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Intrathecal Tigecycline in the Treatment of Hospital-Acquired Meningitis: A Review of Four Cases

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Abstract

Objectives: Carbapenem-resistant *A. baumannii* is a common cause of nosocomial meningitis, and it presents a challenge in terms of treatment because of limited therapeutic options. Intravenous tigecycline has been considered a potential salvage therapy against multi-drug–resistant *Acinetobacter baumannii*. However, its effectiveness is limited by its poor ability to cross the blood–brain barrier. As an alternative treatment option, intrathecal tigecycline has shown promise with its minimal side effects and high concentration in cerebrospinal fluid.
Methods: In this report, we present a series of four cases infected with multi-drug–resistant A. baumannii following neurosurgery and treated with intrathecal tigecycline, including antimicrobial therapy.
Results: The rate of successful microbiological response was 2 out of 3 cases (66%) in whom microbiological response could be tested anytime during the intrathecal therapy, whereas the 30-day survival rate after treatment completion was 1/4 (25%).
Conclusion: Although intrathecal tigecycline treatment has shown relative efficacy in achieving microbiological response, its impact on overall survival is still uncertain. Further studies involving larger groups of patients are necessary to evaluate the outcomes of intrathecal tigecycline therapy.

Keywords: Acinetobacter baumannii; Carbapenem resistant; intrathecal; meningitis; tigecycline

Introduction

Post-operative nervous system infections are common complications of neurosurgery and account for 0.8%–7% of intracranial infections.[1] Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a common cause of nosocomial meningitis, which is a difficult-to-treat nosocomial pathogen because of its limited therapeutic options.[2] CRAB need tailored therapy according to the susceptibility pattern of the infecting strain.[3] The latest Infectious Diseases Society of America guidelines for the management of healthcare-associated ventriculitis and meningitis recommend polymyxins for treatment of cases infected with carbapenem-resistant *Acinetobacter* species.[4] Also, they recommend the addition of intraventricular (IVT) or intrathecal (IT) polymyxins for healthcare-associated CRAB meningitis and ventriculitis, which are difficult to treat with intravenous (IV) polymyxins.[4] However, the use of this treatment is limited owing to the side effects like neurotoxicity observed in up to 21.7% of the patients.[5]

IV tigecycline may be an effective salvage therapy option against multi-drug–resistant *Acinetobacter baumannii*. In a study evaluating the efficacy of tigecycline in 23 patients with CRAB meningitis, the overall end of treatment (EOT) success was 70%.[6] However, it is not recommended as a frontline therapy in intracranial infections because of its relatively poor penetration through the blood–brain barrier.[7] Nevertheless,

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there are case reports presenting IT tigecycline as an alternative treatment with its low side-effect profile and high cerebrospinal fluid (CSF) concentrations.[7,8] Herein, we hypothesized that implementing IT tigecycline as a rescue therapy for CRAB meningitis could potentially decrease microbiological success and mortality and we report a series of four cases infected with post-neurosurgical CRAB meningitis and treated with IT tigecycline, including therapy.

Material/Methods

This study was performed in an 1800+ bedded tertiary-care educational hospital in a 4.500.000+ populated city. We extracted data and outcomes of all adult (>18 years of age) patients with culture-proven hospital-acquired CRAB meningitis cases treated with IT tigecycline, including antibiotic therapy between January 2021 and September 2022. Demographic, clinical, and laboratory findings, pre-disposing factors, as well as information on response to treatment and outcome were obtained retrospectively.

A definite diagnosis of meningitis was on the basis of the isolation of bacteria in at least one CSF culture. Typical CSF findings included a leukocytosis (≥100 leukocytes/mL), with a predominance of polymorphonuclear cells and classical clinical manifestations of meningitis. CDC criteria were used to define nosocomial meningitis.[9,10] CSF samples were obtained by lumbar puncture or percutaneous aspiration of shunt reservoir or puncture of extraventricular drainage tubing. Samples were routinely centrifuged and the pellet was Gram stained. Bacteria were identified using routine microbiological methods. Identification of the bacteria and determination of antimicrobial susceptibility were performed using the VITEK 2 automated system (BioMerieux Inc, Mercy L'etoil, France) and conventional methods. For tigecycline susceptibility, the FDA clinical minimum inhibitory concentration breakpoints for *Enterobacteriaceae* (2 mg/L, sensitive) were used. Other antibacterial susceptibility tests were evaluated according to EUCAST.[11]

During the procedure, the drainage tube was temporarily closed for a duration of 1 hour.

We secured written consent from the patients.

Results

A total of four CRAB meningitis patients (two female, 61.3 ± 15.2 years of age) fulfilled our inclusion criteria. At the time of diagnosis, two cases had fever and three had disturbances in the consciousness. Two patients had leukocytosis, whereas one case did not have leukocytosis, but had polymorphonuclear leukocyte predominance. All cases had CSF pleocytosis (range 150–1000/mm^3). CSF protein level was 542.33 ± 360.65 mg/dL, glucose level was 24.33 ± 36.96 mg/dL. Infecting strains were CRAB in all. The susceptibility patterns were carbapenem resistant in all, and aminoglycoside sensitive in 2 of the 4 cases. All cases had received at least one extended-spectrum antibiotic in the previous month for several nosocomial infections. IT tigecycline dosage was 5 mg q 12 h in all cases. All cases received tigecycline, including combination therapy (two with polymyxin B, one with polymyxin E, and two with meropenem), Cerebrospinal fluid tigecycline level was not known in any case. The rate of successful microbiological response was 2 out of 3 cases in whom microbiological response could be tested anytime during the IT therapy. Survival on 30 days after EOT was 1/4 (25%). Details of the cases are summarized below and in Table 1.

Case 1

Infectious Diseases Department was consulted in a 55-year-old male patient, nine days after a cerebral aneurysm and intracerebral hemorrhage-related neurosurgical operation. On the day of this consultation, he was receiving meropenem and tigecycline treatment for ventilator-associated pneumonia. Lumbar drainage was performed because of ventricular dilatation observed in the patient's follow-up cranial imaging. The CSF sample sent during lumbar drainage application had >1000 leukocytes/mm^3, a glucose level of less than 2 mg/dL, and a protein level of 945 mg/dL (Table 1). Gram-negative bacilli were positive in the Gram staining, so empirical treatment was arranged with cefoperazone–sulbactam, tigecycline, and gentamicin. The CSF culture resulted in CRAB. On the second day of the current treatment, IT tigecycline 2*5 mg was added to the antibacterial regimen. On the fourth day of the current treatment, polymyxin E (IV) and meropenem treatment were added because of insufficient clinical response. Although the patient responded to the IT tigecycline treatment with a fever response on the fifth day, the patient died on day 5 of IT tigecycline, including antimicrobial therapy before another CSF sample could be obtained. Clinical, microbiological, therapeutic, and outcome details of the case are detailed in Table 1.

Case 2

A 77-year-old male patient who underwent surgery for lumbar disc herniation was being monitored with EVD owing to the development of hydrocephalus and IVT hemorrhage. On post-operative day 6, pleocytosis was detected in the CSF sample related to a CSF fistula and collection in the operation line. Empirical treatment with cefepime and vancomycin was initiated upon Infectious Diseases consultation, but vancomycin was discontinued on day 4 of treatment owing to deterioration in renal function and linezolid was started instead. On day 13 of treatment, the repeated CSF culture showed CRAB growth, and the treatment was changed to meropenem, tigecycline (IV, IT), and TMP-SMX. However, because of continued growth in the control CSF culture and progression of CRP, the treatment was revised to include cefoperazone–sulbactam, rifampicin, amikacin (IV, IT), tigecycline (IV, IT), and TMP-SMX. IT treatment was stopped on day 14 (on day 24 of overall antimicrobial treatment) owing to no growth in the repeated CSF culture, but the patient died because of sudden cardiac arrest 4 days after discontinuing IT tigecycline treatment. Clinical, microbiological, therapeutic, and outcome details of the case are detailed in Table 1.

Case 3

A 43-year-old female patient underwent neurosurgery for an aneurysm and intracerebral hemorrhage. On follow-up, the patient was diagnosed with aspiration pneumonia and septic shock 8 days after the operation and was treated with meropenem and tigecycline. On post-operative day 10, a ventriculoperitoneal shunt was inserted. The dose of meropenem was adjusted to 6*1 g owing to the presence of CRAB growth in

TABLE 1. MAIN CHARACTERISTICS OF PATIENTS

Patient no	*Age*	*Gender*	*Fever/ convulsions*	*Disturbances in the level of consciousness/ Glasgow Coma score*	*Nausea, vomiting/ neck stiffness*	*CSF leukocytes; blood leukocytes (blood PML%), etiological agent*	*Susceptibility pattern*	*Previous treatment with failure*	*Underlying condition*	*Treatment and duration*	*Morbidity*	*Outcome*
1	55	M	+/–	+/3	–/–	>1000, 5.64×10^3/µL, %91.4, *Acinetobacter baumannii*	Carbapenem R, Cefoperazone–sulbactam R, Amikacin R, Gentamicin S, Tigecycline MIC:2 mg/L	Meropenem Tigecycline(IV)	Intracranial hemorrhage	Tigecycline(IT) 2*5 mg 5 d, Cefoperazone–sulbactam 3*2 gr 6 d, Tigecycline (iv) 2*50 mg 6 d, Gentamicin 1*240 mg 6 d, Micafungin 1*100 mg 5 d, Colistin 1*300 mg loading, 2*150 mg maintenance 2 d, Meropenem 3*1 gr 2 d	Lumbar drainage	Microbiological failure; died despite addition of colistin on day 5
2	77	M	–/–	+/3	–/+	150, 11.6×10^3/µL, %92, *Acinetobacter baumannii*	Carbapenem R, Cefoperazone–sulbactam R, Amikacin S, Gentamicin R, TMP-SMX[a] S, Tigecycline MIC:2 mg/L	Cefepime, Vancomycin, Linezolid	Operated on because of lumbar disc herniation	Tigecycline(IT) 2*5 mg 14 d, Meropenem 3*2 gr 4 d, Tigecycline 2*50 mg 7 d then 2*100 mg 10 d, TMP-SMX 3*10 mg/kg 7 d, Micafungin 1*100 mg 13 d, Rifampicin 13 d Cefoperazone–sulbactam 3*2 gr, 13 d, Amikacin (IT) 2*10 mg 13 d, Amikacin (IV) 1*15 mg/kg 13 d	EVD[b]	Microbiological cure, but died 4 d later owing to bacteremia *Acinetobacter baumannii*
3	43	F	–/+	–/6	–/+	>1000, 23.95×10^3/µL, %91.3, *Acinetobacter baumannii*	Carbapenem R, Cefoperazone–sulbactam R, Amikacin R, Gentamicin R, TMP-SMX R, Tigecycline MIC:4 mg/L	Meropenem Tigecycline (IV)	Intracranial hemorrhage	Tigecycline(IT) 2*5 mg 12 d Meropenem 6*1 gr 3 d, polymyxin B 2*15.000 IU/kg 45 d, Fosfomycin (IV) 3*4 gr 45 d, Linezolid 2*600 mg 35 d	EVD	Microbiological cure; survival on one-month follow-up after end of treatment
4	70	F	+/+	+/9	–/–	900, 9.93×10^3/µL, %55.4, *Acinetobacter baumannii*	Carbapenem R, Cefoperazon–sulbactam R, Amikacin R, Gentamicin R, TMP-SMX R, Tigecycline MIC: 1 mg/L	Polymyxin B, Tigecycline (iv), Fluconazole	Intracranial tumor	Tigecycline(IT) 2*5 mg 9 d, polymyxin B 2*15.000 IU/kg 14 d, Tigecycline(iv) 2*50 mg 13 d then 2*100 mg 1 d, Fluconazole 1*400 mg loading, 1*200 mg maintenance, 7 d, Micafungin 1*100 mg 3 d	lumbar drainage	Microbiological failure; died on the 9th day of IT treatment

[a]TMP-SMX: Trimethoprim/sulfamethoxazole.
[b]VD: Extraventricular Drain.

the CSF culture sent for control purposes during the operation, and tigecycline treatment was continued.

Because of an increase in pleocytosis in the control CSF sample sent on day 8 of IV tigecycline treatment, the antibacterial regimen was changed to polymyxin B (IV), tigecycline (IV, IT), and fosfomycin (IV). There was no growth in the control CSF culture sent on day 4 of the new treatment, and there was a regression in CSF pleocytosis. However, owing to CRP progression during follow-up, linezolid was added to the patient's treatment. The patient received IT tigecycline treatment for 12 days, and IT treatment was discontinued owing to no growth in the repeated control CSF culture. The patient survived for >1 month after end of therapy. Clinical, microbiological, therapeutic, and outcome details of the case are detailed in Table 1.

Case 4

A 70-year-old female patient who had neurosurgery for an intracranial mass was re-operated on post-neurosurgery day 7 because of discharge and effusion in the operative site. The patient was monitored with lumbar drainage. During the patient's follow-up, on day 11 with lumbar drainage, CRAB growth was found in the CSF culture. The patient's treatment was then arranged to include polymyxin B (IV) and tigecycline. However, continued CRAB growth was found in the CSF culture on day 3 of this regimen, so IT tigecycline was added to the current treatment. Because the CSF culture yielded positive results on day 4 of IT treatment, the patient's medication was adjusted to a high dose of tigecycline at 2*100 mg. Unfortunately, the patient passed away on day 9 of IT tigecycline treatment before the repeated CSF culture could be performed. Clinical, microbiological, therapeutic, and outcome details of the case are detailed in Table 1.

Discussion

Tigecycline is a broad-spectrum bacteriostatic antibiotic that is derived from minocycline and is a member of the glycylcycline class. It works by inhibiting bacterial protein translation, which is achieved by reversible binding to the helical region in the 30S subunit of bacterial ribosomes. Tigecycline was developed specifically to treat polymicrobial infections that are caused by multiple drug-resistant Gram-positive and Gram-negative pathogens.[12]

Tigecycline penetration into the CSF is reported to range between 0% and 52%, depending on the calculation method used, which makes it a considerable alternative agent in the treatment of CRAB.[13] A multi-center study,[6] which was performed in Turkey and France, analyzed the clinical outcomes of 23 CRAB cases treated with tigecycline, including therapy. During the course of tigecycline therapy, 30% (7 out of 23 cases) died, resulting in an overall EOT success rate of 70%. EOT microbiological efficacy data were available for 17 cases with an overall efficacy of 88% (15 out of 17). However, with an additional 27% of patients succumbing to other or subsequent hospital-acquired infections, the overall clinical success rate (defined as symptom relief at the end of treatment and survival one month post-treatment without any relapse or re-infection) fell to 43%. It is worth noting that 11 (47.8%) of these 23 cases received tigecycline therapy as a second-line (or more) treatment and none of these 23 cases was treated with IT tigecycline. From our patient group presented in this article, microbiological success anytime during the IT tigecycline treatment could be tested in three cases, and two of them (67%) were successful, whereas the survival rate 30 days post-treatment was 25% (1 out of 4), aligning with the aforementioned series.[6]

IT antimicrobials are usually used as alternative and salvage treatment regimen.[3] IT application bypasses the blood-CSF barrier and achieves higher/moderate CSF concentrations than IV antimicrobials.[14] All the four presented cases in this article received IT tigecycline as salvage therapy.

Experience related to IT tigecycline is limited to single case reports in the literature. Owing to CRAB meningitis, Li et al.[7] initiated IV treatments along with 1*5 mg IT tigecycline and added IT polymyxin B because of lack of response. They achieved a positive response with the combination of IT and IV treatments, resulting in microbiological success at the EOT. In another case report, Deng et al.[14] used 4 mg IT tigecycline q12h as salvage treatment for a tigecycline-sensitive CRAB meningitis. As a result, they achieved microbiological response at EOT and the patient survived for at least one month. Huang et al.[15] administered IT tigecycline 1*5 mg as the primary treatment on the basis of culture results. They achieved microbiological response at EOT in both cases and observed improvement during long-term clinical follow-up. Wang et al.[16] used IT tigecycline as 10 mg q12 h as a salvage treatment. This approach resulted in microbiological response in the CSF and the patient survived for at least one month.

As far as we know, the herein presented four cases are the most extensive collection of cases on IT tigecycline therapy. It is worth noting that all published cases achieved microbiological success, although our own cases had a success rate of only 66% of the three microbiological response-tested cases and 50% of all cases. However, CSF culture could not be performed in the other two patients, and one patient did show a response in terms of fever reduction. Although there are different recommendations regarding drug dosage, we administered 2*5 mg IT tigecycline in all our cases.

The administration of drugs through IT therapy may result in discomfort such as pain, numbness or abnormal sensations, muscle contractions, and weakness. Other potential side effects may include elevated blood pressure or heart rate, decreased blood pressure leading to fainting, temporary facial weakness on one side of the face, seizures, spinal seizures, and temporary bladder impairment.[16] However, we did not see any remarkable side effect in any of our cases.

What circumstances would make the IT approach superior to the IV approach for treating CRAB meningitis with IT tigecycline? Just like retrospective cohort studies with colistin have shown,[17–19] it is possible that the tigecycline clinical outcomes may be higher with combined IT plus IV tigecycline, versus IV tigecycline alone. However, this needs to be tested in real-life clinical cases. To our knowledge, no randomized controlled study has evaluated the efficacy of any IT antibiotic. Therefore, this comparison might need to be conducted on a retrospective case–control basis. Until more clinical evidence is available, IT tigecycline may be used as a salvage therapy option.

Our study has several limitations: (1) it is a single-center retrospective cohort study, (2) the number of cases is limited to four, (3) CSF tigecycline levels could not be measured, hence, there is a possibility that the IT dose of tigecycline might have been suboptimal, and (4) none of the included cases was performed autopsy, so it is difficult to prove the

direct causal relationship between day 30 mortality and CRAB meningitis. However, to our knowledge, this is the largest dataset related to IT tigecycline.

In conclusion, although IT tigecycline treatment may result in microbiological response, 1-month mortality was relatively low. To fully understand the impact of IT tigecycline on clinical outcomes, it is necessary to conduct further studies. These should include a larger patient pool and involve determining CSF tigecycline levels with a more frequent CSF analysis. Such studies may help us to better understand the potential benefits of this treatment option, perhaps not as a last-line salvage treatment, but as an earlier treatment.

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Authors' Contributions

G.S.I.: Investigation, methodology, and writing; D.A.: Data curation and reviewing and editing; T.Y.: Data curation; E.O.: Data curation; M.S.C.: Data curation; S.A.: Reviewing and editing; B.A.: Writing; and O.R.S.: Investigation, methodology, data curation, writing, and reviewing and editing.

Author Disclosure Statement

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References

1. Pan S, Huang X, Wang Y, et al. Efficacy of intravenous plus intrathecal/intracerebral ventricle injection of polymyxin B for post-neurosurgical intracranial infections due to MDR/XDR Acinectobacter baumannii: A retrospective cohort study. Antimicrob Resist Infect Control 2018;7:8; doi: 10.1186/s13756-018-0305-5
2. Sipahi OR, Nazli Zeka A, Taşbakan M, et al. Pooled analysis of 899 nosocomial meningitis episodes from Turkey. Turk J Med Sci 2017;47(1):29–33; doi: 10.3906/sag-1508-102
3. Bardak-Ozcem S, Sipahi OR. An updated approach to healthcare-associated meningitis. Expert Rev Anti Infect Ther 2014;12(3):333–342; doi: 10.1586/14787210.2014.890049
4. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society Of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis 2017;64(6):e34–e65; doi: 10.1093/cid/ciw861
5. Karaiskos I, Galani L, Baziaka F, et al. Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis: A literature review. Int J Antimicrob Agents 2013;41(6):499–508; doi: 10.1016/j.ijantimicag.2013.02.006
6. Sipahi OR, Mermer S, Demirdal T, et al. Tigecycline in the treatment of multidrug-resistant acinetobacter baumannii meningitis: Results of the Ege study. Clin Neurol Neurosurg 2018;172:31–38; doi: 10.1016/j.clineuro.2018.06.008
7. Li Z, An Y, Li L, et al. Intrathecal injection of tigecycline and polymyxin b in the treatment of extensively drug-resistant intracranial acinetobacter baumannii infection: A case report and review of the literature. Infect Drug Resist 2022;15:1411–1423; doi: 10.2147/IDR.S354460
8. Nau R, Seele J, Djukic M, et al. Pharmacokinetics and pharmacodynamics of antibiotics in central nervous system infections. Curr Opin Infect Dis 2018;31(1):57–68; doi: 10.1097/QCO.0000000000000418
9. Sipahi OR, Bardak S, Turhan T, et al. Linezolid in the treatment of methicillin-resistant staphylococcal post-neurosurgical meningitis: A series of 17 cases. Scand J Infect Dis 2011;43(10):757–764; doi: 10.3109/00365548.2011.585177
10. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16(3):128–140; doi: 10.1016/0196-6553(88)90053-3
11. EUCAST Breakpoint Tables. 12. 2022. Available from: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_12.0_Breakpoint_Tables.pdf [Last accessed: 26February, 2024].
12. Mastroianni A, Vangeli V, Mauro MV, et al. Intrathecal tigecycline is a safe and effective treatment for central nervous system infections. Encephalitis 2023;3(3):87–93; doi: 10.47936/encephalitis.2023.00010
13. Ray L, Levasseur K, Nicolau DP, et al. Cerebral spinal fluid penetration of tigecycline in a patient with Acinetobacter baumannii cerebritis. Ann Pharmacother 2010;44(3):582–586; doi: 10.1345/aph.1M480
14. Deng ZW, Wang J, Qiu CF, et al. A case report of intraventricular and intrathecal tigecycline infusions for an extensively drug-resistant intracranial Acinetobacter baumannii infection. Medicine (Baltimore) 2019;98(15):e15139; doi: 10.1097/MD.0000000000015139
15. Huang G, Lai W, Wu D, et al. Two cases report of intrathecal tigecycline therapy for intracranial infection with acinetobacter baumannii and review of literatures. Infect Drug Resist 2022;15:2211–2217; doi: 10.2147/IDR.S357087
16. Wang L, Zhang J, Yu X, et al. Intrathecal injection of tigecycline in treatment of multidrug-resistant Acinetobacter baumannii meningitis: A case report. Eur J Hosp Pharm 2017;24(3):182–184; doi: 10.1136/ejhpharm-2016-000972
17. Georgakopoulou VE, Spandidos DA, Papalexis P, et al. Outcomes in meningitis-ventriculitis treated with intravenous or intrathecal plus intravenous colistin: A meta-analysis. Exp Ther Med 2023;25(6):293; doi: 10.3892/etm.2023.11992
18. Fotakopoulos G, Makris D, Chatzi M, et al. Outcomes in meningitis/ventriculitis treated with intravenous or intraventricular plus intravenous colistin. Acta Neurochir (Wien)2016;158(3):603–610; discussion 610; doi: 10.1007/s00701-016-2702-y
19. Shofty B, Neuberger A, Naffaa ME, et al. Intrathecal or intraventricular therapy for post-neurosurgical Gram-negative meningitis: Matched cohort study. Clin Microbiol Infect 2016;22(1):66–70; doi: 10.1016/j.cmi.2015.09.023

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