Case Report

Treatment of pulmonary infection of extensively drug-resistant *Acinetobacter baumannii* with intravenous colistin sulfate combined with atomization: a case report

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Abstract: Extensively drug-resistant *Acinetobacter baumannii* (XDRAB) pulmonary infection is a serious respiratory system infection. Patients are often very sick and even need to be admitted to the ICU for treatment. In this case report, we presented our treatment experience of one XDRAB pulmonary infection patient. A 71-year-old male patient was admitted to our hospital complaining of "fatigue accompanied by fever for 2 days and shortness of breath for 1 day". The patient's admission diagnosis was as follows: severe pneumonia, acute respiratory distress syndrome, I type respiratory failure, septic shock, cardiac insufficiency, liver insufficiency, and hypertension. Imipenem/cilastatin sodium combined with moxifloxacin were first applied. Then, tigecycline, imipenem/cilastatin and caspofungin were used. The drug sensitivity results suggested that the XDRAB strain of this patient's sputum culture was sensitive to polymyxin only. Thus, colistin sulfate and cefoperazone/sulbactam were applied. The medication process of the patient was monitored. We found that a colistin sulfate intravenous injection combined with aerosol route combined with cefoperazone/sulbactam was effective in the treatment of XDRAB pulmonary infection, and no adverse drug reactions were observed during the treatment. The anti-infection therapy of intravenous colistin sulfate combined with nebulization and cefoperazone/sulbactam could be a good choice for the treatment of XDRAB lung infections.

Keywords: Colistin sulfate; intravenous combined atomization; extensively drug-resistant *Acinetobacter baumannii* (XDRAB); anti-infective therapy; case report

Submitted Jul 05, 2021. Accepted for publication Aug 18, 2021.
doi: 10.21037/apm-21-2112
View this article at: https://dx.doi.org/10.21037/apm-21-2112

Introduction

In recent years, bacterial resistance has become a major threat to human health. The detection rate of multi-drug resistant bacteria represented by G-bacillus is rising rapidly, bringing great challenges to clinical anti-infection treatment (1). Extensive drug resistance refers to the phenomenon that bacteria are not sensitive to almost all classes of antibiotics except for classes 1–2 (mainly polymyxin and tigecycline) (2). Common strains that are extensively drug resistant (XDR), including *Enterobacteriaceae bacteria*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, and extensively drug-resistant *Acinetobacter baumannii* (XDRAB), are frequently seen in intensive care units (ICUs). There are few effective drugs for the treatment of XDRAB infection, and the pathogens mostly occur in patients with serious underlying diseases, immunodeficiency, or those who have repeatedly used broad-spectrum antibacterial drugs for a long period.

Anti-infection treatment is often unsatisfactory, which has become a very difficult problem in the field of bacterial infection. This study discusses a severe case of XDRAB pulmonary infection in a patient. After the initial anti-XDRAB treatment was ineffective, the treatment was adjusted to colistin sulfate combined with atomization and combined with cefoperazone/sulbactam. Ultimately, the patient was successfully treated and discharged. We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2112).

Case presentation

A 71-year-old male patient was admitted to our hospital complaining of "fatigue accompanied by fever for 2 days and shortness of breath for 1 day," the discontinuous twitching of limbs and urinary incontinence. At admission, his body temperature was 38.8 ℃. The patient was immediately given symptomatic supportive treatment, including oxygen inhalation, anti-infection, and fluid infusion. The patient then developed shortness of breath, and his blood oxygen saturation decreased. The patient was treated with non-invasive ventilator assisted breathing. The patient's routine blood results were as follows: white blood cells (WBCs) 4.59×10^9/L, and N% 83.3%. A computed tomography (CT) scan showed lacunar cerebral infarction on the bilateral basal ganglia, the formation of a softening lesion on the right basal ganglia, chronic bronchitis in both lungs, and inflammations in the upper and middle lobes of the right lung and the lower lobe of left lung. The patient's symptoms worsened, and he was admitted to the ICU for further treatment. The patient's admission diagnosis was as follows: severe pneumonia, acute respiratory distress syndrome, I type respiratory failure, septic shock, cardiac insufficiency, liver insufficiency, and hypertension. After admission to the ICU, the patient was placed on electrocardiogram (ECG) monitoring. The patient was treated with endotracheal intubation ventilator assisted breathing, imipenem/cilastatin 1 g/q8h combined with moxifloxacin 0.4 g/qd for anti-infection, norepinephrine for hypotension, dezocine for analgesia, and dexmedetomidine and propofol for sedation. The patient's fluid and electrolyte balance was maintained, and the patient received other symptomatic supportive treatments. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Clinical symptoms of XDRAB pulmonary infection, and diagnosis

In addition to the usual signs of bacterial infection, such as fever, Leukocytes and/or neutrophils and C-reactive protein increased, the following points should be taken into account to determine lung infection caused by XDRAB: (I) clinical signs and symptoms consistent with pneumonia and imaging findings like: latest, persistent, or aggravated pulmonary exudation, infiltration, or consolidation; (II) patient factors: including underlying disease, immune status, previous use of antibiotics, and other risk factors related to the onset, such as mechanical ventilation time, etc.; (III) if a patient who is receiving antibacterial agents gets better for a while and then suddenly gets worse, and the timing of the deterioration coincides with the appearance of XDRAB in time; (IV) the clinical significance of positive culture results was evaluated in terms of specimen collection method, specimen quality, bacterial concentration (quantitative or semi-quantitative culture), smear findings, etc.; (V) more than two times sputum cultures showed XDRAB dominant growth.

Anti-infective treatment process

On the 3rd day of admission, the patient's examination results were as follows: temperature: 38.5 ℃ with the pumping of 1 μg/(kg·min) norepinephrine; WBC: 2.94×10^9/L; platelet (PLT): 108×10^9/L, N%: 80%; C-reactive protein (CRP): 108.9 mg/L; procalcitonin (PCT) >100 ng/mL; G test: 42.61 pg/mL; and sputum smear: G^- bacillus positive. Based on these results and the epidemiology results in the ICU, the possibility of XDRAB infection was considered highly likely. Moxifloxacin was discontinued. Tigecycline 100 mg q12h [first dose: 200 mg statim (ST)] combined with imipenem/cilastatin were administered for anti-XDRAB treatment. Antifungal therapy was performed with caspofungin 50 mg/qd (initial dose 70 mgST). The patient was treated with continuous renal replacement therapy (CRRT; mode: continuous veno-venous hemofiltration).

On the 10th day of admission, the patient's condition and results were as follows: temperature: 36.7 ℃; endotracheal intubation ventilator assisted breathing; reduction in

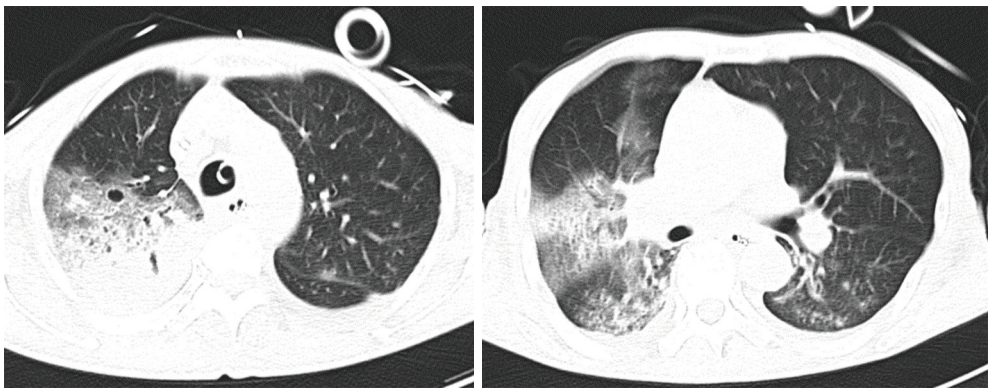

Figure 1 Pulmonary CT before adjustment of colistin sulfate IV combined with atomization pathway and cefoperazone/sulbactam anti-infection regimen.

noradrenaline to 0.05 μg/(kg·min); PCT: 5.2 ng/mL; and CRP: 90.8 mg/L. The patient's routine blood results were as follows: WBC 4.92×10^9/L; N%: 86.4%; and sputum culture: XDRAB (+++). The drug sensitivity results suggested that the bacteria was sensitive to polymyxin only [minimum inhibitory concentration (MIC) ≤1 μg/mL]. The CT scan showed chronic bronchitis of both lungs, and a pneumonia (the results was slightly better than those obtained before). Optimized imipenem/cilastatin was then administered as follows: 0.5 g q8h (micropump 2 h) + 0.5 g q8h (micropump 2 h). The total amount of imipenem in 1 day was still 3 g, with 4 h of micro-pumping during the 8 h administration interval.

On the 13th day of admission, the patient's condition and results were as follows: temperature: 38.1 ℃; tracheotomy and ventilator assisted breathing; CRRT renal replacement therapy. Noradrenaline was discontinued. The patient's previous day's urine output was 580 ml/d. The patient's routine blood results were as follows: WBC: 6.17×10^9/L; PLT: 57×10^9/L; N%: 84.4%; PCT: 3.41 ng/mL; and sputum culture: XDRAB (+++), CT scan (*Figure 1*). The drug sensitivity results suggested that the bacteria was sensitive to polymyxin only (MIC ≤1 μg/mL). Imipenem/cilastatin and tigecycline were discontinued. Colistin sulfate was administered with 750,000 U ivgtt q12 (first dose: 1 million U, ST), 250,000 U aerosol inhalation q12h and combined with cefoperazone/sulbactam (2:1 dosage form) 4.5 g ivgtt q8h for anti-infection treatment.

On the 17th day of admission, the patient's condition and results were as follow: temperature: 37.3 ℃; tracheotomy and oxygen inhalation with mask (5 L/min); CRRT discontinued. The patient's routine blood results were as follows: WBC: 7.1×10^9/L; PLT: 61×10^9/L; N%: 72.1%; PCT: 0.075 ng/mL; Alanine transaminase (ALT): 25.4 μ/L; total bilirubin (TBIL): 27.7 μmol/L; albumin (ALB): 35.8 g/L; and creatinine (Cr): 63 μmol/L. These results indicated the anti-infection therapy was effective.

On the 19th day of admission, after a series of active anti-infection, anti-shock, and other treatments, the patient's respiratory and circulatory systems were stable, and his liver and kidney functions were significantly better than before. The CRRT and ventilator had been stopped, and the patient was inhaling oxygen via a mask instead. After improving, the patient was discharged to the rehabilitation hospital for further treatment. No adverse drug reactions occurred during this treatment.

Analysis of the treatment procedure

Development of initial anti-infection and anti-XDRAB protocols

The patient developed severe pneumonia with unstable respiratory and circulatory conditions. After admission to the ICU, the patient was treated with imipenem/cilastatin combined with moxifloxacin for anti-infection, covering *Enterobacteriaceae bacteria* producing extended spectrum beta-lactamases, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Legionella* and atypical pathogens. On day 3, G-bacilli were found on a sputum smear, and an initial empirical anti-XDRAB regimen of tigecycline combined with imipenem/cilastatin was used. The patient was given a tigecycline dose of 100 mg q12h (first dose: 200 mg). The sputum culture suggested XDRAB. Imipenem MIC >8 μg/mL was administered. Imipenem/cilastatin is carbapenems, time-

dependent antimicrobial agents, and the pharmacokinetics/pharmacodynamics (PK/PD) parameter is T% > MIC. Thus, the administration mode of imipenem/cilastatin was optimized as a delayed infusion therapy. During the 8 h administration interval, the drug was micro-pumped for 4 h, followed by a continuous 2 h of micro-pumping to ensure the stability of the drug (3,4). In relation to Acinetobacter baumannii with decreased sensitivity to carbapenems, such as a MIC of 4–16 mg/L, the T% > MIC time can be prolonged by increasing the administration frequency, increasing the dose of administration, or prolonging the time of intravenous infusion to improve the anti-infection therapeutic effects (5).

The analysis of the readjusted anti-XDRAB protocol

After the treatment of XDRAB with the anti-infection regimen of high-dose tigecycline and the prolonged infusion of imipenem/cilastatin, the patient's body temperature remained high. PCT decreased, but not significantly, and the patient's oxygenation index was not ideal. The sputum culture again suggested XDRAB, and the drug sensitivity results only revealed a sensitivity to polymyxin. In relation to the XDRAB infection, the guidelines recommend sulbactam and its mixture based combination, a tigecycline-based combination, and a polymyxin-based combination (6,7). Combined with the drug sensitivity results of the patient and the previous drug use, the anti-XDRAB regimen was changed again to colistin sulfate combined with cefoperazone/sulbactam. The patient was intravenously administered colistin sulfate combined with nebulization (8). Colistin sulfate can be inhaled and directly act on lung tissue. In patients with severe hospital acquired pneumonia or ventilator associated pneumonia, intravenous infusion and nebulization is recommended to improve the treatment efficacy (9). The patient continued to receive CRRT treatment; however, colistin sulfate was the active ingredient. Only a small amount of drugs were excreted through the kidneys; most of the drugs were excreted in other ways. As the patient's liver function was good, the dosage of colistin sulfate was not adjusted, and the patient continued to be treated with 750,000 U intravenous drip q12h (first dose: 1 million U) combined with 250,000 U atomized q12h.

According to the guidelines, the dosage of cefoperazone/sulbactam for XDRAB treatment should be ≥4 g/d (6). In this study, the dosage of cefoperazone/sulbactam has a ratio of 2:1 with 4.5 g intravenous drop q8h, and the dosage of sulbactam was 4.5 g/d. The patient was treated with colistin sulfate intravenous infusion combined with atomization, which was then combined with cefoperazone/sulbactam for effective anti-pulmonary XDRAB infection treatment. The patient's body temperature and inflammation indexes decreased, and his respiratory circulation stabilized. The patient's liver and kidney function improved after treatment. The CRRT was stopped, the ventilator was removed successfully, and the patient was discharged from hospital.

Discussion

Acinetobacter baumannii is one of the main causes of induced hospital-associated infections (10). There are a number of differences between XDRAB pulmonary infection and common pneumonia. First, the location of the two pulmonary infection is different. XDRAB pulmonary infection mainly occurs in hospitals, especially in patients receiving mechanical ventilation in the ICU. Common pneumonia such as community-acquired pneumonia (CAP) is an infectious lung inflammation that develops outside of the hospital. Secondly, the pathogens of the two types of pneumonia are different. The common pathogens of CAP are *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Klebsiella pneumoniae* and *Staphylococcus aureus*. In addition, the degree of drug resistance of pathogens is different. The pathogens of CAP are highly sensitive to antibacterial drugs, and there are many kinds of anti-infecting drugs available, such as penicillins, cephalosporins, respiratory quinolones, macrolides, etc. However, XDRAB has a high degree of drug resistance, and only polymyxin, tigecycline, sulbactam and its mixture, carbapenems, etc., can be selected as anti-infective drugs.

XDRAB usually causes ventilator-associated pneumonia (11). Due to an increase in the drug-resistant status of *Acinetobacter baumannii* (i.e., XDRAB), there are very few effective drugs for clinical treatment (12). The cause of XDRAB and risk factors includes: a long-time hospital stay, stay in ICU, antibacterial drug exposure, severe basic diseases, mechanical ventilation, invasive operation, etc. Further, there are no clear guidelines on the best treatment for multidrug-resistant *Acinetobacter baumannii* (MDRAB) and XDRAB infections. Polymyxins is a peptide antibiotic that plays an antibacterial role by destroying the integrity of the outer membrane of gram-negative bacteria (13). Colistin drugs have been on the market since the 1950s. Due to the high nephrotoxicity of polymyxin drugs, it was replaced by other safer antimicrobial agents. However, in recent years, with the increasing resistance of G-bacteria,

Table 1 Comparison of clinical use of polymyxins

Characteristics	Drug		
	Polymyxin B sulfate for injection	Sodium polymyxin E mesylate for injection	Colistin sulfate for injection
Category	Polymyxin B	Polymyxin E	Polymyxin E
Drug activity	Active pharmaceutical ingredient	Prodrug	Active pharmaceutical ingredient
Unit conversion	1 mg =10,000 IU	33 mg CBA =1 million IU	1 mg =22,700 IU
Recommended dose	1.25–1.5 mg/kg q12h, 2.0–2.5 mg/kg load capacity (8)	Patients with normal renal function: 4.50–5.45 million IU q12h, 9 million IU load capacity (8)	0.50–0.75 million IU q12h, 1 million IU load capacity
Urine concentration (14)	Low	High	Low
Clearance pathway (15)	Nonrenal pathway	Mainly excreted by the kidneys	Nonrenal pathway
Renal toxicity	Little	Big	Little
	Suggest TDM	Suggest TDM	Suggest TDM
Pigmentation of skin pigment	Incidence 8–15% (16)	None reported	None reported
TDM	Css, avg to 2–4 mg/L	Css, avg to 2 mg/L	Css, avg to 2 mg/L
Atomization inhalation (17)	0.25–0.50 million IU, 2 times/day	50–75 mg CBA, 2–3 times/day	0.25–0.50 million IU, 2 times/day
Intrathecal administration (8)	5 mg/d	0.125 million IU/d	No specific recommendation

TDM, therapeutic drug monitoring; CBA, colistin base activity.

such as XDRAB, the list of drugs available has become limited. The reintroduction of polymyxins in clinical practice is recommended for the treatment of infections caused by G-bacteria that have been identified or are strongly suspected to be resistant to carbapenems, but sensitive to polymyxins, primarily carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant pseudomonas aeruginosa. It may also be that as the quality of the agent has been improved, clinicians' fear of its toxicity has been alleviated, and its clinical application has been promoted. In China, polymyxin B and polymyxin E are commonly used. There are 2 varieties of polymyxin E: polymyxin E mesylate and colistin sulfate.

Colistin sulfate is active *in vitro*. The Clinical and Laboratory Standards Institute (CLSI) indicates that colistin sulfate can be used in microbial susceptibility tests, and that colistin and polymyxin B are equivalent drugs. The MIC of colistin can predict the MIC of polymyxin B, and the reverse prediction can also be drawn. However, in 2020, the CLSI updated the drug sensitivity test requirements for polymyxin drugs. In relation to *Enterobacteria*, *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, the MIC of polymyxin drugs ≤2 mg/L was considered intermediary, and ≥4 mg/L was considered resistant. In addition, the "Expert Consensus on Drug Sensitivity Detection and Clinical Understanding of Polymyxin" of China also noted that the drug sensitivity results of colistin and polymyxin B are equivalent. Testing 1 drug can predict the sensitivity of another drug; thus, it is necessary to use a reliable method to test the MIC of polymyxin drugs (14). The consensus suggested that for *Enterobacteria*, *Pseudomonas aeruginosa*, or *Acinetobacter baumannii*, the MIC breaking point of polymyxins was less than 2 mg/L for sensitivity, and ≥4 mg/L for resistance. Comparisons of the clinical use characteristics of polymyxin drugs are shown in *Table 1*.

In 2019, the "Infectious Diseases Society of America (IDSA)" and 6 other societies jointly initiated and signed the "International Consensus Guidelines for the Rational Use of Polymyxins" (8) to guide the correct application of polymyxins in adult patients. Subsequently, China organized national experts in relevant fields to discuss the clinical application of polymyxin, and formulated the "Chinese Expert Consensus on Clinical Application of Polymyxin",

which provided recommendations for clinical treatment of polymyxin B and colistin mesylate.

Colistin has been widely used to treat carbapenem-resistant Acinetobacter infections (18-21). Colistin has been used to treat XDRAB and MDRAB in recent clinical work (22). However, colistin has some disadvantages, such as low plasma concentrations, toxicity, lipopolysaccharide modification, and heteroresistance (21,23-25). A high dose of sulbactam combined with other antimicrobial agents is effective in the treatment of XDRAB infection (26-28). Combination therapy is more effective against such infections (29-31). Significant synergistic effects may occur when high doses of sulbactam (≥4 g/d) are administered (32). Consequently, other drugs, such as anti-gram-positive bacterial antibiotics, are used simultaneously to treat MDRAB infection (33-37). The nephrotoxicity of patients undergoing treatment regimens (including colistin combined with high doses of sulbactam, or carbapenems) was significantly lower than that of patients treated with colistin combined with another antimicrobial agent (levofloxacin, tigecycline, or others). These combined assessments suggest that high doses of sulbactam in combination with other antimicrobial agents may be a promising treatment option for patients infected with XDRAB.

Several meta-analyses have examined the efficacy and safety of colistin, sulbactam, and tigecycline alone or in combination with XDRAB and MDRAB (27,28,38). The effectiveness of the treatments varies from study to study for several reasons. First, the sample sizes have differed. Second, only the results of high-quality randomized control studies are convincing. Three studies (comprising a total of 61 patients) used a combination regimen of sulbactam, in which patients received 8–9 g of sulbactam daily (39-41). In 5 studies (comprising a total of 301 patients), sulbactam was used at 4–6 g per day in combination therapy (42,43). In 7 studies (comprising a total 669 patients), colistin was used for XDRAB infection in combination regimens (42-48). In most of these studies, colistin-based combination regimens were used. Thus, colistin combination regimens occupy the leading position in anti-XDRAB treatment regimens.

In the present case, on the 3rd day, tigecycline combined with imipenem/cilastatin was administered. Due to the great difference in sensitivity of tigecycline to XDRAB and the increasing trend of drug resistance, it is difficult for conventional doses to reach effective therapeutic concentrations. Thus, doses should be increased and used in combination with other antimicrobial agents. In addition, research has proven the efficacy and safety of high-dose tigecycline in the treatment of severe bacterial infections, and that high-dose tigecycline is more effective than low-dose regimens for severe patients with refractory infections (49). However, the body temperature of the patient in this case remained high. Thus, the therapeutic regimen was changed. Colistin sulfate combined with cefoperazone/sulbactam were administered. After treatment, the patient's body temperature and inflammation indexes decreased, respiratory and circulatory systems stabilized, and liver and kidney function improved. The CRRT and ventilator were removed successfully, and the patient was discharged from hospital.

The application of polymyxin-based combination therapy showed good treatment effects; however, the evidence level is low. Multi-center and large sample studies should be conducted to gather further evidence to support this conclusion.

Recommendations for the diagnosis and treatment of XDRAB pulmonary infections: XDRAB detection rates are common in the ICU, and attention should be paid to the distinction between "colonization" and "infection" before initiating targeted anti-XDRAB infection therapy. If the evaluation results are pathogenic bacteria, targeted anti-infection therapy should be implemented, such as two or three combination regimens based on sulbactam and its mixture, tigecycline, and polymyxin. Colistin sulfate intravenous atomization regimen combined with cefoperazone/sulbactam can be used as an option for the treatment of XDRAB pulmonary infection.

In summary, the patient, who was infected with XDRAB and admitted to the ICU of our hospital, was treated colistin sulfate, which was shown to have good clinical efficacy. Notably, no obvious adverse reactions were observed. The combination of intravenous atomization and cefoperazone/sulbactam could be a good choice for treating pulmonary infection caused by XDRAB.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2112

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2112). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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(English Language Editor: L. Huleatt)

Cite this article as: Xue X, Zhou T, Wang G, Zhou S. Treatment of pulmonary infection of extensively drug-resistant Acinetobacter baumannii with intravenous colistin sulfate combined with atomization: a case report. Ann Palliat Med 2021;10(8):9288-9296. doi: 10.21037/apm-21-2112

