranges of two study medications are like the followings; Colistin-Susceptible: MIC≤2 mg/L, Intermediate susceptible: 2 mg/L<MIC<4 mg/L, Resistant: MIC≥4 mg/L. Minocycline-Susceptible: MIC≤4 mg/L, Intermediate susceptible: 4 mg/L<MIC<16 mg/L, Resistant:
MIC ≥ 16 mg/L. Amikacin, aztreonam, cefazidime, colistin, ceftazidine, imipenem, meropenem, piperacillin, trimethoprim/sulfamethoxazole, piperacillin/tazobactam, tobramycin, ticarcillin/clavulanic acid, ticarcillin, ampicillin/sulbactam, minocycline, levofloxacin, gentamicin, and ciprofloxacin were included in this sensitivity test. The patients who were prescribed both colistin and tigecycline, used one drug but not in consecutive manners, or on antibiotics (colistin or tigecycline) at the time of admission were excluded.

Definition of A. baumannii Infection Multi drug resistant A. baumannii (MDR-AB) means A. baumannii resistant to at least three classes of antimicrobial agents among penicillins, cephalosporins, fluoroquinolones or aminoglycosides. Extensively drug resistant A. baumannii (XDR-AB) means carbapenem resistant A. baumannii infection, worse than MDR-AB, susceptible only a few anti-microbials.

A. baumannii infection type was defined by doctors’ clinical record based on the clinical sign and positive culture together with the positive relationship with infection type and A. baumannii. Thus, A. baumannii infection type can be a case; (1) the positive relationship between A. baumannii and infection, (2) A. baumannii was identified in the culture and (3) clinical sign and symptom is aligned with infection type. If A. baumannii was found in the various sites, then infection type was clarified with the above mentioned criteria.

Endpoints The main efficacy endpoints were treatment success rate, negative conversion rate and mortality rate during hospital stay. Other efficacy endpoints were length of hospital stay, length of ICU stay and length of antibiotics use. Safety endpoints in the laboratory values were nephrotoxicity, hematologic toxicity, and hepatotoxicity based on the lab results. Clinical safety endpoints were evaluated by adverse events in the medical record focusing gastrointestinal (GI) toxicity and neurotoxicity. Treatment success or failure was determined by the negative conversion and clinical improvement. Negative conversion was defined by the two consecutive negative culture results after the use of colistin or tigecycline. Clinical improvement was defined when patients discharged after the discontinuation of antibiotics due to better clinical status. Treatment success was considered when the patient discharged with clinical improvement, regardless of culture conversion, and treatment failure was when it was impossible to decide or patient became worsened clinically with either persistent or non-applicable culture results.

Nephrotoxicity was defined when serum creatinine (Scr) became more than 2 mg/dL if the baseline Scr was normal (equal or less than 1.2 mg/dL) or when Scr increased by 50% or more if the baseline Scr was more than 1.2 mg/dL. For the other evaluation of nephrotoxicity, the median difference of Scr and blood urea nitrogen (BUN) between before and after the antibiotics use were measured and analyzed.

Hematologic adverse events in the laboratory values were defined when platelet decreased lower than lower limit of normal (LLN) from the normal baseline or decrease more than 50% from the abnormal baseline less than LLN. Hepatic adverse event in the laboratory values were defined like the followings;
1. Serum alkaline phosphatase (ALP) or total bilirubine increase was defined
   a. From the normal baseline-more than 2 times the upper limit of normal (ULN)
the closest time of antibiotics administration \( (p=0.018) \). There were no clinically significant differences in the ventilator use rate (colistin 87.2% \( \text{vs.} \) tigecycline 81.3%) and intubation rates (colistin 87.2% \( \text{vs.} \) tigecycline 87.5%), and both groups showed increased respiratory device use due to acute respiratory distress syndrome, pneumonia, and etc. There was no difference between the two groups regarding infection type. Pneumonia was the most frequently found infection type and bacteremia was the second most frequent one. Eleven patients had multiple \( A. \) baumannii infection types (Table 1).

Patients who were treated with multiple antibiotics due to concurrent micro-organisms were also included in this study. At the time point of colistin or tigecycline treatment for \( A. \) baumannii infection, 15 patients had more than 2 micro-organisms in the same specimen that \( A. \) baumannii infection, 15 patients had more than 2 micro-organisms. Two out of 4 patients had showed multiple organisms. Four out of 11 patients had \( Pseudomonas \) aeruginosa. In other cases, \( Enterococcus \) faecium, \( Staphylococcus \) aureus, \( Klebsiella \) pneumonia, \( Enterobacter \) cloacae, \( Streptococcus \) viridians, \( Escherichia \) coli were found. In the tigecycline group, 4 out of 16 patients have showed multiple organisms. Two out of 4 patients had \( Pseudomonas \) aeruginosa. In other cases, \( Enterococcus \) faecium, \( Staphylococcus \) aureus, \( Klebsiella \) pneumonia, \( Stenotrophomonas \) maltophilia, \( Escherichia \) coli were found.

Sensitivity test showed 100% susceptibility for colistin \( A. \) baumannii found. In \( Enterococcus \) faecium, \( Staphylococcus \) aureus, \( Klebsiella \) pneumonia, \( Stenotrophomonas \) maltophilia, \( Escherichia \) coli were found.

In the poor renal function patient population at the baseline, showed 38.7% nephrotoxicity, but the tigecycline group 9.0%. In the baseline Scr normal patient population, the colistin group showed 38.7% nephrotoxicity, but the tigecycline group 9.0%. In the poor renal function patient population at the baseline, the colistin group showed 62.5% nephrotoxicity comparing with 20.0% of the tigecycline group. The median of Scr difference before and after the use of colistin was 1.1 (0.5–1.5) mg/dL against 0.2 (0.1–0.8) mg/dL of the tigecycline group \( (p=0.015) \), but BUN did not show any significant difference (Table 3).

### Treatment Results
The overall treatment success rate was 47.3%, there was no statistically significant difference regarding treatment success rate between colistin group and tigecycline group (48.7% \( \text{vs.} \) 43.8%, \( p=0.737 \)). Negative conversion rate of the colistin group was significantly higher than that of the tigecycline group (46.2% \( \text{vs.} \) 12.5%, \( p=0.049 \)). There was no statistically significant difference about mortality rate during hospital stay between two groups (43.6% \( \text{vs.} \) 56.3%, \( p=0.393 \)). The median length of hospital stay, ICU stay and antibiotics use did not differ between the two groups (Table 2).

Additional analysis result, median hospital stay in the survival patients from the two groups were not statistically different (91.0 d \( \text{vs.} \) 67.0 d, \( p=0.799 \)). Median hospital stay of survived patients from colistin group was 91.0 d which is longer than the total survival and mortality patients’ hospital stay, 46.0 d. Median hospital stay of survived patients from tigecycline group was 67.0 d which is shorter than the total survival and mortality patients’ hospital stay, 72.5 d. In conclusion, only colistin group’s hospital stay was shortened by mortality cases.

### Adverse Events
Nephrotoxicity cases defined by Scr change were observed more frequently in the colistin group (43.6%) against the tigecycline group (12.5%) \( (p=0.028) \). In the baseline Scr normal patient population, the colistin group showed 38.7% nephrotoxicity, but the tigecycline group 9.0%. In the poor renal function patient population at the baseline, the colistin group showed 62.5% nephrotoxicity comparing with 20.0% of the tigecycline group. The median of Scr difference before and after the use of colistin was 1.1 (0.5–1.5) mg/dL against 0.2 (0.1–0.8) mg/dL of the tigecycline group \( (p=0.015) \), but BUN did not show any significant difference (Table 3).

Multivariate analysis to explore concomitant antimicrobials’ effect on the nephrotoxicity was not applicable due to small patient population and limited cases for the nephrotoxicity.

### Table 1. Comparison of Baseline Characteristics between Two Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Colistin ((n=39))</th>
<th>Tigecycline ((n=16))</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±S.D.</td>
<td>59.0±19.2</td>
<td>60.1±12.3</td>
<td>0.054</td>
</tr>
<tr>
<td>Male gender, (n) (%)</td>
<td>24 (61.5)</td>
<td>9 (56.3)</td>
<td>0.716</td>
</tr>
<tr>
<td>Co-morbidities, (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (28.2)</td>
<td>6 (37.5)</td>
<td>0.498</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (18.0)</td>
<td>3 (18.8)</td>
<td>0.944</td>
</tr>
<tr>
<td>Hepatic disorder (^a)</td>
<td>8 (20.5)</td>
<td>3 (18.8)</td>
<td>0.882</td>
</tr>
<tr>
<td>Renal disorder (^b)</td>
<td>5 (12.8)</td>
<td>1 (6.3)</td>
<td>0.478</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5 (12.8)</td>
<td>2 (12.5)</td>
<td>0.974</td>
</tr>
<tr>
<td>Baseline lab, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells, (×10^3/\text{mm}^3)</td>
<td>11.4 (7.6–14.5)</td>
<td>10.3 (7.0–18.4)</td>
<td>0.941</td>
</tr>
<tr>
<td>C-Reactive protein, mg/dL</td>
<td>10.6 (5.7–14.8)</td>
<td>15.6 (11.2–19.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>26.7 (15.8–44.6)</td>
<td>25.7 (12.9–47.9)</td>
<td>0.956</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.8 (0.5–1.1)</td>
<td>0.9 (0.6–1.3)</td>
<td>0.795</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>73.4 (44.3–98.6)</td>
<td>61.2 (49.6–133.6)</td>
<td>0.831</td>
</tr>
<tr>
<td>Respiratory device during admission, (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>34 (87.2)</td>
<td>13 (81.3)</td>
<td>0.571</td>
</tr>
<tr>
<td>Intubation</td>
<td>34 (87.2)</td>
<td>14 (87.5)</td>
<td>0.974</td>
</tr>
<tr>
<td>Type of ( A. ) baumannii infection, (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>30 (76.9)</td>
<td>11 (68.8)</td>
<td>0.519</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>8 (20.5)</td>
<td>5 (31.3)</td>
<td>0.489</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4 (10.3)</td>
<td>1 (6.3)</td>
<td>0.999</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1 (2.6)</td>
<td>2 (12.5)</td>
<td>0.200</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (2.6)</td>
<td>1 (6.3)</td>
<td>0.501</td>
</tr>
<tr>
<td>Biliary tract infection</td>
<td>1 (2.6)</td>
<td>1 (6.3)</td>
<td>0.501</td>
</tr>
</tbody>
</table>

S.D.: standard deviation, IQR: interquartile range, BAL: bronchoalveolar lavage. a) Hepatic disorder: hepatitis, liver cirrhosis, hepatocellular carcinoma, cholecystitis, liver transplantation (HBV carrier). b) Renal disorder: chronic renal failure, pyelonephritis, acute kidney injury. c) Infection types were counted multiple times when applicable.
Univariate analysis also showed wide confidence intervals. Patients together with nephrotoxic amphotericin B showed increase risk for nephrotoxicity (odds ratio 7.0, 95% CI 1.2–40.1; \( p = 0.029 \)) even against colistin only patient group. Regardless of concomitant antimicrobials therapy, colistin group have 5.4 times higher risk of nephrotoxicity against tigecycline patient group (odds ratio 5.4, 95% CI 1.1–27.1; \( p = 0.040 \)) (Table 4).

There was no significant difference between two groups in the decrease of platelet count and increase of ALP, ALT, AST, total bilirubin, amylase, INR, PT, and aPTT in order to check hematological and hepatic toxicity (Table 5).

Colistin group showed significantly higher adverse events; nausea/vomiting against tigecycline group (35.9% vs. 6.3%, \( p = 0.025 \)). However, abdominal pain was more frequent in the tigecycline group than in colistin group (2.6% vs. 18.8%,...
p=0.036). There was no significantly different in diarrhea, neurologic disorder and electrolyte imbalance.

Other adverse events profile were similar to package insert information; skin rash, urticaria, itching, fever in colistin group and itching, fever, hypoalbuminemia in tigecycline group.

**Prognosis** Among the total 55 patients, in-hospital mortality rate was 47.3% (26 patients). Underlying diseases of passed patients were like the following: solid tumor 30.8% (8 patients) and hematologic malignancy 19.2% (5 patients). Most causes of death were sepsis and pneumonia.

**DISCUSSION**

Since 1980s, *A. baumannii* has been isolated as one of the major nosocomial infection, and as of recently, multi drug resistant *A. baumannii* (MDR-AB) began to expand, resulting pandrug-resistant strains that are resistant to all standard antimicrobial agents in some area. 11–13) Carbapenem resistant *A. baumannii*, which is only susceptible to a few antibiotics, is a worldwide phenomenon 14) and resistance rate is as high as 50–60% in some institutions. 15,16) In the XDR-AB infection, colistin can be considered firstly due to its high susceptibility in the microbiology study. As an alternative, tigecycline can be considered if there is minocycline susceptibility. Usually, drug has been chosen based on the patient clinical situation however, there is no previous comparison between these two in the XDR-AB infection. Therefore, this retrospective study has value despite of its limitations as a comparison of colistin vs. tigecycline in the XDR-AB infection.

Considering the majority of our patients were in the ICUs, 47.3% mortality rates in this study is similar with other reported data. Crude mortality due to hospital acquired pneumonia by MDR-AB ranges around 30–75%, and this is more interpreted with the effects from underlying disease and related immunocompromise. Therefore, critically ill patients are easier to show high mortality and morbidity. 10) Mortality rate due to *A. baumannii* infection was reported, ranging 7.8–43%. In addition, there is another report that patients in the ICU showed higher mortality rate than patients in the general ward. 17)

Colistimethate, used in our hospital, is hydrolyzed and become active form of colistin, resulting in bacterioidal effect by increasing bacterial cell membrane permeability and breaking cell membrane. 18) It is effective to the Gram negative bacteria and can be used to the multidrug resistant *P. aeruginosa* or *A. baumannii* infection as first line. The treatment success rate of colistin ranges 57–77% in the critically ill patients with various manifestation and intravenous (i.v.) colistin showed 56–61% of the treatment success rate in pneumonia. 19) There is also a report showing only 25% treatment success rate in the pneumonia patient. 19) However, this result only came from i.v. colistin treatment which distribution to lung and cerebrospinal fluid is low. 20) Inhaled colistin can be considered based on the better result from colistin inhalation treatment in patients with ventilator associated pneumonia. 21) Therefore, relatively low treatment success rate (48.7%) in our study may be related with low distribution of colistin to lung tissue and relatively many pneumonia patients.

In our study, the tigecycline treatment success rate (43.8%) was lower than previous reports and mortality rate (56.3%) was higher. Minocycline derivate, tigecycline is bacteriostatic, broad-spectrum i.v. antibiotics approved for complicated soft tissue infection, community acquired pneumonia, intra-abdominal infection and intraperitoneal infection by the U.S. Food and Drug Administration (FDA). It is not necessary to do dose modification in renal disease because it is not excreted to the kidney like colistin. The major adverse events are GI troubles: nausea, vomiting, and diarrhea. 22) Current CLSI do not suggest tigecycline’s susceptibility criteria against *A. baumannii*. Most clinical studies of tigecycline against MDR-AB infections are retrospective, non-comparative as a part of a combination therapy with other antibiotics. In the ventilator associated pneumonia patients, two studies showed 69–84% clinical treatment success rates. However, the treatment success rate in these studies was lower especially when sepsis accompanies. Besides, resistance has been observed during tigecycline therapy in some patients. 9,10) There is one study reported 41% of mortality rate when tigecycline was used for the MDR-AB infection. 22)

In our retrospective comparison study, negative conversion rate by colistin was 46.2%, compared with 12.5% of tigecycline. However, negative conversion rate was not able to make any difference in the treatment success rate. In vitro study, colistin susceptibility to *Acinetobacter* isolates was more than 98% 4) and tigecycline was 80.9–93.1%. 23) However there was no head to head comparative clinical study, despite superior result of colistin in *in-vitro* study. Because we defined treatment success if there was clinical improvement and antibiotics could be stopped regardless of negative conversion, tigecycline group cases were able to be captured as a treatment success, even if it failed to convert negatively.

Mortality rate during hospital stay was not significantly different between two groups because patient population from the colistin group, who was not able to change negatively showed higher mortality rate, compared with the patient population from the tigecycline group, not showing negative conversion. The number of malignancy patient from all the patients was higher in the underlying disease analysis; and therefore, it may be possible to think risk factor for the higher mortality rate.

When subgroup analysis was applied for the concomitant antimicrobials with colistin or tigecycline for more than five days-extended spectrum β lactamase inhibitor, fluoroquinolone, aminoglycoside, the 3rd generation cephalosporin (cefazidime), carbapenem, known to be effective traditionally against Gram negative rods infection—to explore the effect for negative conversion rate and treatment success rate, there was no significant difference.

Colistin’s representative adverse event, nephrotoxicity, was observed higher (43.6%) significantly when compared with tigecycline (12.5%). Though there is an article reporting 20% of nephrotoxicity, the frequency ranges 5–58% with different definition of nephrotoxicity by articles, and it is difficult to set the frequency. 8,24) There are various factors-clinical state and administration of nephrotoxin-influencing nephrotoxicity evaluation even though colistin may result in hematuria, proteinuria, oliguria or acute renal failure, which can suggest nephrotoxic status. 7,16,25) Therefore, it is not easy to evaluate nephrotoxicity. As one of the efforts to identify the predisposing factor of nephrotoxicity, concomitant antimicrobials uses were analyzed and it was possible to confirm higher nephrotoxicity rate with amphotericin B concomitant use in
the colistin group. Amphotericin B concomitant use increase nephrotoxicity risk 7 times significantly but vacuemycin risk was not statistically significant. Aminoglycoside concomitant use patients were 3 in total (2 with colistin, 1 with tigecycline) but it was too small to talk about nephrotoxicity risk statistically. Based on this analysis showing other medications acted as potential nephrotoxins, it would be appropriate to think that actual nephrotoxicity of colistin use can be lower than currently reported. It was not possible to confirm whether this nephrotoxicity was reversible or not, and if it was reversible, how many hours it would take to return to normal status due to the nature of this study method.

Laboratory value abnormalities focusing on the hematologic toxicity or hepatic toxicity were not different from the two cohorts. In the tigecycline registration study submitted to the FDA, abnormal liver function test results or thrombocytopenia rates were similar with comparator as 2–5% in the package insert. However, as pointed out as our limitation, relatively in-homogeneous patient population in our retrospective study might contribute to the higher rate of thrombocytopenia or abnormal liver function test results. Thus, if further causality assessment were possible, the rate could be changed.

Totally 20.5% neurotoxicity rate was observed in our study but it should be understood in the context of retrospective study design and influence of sedation in ICUs. In early studies, neurotoxicity was reported about 7% and occurred within 4d of antibiotics treatment initiation in most patients. However, in other study after 1999, there were only 2 patients who reported neurotoxicity among 230 patients of colistin treated patients, suggesting less frequent neurotoxicity than previously reported. Nevertheless, it would be rational to consider that a lot of patients were in a sedated or paralyzed status and difficult to discover delicate neuronal adverse events. In a study done in 31 cystic fibrosis patients, 21 patients (68%) were reported neurologic adverse events, like paresthesia or ataxia.

There are several limitations in this study. This is retrospective study based on the medical record. The efficacy analysis may be affected by the retrospective nature of this study incorporating multiple causative organisms together with A. baumannii and concomitant use of antibiotics resulting in inhomogeneous patient population. Patient numbers are too small. We were not able to provide detailed severity information of patients and included tigecycline immediately susceptible patients. Randomization was not able to be used. However, most previous studies evaluating therapeutic efficacy of antibiotics against MDR-AB were uncontrolled case series, animal models or in vitro studies without appropriate comparison. Moreover, there were conflicting results in the combination therapy, and there is limited data for the efficacy of therapeutic antibiotics against MDR-AB infection and no data against XDR-AB infection. This study compared the only therapeutic options—colistin and tigecycline—in this XDR-AB infection, therefore, despite the retrospective nature of this study with small number of patients and disproportional patient population, this study gave us useful information evaluating efficacy and safety of these two antibiotics for the XDR-AB infection patient and future study direction. It may reveal the clinical evidence from real life clinical situation due to coinfecction and concurrent antibiotics use which is also very easy to be found in the real life situation.

Prospective, randomized, controlled study will be necessary in order to give detailed confirmatory information about efficacy in a statistically sufficient patient numbers. It may also be necessary to develop new combination therapy information as a stepping stone in the situation that we cannot guarantee the future development. In this study, concomitant antimicrobial uses were analyzed to explore the relationship between concomitant antibiotics and treatment success rate/negative conversion rate and concluded there were no statistically significance. Large, controlled study will be necessary to confirm the effect of combination therapy and overcome these limitations of this retrospective study.

In conclusion, colistin, rising antibiotics for the multidrug resistant Gram negative bacterial infection, shows high susceptibility against XDR-AB infection and is drug of choice, despite the limited treatment success rate. Therefore, colistin used widely in the clinical field and tigecycline can be used despite the limited clinical data as an alternative. Especially, in the renal function compromised patients who cannot be treated with colistin, tigecycline can be a significantly important alternative based on the result of this analysis. Colistin showed better negative conversion, but treatment success rate and mortality rate were not different between these two antibiotics for XDR-AB infection.

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