

# A combined strategy for postoperative patients with central nervous system infections caused by XDR/PDR *Acinetobacter baumannii*: a retrospective study

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# Abstract

**Background** Postoperative central nervous system infections (PCNSIs) caused by extensively drug-resistant (XDR) or pandrug-resistant (PDR) *Acinetobacter baumannii* are rare but intractable problems. To investigate a potential combined strategy to treat AB organisms that are resistant to not only meropenem but also colistin. **Methods** We retrospectively reviewed cerebrospinal fluid positive culture isolates of AB in patients who underwent neurosurgery. Medical records were collected by standard forms and analyzed. **Results** 16 patients met the criteria and most patients were middle-aged men who had undergone craniotomy or endonasal transsphenoidal surgery. 68.8% AB isolates were XDR bacteria, and 18.8% isolates were PDR bacteria. 12 patients were treated by meropenem-based regimen strategy. Another 4 patients were administered tetracycline-based regimens. 93.8% patients were treated with therapeutic drainage, and strict hygiene rules were followed. Finally, 12 patients survived their infections, and the average Glasgow Outcome Scale score was  $2.9 \pm 1.4$  at discharge. And the mortality rates of carbapenem-resistant AB (CRAB) were 8.3%. **Conclusions** PCNSIs caused by XDR/PDR AB are a rare and serious complication. Combined therapy based on the individual situation, including appropriate antimicrobial agents, surgical management and strict hygiene management, might be an effective therapeutic strategy.

## Background

Postoperative central nervous system infections (PCNSIs) are an uncommon but serious complication in neurosurgery, with an infection rate ranging from 4.5% to 7.4%(1, 2). Due to the advent of the sterile field and prudent antibiotic use during the perioperative period, the overall mortality rate of PCNSIs has dropped drastically in the past several years, from 34% in 2005(3) to 1.8% in a recent study; however, this mortality rate is still 3.78 times that of non-PCNSI patients(2). Although most PCNSIs are caused by gram-positive bacteria, there has been a trend toward gram-negative organisms in the recent literature. The incidence of *Acinetobacter baumannii*(AB) is considered to vary, accounting for 15.7% to 24.2% of the gram-negative organisms(4, 5).

The emergence of MDR-AB has become a serious medical problem worldwide, and the probable MDR rate ranges from 50% to 70% (6). More seriously, the decreasing sensitivity for various commonly used antibiotics, especially the resistance to carbapenems (CRAB), has increased from 31% to 66.7% in China, even reaching 80% in some reports(7). The mortality rate of CRAB is higher than the sensitivity rate, usually exceeding 30% and even reaching 72.7%(8).

The major treatment for AB is antimicrobial agents in central nervous system (CNS) infections, which is complicated by both susceptibility and the existence of the blood–brain barrier (BBB) (9). Meropenem is recommended as an initial therapy for meningitis (10). Polymyxins, tigecycline and sulbactam are the most commonly used therapies in carbapenem-resistant and extensively drug-resistant (XDR) AB infections (11). Colistimethate sodium or polymyxin B is recommended for CNS infections that are resistant to carbapenems. However, the colistin resistance in XDR AB has increased rapidly, from less than 10%to approximately 50%(12), and the use of colistin for humans is still not approved in China,

considering its significant toxicity(13). How to treat XDR *AB* that is resistant not only to meropenem but also to colistin is an intractable problem.

Tigecycline is a broad-spectrum glycylicycline antimicrobial agent with *in vitro* activity against MDR gram-negative bacteria such as MDR-AB (14). Although previous reviews do not recommend tigecycline for meningitis due to poor penetration of the BBB (10, 15), there have been some successful cases(16, 17). Sulbactam is of potential use in serious *AB* infections given its *in vitro* activity against the organism, including some carbapenem-resistant strains(18). The synergistic effect of sulbactam with meropenem, colistin or tigecycline was observed *in vitro* (19). sulfamethoxazole-trimethoprim (SMZ-TMP) was considered an alternative therapy against some gram-negative bacteria(10) because of its high concentration in the CSF and the hope of obtaining a possible synergistic effect.

Besides antimicrobial agents, combined therapeutic strategies in CNS infection should not be ignored; these strategies include complete removal of an infected CSF shunt, replacement with an external ventricular drain (EVD)(10), hand hygiene, contact precautions and standard dressing changes(9).

## Methods

We performed a retrospective clinical study of PCNSIs caused by *AB* during the period between January 2010 and December 2018. Our hospital is a university general hospital and tertiary referral center in northern China, where the department of neurosurgery conducts approximately 1200 operations each year(7).

The patients were identified by reviewing CSF *AB* positive culture isolates from neurosurgery department via a computerized log containing records, as our team previous reported(7). The cultures were analyzed by the microbiology laboratory of the hospital using the BioMerieux API or VITEK System. Culture contamination was determined by specialists from the clinical laboratory and neurosurgery, which was based on the identity of the microorganism itself and its clinical features(10). A disk diffusion method with a MicroScan WalkAway 96 system was used to determine antibiotic susceptibility according to the standards established by the Clinical and Laboratory Standards Institute (20). The resistance of *AB* was described as MDR, XDR and pandrug-resistant (PDR), defined by the teams of Magiorakos, on the basis of the susceptibility to certain antimicrobial categories(21). Specifically, there are 9 categories with 22 antimicrobial agents for *Acinetobacter spp.* MDR was defined as nonsusceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories. XDR was defined as nonsusceptible to  $\geq 1$  agent in all but  $\leq 2$  categories, and PDR was nonsusceptible to all antimicrobial agents listed.

Patients with *AB* isolates from CSF were collected from medical records using previously designed standardized evaluation forms that included demographic characteristics, types of neurosurgery, laboratory data, antimicrobial susceptibility testing, therapy information and outcome information. Glasgow Outcome Scale (GOS) scores were recorded at hospital discharge. Patients who met the diagnostic criteria of PCNSIs were included in the analysis; these criteria included a history of surgery, clinical signs of meningitis (fever, meningeal signs, low consciousness level), a low glucose level (2.3

mmol/L) and an elevated protein level (0.45 g/L) in the CSF, and infection acquired more than 48 h after admission to the hospital.

The results of analyses of continuous variables are expressed herein as the median, interquartile range (IQR) or mean  $\pm$  SD.

## Results

During 2010-2018, there were approximately 9000 in-hospital patients treated with approximately 10,000 operations in the department of neurosurgery. There were 16 patients with PCNSIs caused by *AB* over the past 9 years, with an incidence of approximately 0.17%. Most patients were middle-aged men (9 cases), and the primary diseases were different, including pituitary lesions, hemorrhage and cerebral. 4 patients were comatose, with a GCS of less than 7 on admission. Most patients underwent craniotomy (7 cases) or endonasal transsphenoidal surgery (6 cases) and were in the hospital for 19 (IQR=15.75) days before the onset of CNS infections caused by *AB*. 4 patients with PCNSIs transferred from other hospitals.

As shown in table 1, all patients had fever ( $>38.5^{\circ}\text{C}$ ) with neck stiffness or meningeal signs, and 10 patients had leukocytosis ( $>10 \times 10^9/\text{L}$ ) with a polymorphonuclear predominance. The CSF changes showed a high leukocyte count, low glucose level and elevated protein level. 11 (68.8%) *AB* isolates from CSF were XDR bacteria, and 3 (18.8%) were PDR bacteria. Only 1 isolate was MDR, and 1 isolate was resistant to fewer than 3 antimicrobial categories. 10 patients had a pulmonary infection, and in 7 patients, *AB* was isolated from other samples besides the CSF, such as blood and sputum.

As shown in the table 2, although most isolates (75%) were resistant to meropenem, meropenem was still used as a basic treatment in 12 patients (75%), which was combined with sulbactam in 4 patients, minocycline in 5 patients and SMZ-TMP in 4 patients. Four patients were only treated by tetracyclines combined with SMZ-TMP without meropenem; 3 patients, with tigecycline; and 1 patient, with minocycline. SMZ-TMP was used in 8 patients, and sulbactam was used in 5 patients. All antibiotics were administered via intravenous infusion, and no antibiotics were administered via intrathecal injection. Most patients underwent external drainage. In total, 93.8% of patients underwent therapeutic drainage and 4 patients were treated with a ventriculoperitoneal (VP) shunt immediately after recovery from the infection. Hygiene management rules, such as avoiding routine CSF samples, not changing drainage bags routinely and performing routine catheter changes, were followed.

Of the 16 patients analyzed, cure of the PCNSIs were achieved in 12 cases, but the remaining 4 patients (25%) died as a direct consequence of the infection, of whom 3 of 4 underwent an endonasal transsphenoidal approach and were sensitive to meropenem. The mortality rates of PCNSIs caused by CRAB were 8.3% (1/12). The median number of hospitalization days was 48 (IQR=60) days. The GOS score in approximately half of the patients (7 cases) was above 4 points, and the average score was  $2.9 \pm 1.4$  at discharge.

## Discussion

PCNSIs caused by *AB* are still a serious but rare condition. In the present research, the morbidity was approximately 0.17% and accounted for 44.4% of the gram-negative organisms(7), which was similar to the findings of previous studies(22). The mortality was reported to be over 30% in some previous studies and even over 70% when the isolates were resistant to carbapenems(8), which are higher rates than that found in our study (25%). Especially, only 1 of 4 death cases were resistant to the meropenem and the mortality rates of CRAB were only 8.3% (1/12). The meningitis-related nerve defects in these patients were also catastrophic consequences. The average GCS score was 12.5 before the surgery, and the GOS score was only 2.9 after PCNSIs caused by *AB*, which means that most patients experienced severe injury with a permanent need for help with daily living.

Given the currently increasing threat of XDR and PDR-AB, the appropriate combined strategy needs to be explored. Most isolates in our study were XDR (68.8%) or PDR (18.8%), of which 75% were resistant to carbapenems. Similar trends were also observed in bloodstream infections, with a CRAB of approximately 90%(4). Despite the recent trend toward polymyxins, there is some hesitancy to their use because of their toxicity profile(11), and they are still not available in China. How to choose appropriate antimicrobial agents is crucial for the survival and favorable outcome of patients. Additionally, surgical management and hygiene management should not be ignored.

Carbapenem-based combination therapy was used in our case series even in infections resistant to carbapenems. 12 of 16 cases involved carbapenem-resistant isolates, and 8 cases were treated by meropenem. Finally, 7 patients were cured of CNS infections caused by CRAB. The possible reasons were as follows: First, full-dosage meropenem (2g Q8h) was applied in most patients to maintain an effective concentration in the CSF. Second, 4 of 8 patients were treated with sulbactam-meropenem combination therapy. The sulbactam itself possesses direct bactericidal activity and showed synergistic effects *in vitro* combined with meropenem. Although clinical experience with sulbactam in the treatment of *AB* meningitis has been mixed(9), which most often combined with ampicillin or cefoperazone. However, the combination of sulbactam-meropenem was limit experience. From the results of our study, sulbactam, as a single agent combined with meropenem, showed good effects in CRAB meningitis. Third, 3 of 8 patients were treated with a minocycline combination.

Tetracyclines, such as tigecycline and minocycline, are another potential choice. In the present study, 10 of 16 patients underwent susceptibility testing for minocycline and tigecycline, and 4 and 6 isolates, respectively, were sensitive. Except for meningitis, tigecycline is regarded as the first agent in the glycylycylcline class, which is less prone to efflux-mediated resistance and ribosomal protection resistance(11). However, there are many concerns in CNS infections. First, the penetration of tigecycline into the CSF is minimal, even in patients with meningeal inflammation(23). Second, a previous systematic review reported that there was no significant difference in mortality compared with that in control groups (24). However, since Wadi et al.(25) in 2007 reported a meningitis patient successful treated by tigecycline, many researchers have tried to use tigecycline as a combination therapeutic strategy by intravenous administration(26), and 2 cases have been treated by intraventricular injection(16, 17). In the present study, 3 patients with CRAB were successfully treated with tigecycline

through intravenous injections of minocycline combined with SMZ-TMP. Tigecycline could be considered a valuable therapy in managing life-threatening CRAB CNS infections. Minocycline is recommended as an alternative therapy against MDR *AB*(11, 27), even for minocycline-resistant *AB*(28). Additionally, minocycline allows greater penetration of the BBB (29). In the present study, 9 of 16 patients were treated with minocycline as the context of combination therapy or as step-down therapy through intravenous or oral formulations.

SMZ-TMP is recommended by the IDSA as an alternative therapy to treat infections caused by gram-negative bacilli that hyperproduce  $\beta$ -lactamase(10). Furthermore, considering the activity of SMZ-TMP against MDR-AB *in vitro*, Garnacho M et al.(27) have suggested SMZ-TMP as an alternative therapy for CRAB infection. In the present study, 3 of 16 isolates were sensitive to SMZ-TMP, and 8 of 16 patients were treated with a combination. Clinical experience is lacking, however, some *in vitro* studies have shown a synergistic effect in combination with imipenem (62%) and colistin(30).

Besides the antibiotic strategy, as a nosocomial infection, surgical management and hygiene management should be considered in PCNSIs. Once the patients were diagnosed with PCNSIs, we not only completely removed any surgical implements, as the IDSA recommends(10) but also performed therapeutic CSF drainage in 93.8% patients, which could eliminate viable bacteria and reduce excitotoxic elements in the infected CSF as well as control intracranial pressure (ICP) (31). Ren et al. also reported that adjuvant closed continuous LD can lead to lower mortality and an improved GOS score, which was found in a retrospective series including 1062 patients with meningitis after neurosurgery. As surgical management, concerns about the complications of therapeutic CSF drainage, especially the recurrence of infection, are another important issues.

Hygiene management is a crucial rule throughout the treatment of PCNSIs, especially for patients with therapeutic CSF drainage. Twelve patients in this study were treated with LD, and 3 patients were treated with an EVD. All the procedures followed the rules suggested by the Neurocritical Care Society, using an EVD management bundle that includes aseptic insertion, limits manipulation of the closed system, and standardizes dressings and weaning. Based on these principles, all the EVDs in the present study were inserted in the operating room, and LD was conducted outside the operating room, with all procedures performed by trained neurosurgeons following a normal protocol. We tried to avoid routine CSF samples, especially those from the collection-device drainage bags. The duration of the EVD or LD catheter implementation was not over 7-14 days, and the changes were routine. For less manipulation, no antibiotics were administered by intrathecal injection.

Four patients did not survive the infection; however, 3 of them were sensitive to meropenem and were administered the proper antibiotic strategy. Unfortunately, these 3 patients were diagnosed with a mass in the sellar area and treated by endonasal transsphenoidal surgery. These findings may be related to the following three points. First, approximately half of the neurosurgery operations at our hospital involved the endonasal transsphenoidal approach, and the percentage involving PCNSIs was also nearly 50%, as previously reported(7). Second, CSF rhinorrhea, a complication of the surgery, is an important risk factor

in PCNSIs(10). It was hard to avoid recurrent infection during persistent CSF leakages, especially those that failed to be repaired. Third, both the surgery in the sellar area and the primary localization of the infection could lead to hypopituitarism or hypothalamic–pituitary dysfunction(32), which resulted in water-electrolyte imbalance, euthyroid sick syndrome, hypocortisolemia, etc.

Our study has the following limitations. First, it was a retrospective study including a small number of patients with inherent weaknesses. However, the PCNSIs caused by drug-resistant AB is a rare condition that is difficult to handle. To the best of our knowledge, this is the largest study to date on PCNSIs caused by XDR/PDR AB. Second, although the antibiotic regimens used are all appropriate, they were not standardized, which limited the summary of the potential rules. The antibiotic choice made by the multiple disciplinary team was based on the individual patient situation. Third, there were 3 isolates judged as XDR AB because of the lack of susceptibility test results for the tetracycline categories, which underestimated the incidence of PDR. Fourth, because polymyxins are not available in China, the clinical bacteriology laboratories in our hospital did not test the colistin or polymyxin B susceptibility in AB. We regarded these isolates resistant to the polymyxin category.

## Conclusions

PCNSIs caused by XDR/PDR AB are a rare and serious complication. A combination therapy based on the individual situation might be an effective therapeutic strategy, which includes appropriate antimicrobial agents, surgical management and strict hygiene management. Carbapenem-based or tigecycline-based combinations with sulbactam or minocycline could be potential antibiotic choices. Removal of surgical implements and therapeutic CSF drainage as adjuvant therapy might be potentially beneficial therapy.

## Abbreviations

PCNSIs: Postoperative central nervous system infections; XDR: extensively drug-resistant; PDR: pandrug-resistant; MDR: multidrug-resistant; CRAB: carbapenem-resistant *A. baumannii*; BBB: blood–brain barrier; CNS: central nervous system; SMZ-TMP: sulfamethoxazole-trimethoprim; EVD: external ventricular drain; LD: lumbar drainage; VP: ventriculoperitoneal; PUMCH: Peking Union Medical College Hospital; CSF: cerebrospinal fluid; GCS: Glasgow Outcome Scale; IQR: interquartile range;

## Declarations

### Consent for publication

Not Applicable.

### Availability of supporting data

All the data and material in this study were available.

## Competing interests

The authors declare that they have no competing interests.

## Ethical approval

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH) and written informed consents were obtained from all patients.

## Declaration of conflicting interests

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article. All authors declare no competing interests.

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## Author's contributions

CJB and CYH contributed equally to the manuscript. CJB and CYH did the main study analysis and co-wrote the manuscript. Wu H and MBT collected the medical records, managed data processes and supervised by MWB. ZX designed the statistical plan. MXJ, as infection professors, participated in making the antibiotic strategy and reviewed the results. Wang H majored in clinical microbiology led the microbiological aspects. ZW, as a clinical pharmacist, participated in making the antibiotic strategy and standard forms. WRZ reviewed the study results and edited the manuscript. WJJ co-wrote the standard forms used to collect data, was study chief investigator and edited the manuscript.

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## Tables

Table 1 Demographic and clinical characteristics of 16 patients with PCNSIs caused by *Acinetobacter baumannii*

Characteristic	Value (N=16)
Demographic parameters	
Mean age (yr)	41.7
Sex, male :female	11:5
GCS	12.5±4.4
Interval between infection and the initial neurosurgery (median)	19 (IQR=15.75)
In hospital days(median)	48 (IQR=60)
Death case	4 (25%)
GOS	2.9±1.4
Operation types	
Endonasal transsphenoidal approach	6(37.5%)
Craniotomy	7(43.8%)
Burr hole drilling	2(12.5%)
Others	1(6.2%)
CSF data	
Leukocyte count (10 <sup>6</sup> /L)	median=1600(IQR=4763)
Glucose level (mmol/L)	median=1.8(IQR=1.55)
Protein level (g/L)	median=1.3(IQR=5.3)
Resistance	
PDR	3(18.8%)
XDR	11(68.8%)
MDR	1(6.3%)
Acinetobacter isolates from other source	7(43.8%)

IQR, interquartile range

Table 2

Interventions	Value (N=16)
<b>Antibiotic</b>	
Meropenem	2
Meropenem + Sulbactam	4
Meropenem+SMZ-TMP /Tetracyclines	6
Meropenem + third-generation cephalosporins	3
Tetracyclines-based combination	4
<b>Drainage</b>	
LD	12
EVD	3
VP shunt	4

LD, lumbar drainage; EVD, external ventricular drainage; VP, ventriculoperitoneal;

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