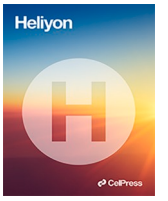
Heliyon 10 (2024) e40988

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Analysis of anti-infective therapy in a challenging case of brainstem hemorrhage complicated with pneumonia

Tiankun Wu [a,*], Xing Meng [b], Nan Chen [a], Hongyu Wang [c], Honghui Yang [d,**]

[a] Department of Pharmacy, The Fifth Clinical Medical College of Henan University of Chinese Medicine (Zhengzhou People's Hospital), Zhengzhou, China
[b] Emergency Department, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[c] Department of Emergency Intensive Care Unit, The Fifth Clinical Medical College of Henan University of Chinese Medicine (Zhengzhou People's Hospital), Zhengzhou, China
[d] Department of Cardiology, Heart Center of Henan Provincial People's Hospital, Central China Fuwai Hospital of Zhengzhou University, Zhengzhou, China

ARTICLE INFO

Keywords:
Brainstem hemorrhage
Pneumonia
Anti-infective therapy

ABSTRACT

We present a highly challenging case of brainstem hemorrhage complicated with pneumonia in a 41-year-old male patient. The patient had intermittent and recurrent fever for nearly two months from June 24, 2022 to August 22, 2022, along with extremely unstable vital signs. Multiple consultations were conducted among clinicians and pharmacists. In view of the patient's actual situation, they initially carried out empirical treatment and then comprehensively considered factors such as the characteristics of anti-infective drugs, interactions, susceptibility testing, and blood drug concentration to analyze and adjust the types and dosages of drugs and implement individualized therapy. Eventually, the patient's body temperature returned to normal, vital signs stabilized, and the patient was discharged smoothly. The author presents this case with the intention of providing a valuable reference for the treatment of patients with cerebral hemorrhage and pneumonia.

1. Introduction

Brainstem hemorrhage is a severe neurological disorder associated with high mortality and disability [1]. The etiologies of brainstem hemorrhage include primary hypertension, cerebrovascular malformation, brain tumor, cerebral atherosclerosis, trauma, long-term drinking, etc [2]. In this case, the possible causes could be long-term alcohol consumption (with an 18-year history and an average daily intake of about 50ml), as well as smoking (a 20-year history with an average daily consumption of 1 box). The patient's history of hypertension prior to the brainstem hemorrhage was unknown, and he had not taken any antihypertensive drugs before the onset of the disease.

Patients with brainstem hemorrhage are susceptible to lung infection due to consciousness and swallowing impairments [3]. Anti-infective drugs are of vital importance for treating cerebral hemorrhage combined with pneumonia, yet diverse and complex pathogens, including drug-resistant bacteria, pose challenges. Comprehensive consideration and exploration of the appropriate

* Corresponding author.
** Corresponding author.
E-mail addresses: 15939031335@163.com (T. Wu), yanghonghui@zzu.edu.cn (H. Yang).

https://doi.org/10.1016/j.heliyon.2024.e40988
Received 26 September 2024; Received in revised form 3 December 2024; Accepted 4 December 2024
Available online 5 December 2024

medication plan are highly important for improving patient prognosis.

The objective of this case study is to perform an in-depth analysis of the anti-infective treatment strategies employed in a complex case of brainstem hemorrhage accompanied by pneumonia, to investigate the efficacy and potential limitations of various drug regimens, and to offer practical insights and recommendations for similar clinical scenarios, thereby enhancing the treatment outcome and prognosis of such patients.

2. Case presentation

A 41-year-old male was admitted to Zhengzhou People's Hospital on June 24, 2022, due to sudden loss of consciousness for 2 hours. He was diagnosed with cerebral infarction at a local hospital and subsequently transferred to our hospital with loss of consciousness (GCS score of 3), nausea, vomiting for four times, a high fever (39.2 °C) and extremely unstable vital signs. After admission, the diagnosis was brainstem hemorrhage. The pulse (P) was 106 beats per minute, the respiratory rate (R) was 26 beats per minute, and the blood pressure (BP) was 211/132 mmHg. He had limb convulsions, deep coma, and signs of lung infection. Relevant tests showed elevated white blood cell count and C-reactive protein.

During the nearly two-month hospitalization, the patient received symptomatic and supportive treatment, including anti-infection, anti-epilepsy, blood pressure control, and maintenance of water and electrolyte balance. Anti-infective treatment was adjusted multiple times based on the patient's condition and test results. Initially, piperacillin-tazobactam sodium was used, but later cefoperazone sodium and sulbactam sodium, vancomycin, and levofloxacin were administered. When Pseudomonas aeruginosa was found to be multidrug-resistant, polymyxin and meropenem were used. Later, due to the development of Staphylococcus capitis infection, vancomycin was used. Ceftazidime was used to cover Pseudomonal infection. Eventually, the patient's condition improved, with stable vital signs, and he was discharged.

The initial treatment drugs after admission were Piperacillin sodium and tazobactam sodium for injection (ivgtt), Mannitol injection (ivgtt), Sodium nitroprusside for injection (Infusion by micro-infusion pump), Ambroxol hydrochloride for injection (iv), Budesonide suspension for inhalation (Compressed nebulization inhalation), Levosalbutamol hydrochloride nebulised inhalation solution (Compressed nebulization inhalation), Phenobarbital sodium injection (im), Propofol medium and long chain fat emulsion injection (Infusion by micro-infusion pump), Remifentanil hydrochloride for injection (Infusion by micro-infusion pump), Enteral nutritional suspension (sp) (Nasal feeding), Compound amino acid injection (18aa-v-sf) (ivgtt), ω-3 fish oil fat emulsion injection (ivgtt), Hemocoagulase bothrops atrox for injection (iv), Tranexamic acid and sodium chloride injection (ivgtt). See Table 1. The patient's medication after discharge is shown in Table 2.

3. Discussion

Cerebral hemorrhage is an acute cerebrovascular disease with high incidence, recurrence, disability, mortality, and treatment costs. Brain stem hemorrhage is the deadliest subtype of cerebral hemorrhage [4]. Once combined with pulmonary infection, the mortality rate rises significantly [5].

Stable blood pressure is crucial for organ function. During treatment involving blood pressure reduction, analgesia, and sedation, we closely monitored patients' vital signs based on their conditions. Using sodium nitroprusside for blood pressure reduction and remifentanil and propofol for analgesia and sedation, we closely observed blood pressure and breathing. Drug doses were strictly controlled, adjusted timely, and tapered gradually when stopping. For patients with brainstem hemorrhage, multiple factors should be taken into account in drug selection, and the doses should be adjusted in a timely manner according to the responses [6,7].

At the beginning of treatment, the patient, with cerebral hemorrhage and pneumonia, was in a critical state. Piperacillin tazobactam sodium for injection was administered empirically in accordance with relevant guidelines and the pathogen distribution and drug susceptibility data in our hospital recently [8]. However, two days later, relevant examinations and laboratory results showed

Table 1
Initial treatment medication.

Initial treatment medication	[a]Dosage	Function
Piperacillin sodium and tazobactam sodium for injection	4.5g q8h	Anti-infection
Mannitol injection	125ml 25g q12h	Lower intracranial pressure
Sodium nitroprusside for injection	50mg + 50ml5%GS prn	
Ambroxol hydrochloride for injection	30mg qd	Dissipating phlegm
Budesonide suspension for inhalation	1mg q12h	
Levosalbutamol hydrochloride nebulised inhalation solution	0.63mg q8h	
Phenobarbital sodium injection	0.1g q12h	Antiepileptic
Propofol medium and long chain fat emulsion injection	0.6g prn	Sedation and pain relief
Remifentanil hydrochloride for injection	2mg + 48ml0.9 % NS prn	
Enteral nutritional suspension (sp)	500ml qd	Nutritional support
Compound amino acid injection (18aa-v-sf)	500ml qd	
ω-3 fish oil fat emulsion injection	100ml 10g qd	
Hemocoagulase bothrops atrox for injection	2IU + 10mlNS qd	Hemostasis
Tranexamic acid and sodium chloride injection	100ml 0.5g qd	

[a] Dosages were determined considering the patient's weight, age, and overall condition in accordance with established clinical protocols.

Table 2
Discharge treatment medication.

Discharge treatment medication	[a]Dosage	Function
Perindopril and indapamide tablets	(4 + 25)mg qd	Lower blood pressure
Amlodipine tesylate tablets	5mg qd	
Bisoprolol fumarate tablets	5mg qd	
Mosapride Citrate Tablets	5mg tid	Promote gastrointestinal peristalsis
Dimethicone tablets	50mg tid	Relieve gastrointestinal flatulence
Lactulose oral solution	15mg tid	Regulate the physiological rhythm of the colon and promote defecation
Oral rehydration salt powder III	5.125g bid	Supplement electrolytes
Rosuvastatin calcium tablets	10mg qn	Reduce blood lipids and protect blood vessels
Dexzopiclone tablets	1mg qn	Help sleep
Suhexiang pills	3g bid	Awakening the mind and activating qi to relieve pain

[a] Dosages were determined considering the patient's weight, age, and overall condition in accordance with established clinical protocols.

that the pulmonary infection had worsened, and the possibility of intracranial infection could not be excluded. For intracranial infection, the typical bacteria initially considered were Pseudomonas aeruginosa (PA) and Methicillin-resistant staphylococcus aureus (MRSA). Hence, cefoperazone sodium and sulbactam sodium (covering PA) and vancomycin (covering MRSA) were used instead, and subsequently combined with levofloxacin injection as PA and *Klebsiella pneumoniae* (KP) were cultured from the patient's bronchoalveolar lavage fluid and were sensitive to levofloxacin [9]. Unfortunately, the patient's body temperature rose intermittently and the infection indicators increased to some extent. The anti-infection treatment was ineffective. Subsequently, a multidisciplinary consultation was conducted. Based on the drug sensitivity results, cefoperazone sulbactam and levofloxacin injection were discontinued, and the treatment was adjusted to a combined anti-infective therapy of 75mg of polymyxin B q12h +1g of meropenem q8h. Later, the dose of polymyxin B was increased to 100 mg based on the polymyxin B AUC 24h value of 42.493 (50–100)mg.h/L, and the treatment was stopped after the body temperature returned to normal [10].

The adverse effects related to polymyxins are mainly nephrotoxicity, neurotoxicity, and skin pigmentation, etc. The renal toxicity related to polymyxins is associated with the receptor-mediated cumulative intake of colistin on the membrane protein of the proximal renal tubule, leading to apoptosis. Compared to colistin methanesulfonate sodium, the incidence of acute kidney injury caused by polymyxin B sulfate is relatively low [11]. The renal toxicity induced by polymyxins is mainly mild, and renal function usually recovers gradually after drug withdrawal. To prevent renal toxicity when administering polymyxins, the recommended dose should not be exceeded. At the same time, therapeutic drug monitoring (TDM) should be carried out, and the combined use with other nephrotoxic drugs should be avoided [10].

Ten days after the patient's body temperature normalized and they were transferred to the general neurosurgery department, the patient suddenly developed a fever of 38.6 °C, and infectious shock or septic shock could not be excluded. The patient was transferred to the ICU for resuscitation, and cefoperazone sodium sulbactam sodium was used as the anti-infective drug. After the temperature returned to normal, the patient was transferred back to the neurosurgery department.

Cefoperazone, a third-generation cephalosporin with broad-spectrum antibacterial activity and the ability to penetrate bacterial cell membranes, is effective against common multidrug-resistant pathogens of hospital-acquired pneumonia (HAP) and healthcare-associated pneumonia (HCAP), and can cover PA [12]. For HCAP patients, 2g of cefoperazone sulbactam every 12 hours is comparable to 2g of cefepime every 8 hours. A study has compared the effects of cefoperazone sulbactam and piperacillin tazobactam in the treatment of Gram-negative nosocomial infections, and found that the efficacy and safety of the two were comparable. Cefoperazone sulbactam may be used as an alternative to piperacillin tazobactam [13].

Two days after being transferred to neurosurgery, the patient suddenly developed a fever. It was found that the bacteria at the tip of the central venous catheter were Staphylococcus capitis, which was sensitive to vancomycin. At the same time, sputum culture showed that PA was sensitive to ceftazidime. Therefore, a combination of vancomycin and ceftazidime was used for anti-infection treatment, and the patient's body temperature returned to normal after one week. In the intensive care unit, ceftazidime can be combined with vancomycin for immunocompromised critically ill patients with severe and life-threatening infections [14]. Subsequently, symptomatic treatment such as maintaining electrolyte balance was continued, and traditional Chinese medicine treatment was assisted to accelerate rehabilitation and prevent complications. Eventually, the patient was discharged from the hospital for continued rehabilitation.

Currently, although some novel treatment approaches (such as phage therapy, nano-therapy, precision medicine based on molecular screening of drug-resistant genes, immunotherapy, and microbiota transplantation therapy, as well as new antibiotics treatment) for anti-MDRO infections have emerged, the development of new antibacterial drugs lags behind the development of drug resistance, and the options for clinical anti-infection treatment are relatively limited [15–18], which significantly affects the survival rate of patients. Therefore, combination therapy has been used empirically to treat MDRO infections. Especially, treatment regimens based on polymyxins are also relatively common. In this case, after the patient's body temperature rose repeatedly, polymyxin B and meropenem were used based on the results of the multidisciplinary consultation and the drug sensitivity test. Zhao YC et al. [19] believed that Combining polymyxin B with other antibiotics, especially β-lactam drugs, improves survival rates. Chen Y et al. [20] reported that the novel 2-aminothiazole analogue serves as both a synergist of polymyxin E and an antimicrobial agent against multi-drug resistant Gram-positive bacteria, providing a new therapeutic option for mixed infections. When using polymyxin B in this case, aerosolized inhalation of polymyxin was not incorporated. Wang L et al. [21] believe that the actual therapeutic effect of

intravenous combined with aerosolized treatment for VAP is still unclear, and this strategy is not recommended currently.

In neurocritical care, in addition to the standardized anti-infective treatment for multidrug-resistant organisms (MDRO), the preventive measures for pulmonary infections, mainly covering strategies related to devices, operations, nursing, and treatment, cannot be ignored.

In the complex and variable anti-infective treatment process, factors such as empirical treatment, drug sensitivity tests, interactions, dosage, and individualized care based on symptoms and drug analysis can affect the patient's outcome. This case shows uniqueness in addressing challenges, but it is a single-case study involving a young patient. Future research will explore more similar cases, focus on precise biomarkers for early infection detection, and investigate the optimal combination and timing of antibiotics based on individual characteristics. We will also strive for more refined standards for antibiotic escalation to optimize treatment and minimize risks.

4. Conclusion

Brainstem hemorrhage, characterized by its specific bleeding location, rapid progression, high surgical difficulty, and significant risks, is typically managed conservatively and represents a critical neurological disorder with the poorest prognosis among cerebrovascular diseases. Managing its complications, particularly respiratory infections, is vital for patient survival.

When treating patients with brainstem hemorrhage, several key points should be noted. Firstly, promptly transfer patients to superior hospitals if the primary treatment is ineffective. Secondly, provide meticulous care and manage infections to prevent and detect HAP/VAP early. In the initial anti-infection treatment, avoid carbapenems as they tend to cause resistance despite short-term efficacy. 2–3 days after empirical treatment, determine whether to adjust antibiotics based on guidelines and patient-related factors. Once the pathogen and drug sensitivity results are available, select targeted narrow-spectrum antibiotics, individualized or in combination if necessary, for the optimal therapy. Conditional hospitals can adopt new approaches (such as drug resistance gene detection, nanotherapy, etc.). Thirdly, blood pressure management is essential for the patient. Ensure individualized control and avoid large fluctuations. Finally, guide rehabilitation and conduct regular follow-up after discharge.

4.1. Follow-up

During the two-year follow-up after discharge, the patient adhered to the prescribed medication, had regular reexaminations, and underwent intermittent rehabilitation. Clinician and patient assessment indicated stable vital signs. Important tests showed no abnormalities. The patient tolerated the intervention well. No adverse or unanticipated events were reported.

Brief statement on ethical challenges

In the critical case of 41-year-old male with brainstem hemorrhage and pneumonia, we thoroughly considered the drug efficacy and potential adverse reactions. A personalized treatment plan was formulated based on his specific conditions. When using sedatives for antihypertensive treatment, the dose was strictly controlled to prevent oversedation. Drug types and doses were determined carefully, and potential interactions were fully considered. The patient's vital signs and adverse reactions were closely monitored to promptly detect and handle any issues. All treatments adhered to ethical and clinical guidelines for the best outcome and minimal harm.

CRediT authorship contribution statement

Tiankun Wu: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Xing Meng:** Writing – review & editing, Validation, Conceptualization. **Nan Chen:** Writing – review & editing, Supervision, Conceptualization. **Hongyu Wang:** Writing – original draft, Data curation, Conceptualization. **Honghui Yang:** Writing - review & editing, Conceptualization, Supervision, Validation.

Ethics statement

This case report submission to Heliyon complies with Elsevier's patient consent policies.

Before submission, we have ensured that written informed consent was obtained from the patient to publish the clinical condition, study findings, de-identified images, clinical reports, and all other relevant information. The patient was informed that the publication would be freely and widely accessible to the public, could be promoted on websites, might appear in news and/or social media, and could be used for future research advancements.

We have taken the responsibility to remove all patient-identifying information, including but not limited to name, patient record numbers, patient codes, physical identifiers, medical record numbers, and distinguishing characteristics from all reports and images before submitting the manuscript.

A signed Case Report Declaration Form by the corresponding author has been submitted to confirm that the original informed consent was obtained. We adhere to institutional guidelines and local laws by retaining the signed, original informed consent at all times.

We are committed to protecting the patient's privacy and confidentiality and conducting the publication process in an ethical and

responsible manner.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the editor and the reviewers for their pertinent feedback and suggestions, which have led to significant improvements of this paper. We thank the Noncommunicable Chronic Diseases - National Science and Technology Major Project (2023ZD0503502) for its support. We also thank Sali Zhang from the Medical Records Department of Zhengzhou People's Hospital for providing data retrieval and support platform.

References

[1] K.C. Teo, S.M. Fong, W.C.Y. Leung, et al., Location-specific hematoma volume cutoff and clinical outcomes in intracerebral hemorrhage, Stroke 54 (6) (2023) 1548–1557, https://doi.org/10.1161/strokeaha.122.041246.
[2] J. Zhou, A. Ping, J. Mao, et al., ZJUSAH classification: a new classification for primary brainstem hemorrhage, Life 13 (3) (2023), https://doi.org/10.3390/life13030846.
[3] H. Mao, Y. Lyu, Y. Li, et al., Clinical study on swallowing function of brainstem stroke by tDCS, Neurol. Sci. 43 (1) (2022) 477–484, https://doi.org/10.1007/s10072-021-05247-6.
[4] S.M. Greenberg, W.C. Ziai, C. Cordonnier, et al., Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American heart association/American stroke association, Stroke 53 (7) (2022) e282–e361, https://doi.org/10.1161/str.0000000000000407, 2022.
[5] A. Hinduja, J. Dibu, E. Achi, et al., Nosocomial infections in patients with spontaneous intracerebral hemorrhage, Am. J. Crit. Care 24 (3) (2015) 227–231, https://doi.org/10.4037/ajcc2015422.
[6] W. Saasouh, N. Manafi, A. Manzoor, et al., Mitigating intraoperative hypotension: a review and update on recent advances, Adv. Anesth. 42 (1) (2024) 67–84, https://doi.org/10.1016/j.aan.2024.07.006.
[7] J.X.C. Ke, T.T.H. Jen, S.K.W. Schwarz, Minimal intraoperative blood pressure threshold and postoperative outcomes. Comment on Br J Anaesth 2023; 131: 823-31, Br. J. Anaesth. 132 (2) (2024) 450–451, https://doi.org/10.1016/j.bja.2023.11.042.
[8] A. Torres, M.S. Niederman, J. Chastre, et al., International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT), Eur. Respir. J. 50 (3) (2017), https://doi.org/10.1183/13993003.00582-2017.
[9] P.D. Tamma, E.L. Heil, J.A. Justo, et al., Infectious diseases society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections, Clin. Infect. Dis. (2024), https://doi.org/10.1093/cid/ciae403.
[10] B.T. Tsuji, J.M. Pogue, A.P. Zavascki, et al., International consensus guidelines for the optimal use of the polymyxins: endorsed by the American college of clinical pharmacy (ACCP), European society of clinical microbiology and infectious diseases (ESCMID), infectious diseases society of America (IDSA), international society for anti-infective pharmacology (ISAP), society of critical care medicine (SCCM), and society of infectious diseases pharmacists (SIDP), Pharmacotherapy 39 (1) (2019) 10–39, https://doi.org/10.1002/phar.2209.
[11] P. Aysert-Yildiz, Ö. Özgen-Top, A.F. Şentürk, et al., Polymyxin B vs. colistin: the comparison of neurotoxic and nephrotoxic effects of the two polymyxins, BMC Infect. Dis. 24 (1) (2024) 862, https://doi.org/10.1186/s12879-024-09759-2.
[12] M.J. Sheu, C.C. Chen, Y.C. Lu, et al., In vitro antimicrobial activity of various cefoperazone/sulbactam products, Antibiotics 9 (2) (2020), https://doi.org/10.3390/antibiotics9020077.
[13] E. Guclu, G. Kaya, A. Ogutlu, et al., The effect of cefoperazone sulbactam and piperacillin tazobactam on mortality in Gram-negative nosocomial infections, J. Chemother. 32 (3) (2020) 118–123, https://doi.org/10.1080/1120009x.2020.1730087.
[14] G. Tiseo, G. Brigante, D.R. Giacobbe, et al., Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian society of infection and tropical diseases (SIMIT), the Italian society of anti-infective therapy (SITA), the Italian group for antimicrobial stewardship (GISA), the Italian association of clinical microbiologists (AMCLI) and the Italian society of microbiology (SIM), Int. J. Antimicrob. Agents 60 (2) (2022) 106611, https://doi.org/10.1016/j.ijantimicag.2022.106611.
[15] A. Simons, K. Alhanout, R.E. Duval, Bacteriocins, antimicrobial peptides from bacterial origin: overview of their biology and their impact against multidrug-resistant bacteria, Microorganisms 8 (5) (2020), https://doi.org/10.3390/microorganisms8050639.
[16] K. Jani, S. Mehta, R. Patel, et al., Focused insights into liposomal nanotherapeutics for antimicrobial treatment, Curr. Med. Chem. (2024), https://doi.org/10.2174/0109298673322058241003073312.
[17] M.D.S. Chagas, F. Medeiros Filho, M.T. Dos Santos, et al., An Updated Gene Regulatory Network Reconstruction of Multidrug-Resistant Pseudomonas aeruginosa CCBH4851, vol. 117, Mem Inst Oswaldo Cruz, 2022 e220111, https://doi.org/10.1590/0074-02760220111.
[18] K.S. Allemailem, Recent advances in understanding the molecular mechanisms of multidrug resistance and novel approaches of CRISPR/Cas9-Based genome-editing to combat this health emergency, Int. J. Nanomed. 19 (2024) 1125–1143, https://doi.org/10.2147/ijn.S453566.
[19] Y.C. Zhao, C.Y. Wang, J.Y. Liu, et al., Factors affecting the effectiveness and safety of polymyxin B in the treatment of Gram-negative bacterial infections: a meta-analysis of 96 articles, Int. J. Antimicrob. Agents 64 (3) (2024) 107262, https://doi.org/10.1016/j.ijantimicag.2024.107262.
[20] Y. Chen, Z. Li, T. Lin, et al., Novel 2-aminothiazole analogues both as polymyxin E synergist and antimicrobial agent against multidrug-resistant Gram-positive bacteria, Eur. J. Med. Chem. 279 (2024) 116879, https://doi.org/10.1016/j.ejmech.2024.116879.
[21] L. Wang, C. Xu, L. Si, et al., Polymyxin-containing regimens for treating of pneumonia caused by multidrug-resistant gram-negative bacteria: mind the breakpoints and the standardization of nebulization therapy, Crit. Care 28 (1) (2024) 324, https://doi.org/10.1186/s13054-024-05111-x.