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Case Report

Tigecycline use in two cases with multidrug-resistant *Acinetobacter baumannii* meningitis

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ABSTRACT

The treatment of post-surgical meningitis due to multidrug-resistant (MDR) *Acinetobacter baumannii* is a therapeutic dilemma. The cases of two patients with MDR *A. baumannii* meningitis secondary to surgical site infections, successfully treated with combination regimens including tigecycline, are presented.

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1. Introduction

Acinetobacter baumannii is an aerobic, non-fermentative, oxidase-negative, Gram-negative coccobacillus that is ubiquitous in the environment.[1] Although the isolation of these organisms from clinical specimens may result from colonization, *A. baumannii* has potential to cause a wide spectrum of nosocomial infections such as pneumonia, bacteremia, urinary tract infections, and meningitis.[1,2] *A. baumannii* meningitis in post-neurosurgical patients and outbreaks following neurosurgical procedures have been reported.[2–4] The emergence of multidrug resistance in Acinetobacter isolates may pose a significant problem in nosocomial infections.

We report two cases of multidrug-resistant (MDR) *A. baumannii* meningitis secondary to surgical site infections following neurosurgical procedures, treated with combination regimens including tigecycline.

2. Case reports

2.1. Case 1

A 48-year-old male underwent surgery following a car accident and had spinal instrumentation due to a T6 vertebral fracture. He was discharged after the surgery but returned to the emergency service a week later with headache, backache, and discharge from his surgical wound. On admission he was conscious and had a fever of 39 °C. Physical examination revealed neck stiffness and a purulent discharge from the surgical site. He had a marked leukocytosis (32.4×10^9/l); biochemical parameters were within normal limits.

A lumbar puncture was performed. Cerebrospinal fluid (CSF) examination revealed a white blood cell count of 1350×10^6/l (95% polymorphonuclear leukocytes), glucose of 10 mg/dl, and total protein of 552 mg/dl; a simultaneous blood glucose was 72 mg/dl. After obtaining surgical site discharge, CSF, and blood cultures, vancomycin 2×1 g/day IV and meropenem 3×2 g/day IV were initiated empirically.

On the following day, cultures of surgical site discharge and CSF grew *A. baumannii*. Netilmicin 1×400 mg/day IV was added to the empirical regimen pending susceptibility testing results in accordance with our local surveillance findings. On the third day, it was shown that both isolates had the same susceptibility pattern and were only susceptible to tigecycline and netilmicin by the disk diffusion method. The minimum inhibitory concentration (MIC) for tigecycline was 0.38 μg/ml by Etest (AB Biodisk, Solna, Sweden). The patient was still febrile; vancomycin was discontinued and tigecycline was added at 50 mg every 12 h following a loading dose of 100 mg.

After the new combination therapy, the patient's temperature returned to normal and the surgical site discharge was reduced. Netilmicin was continued for two weeks and meropenem and

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tigecycline were continued for three weeks. At the end of the third week the patient had no evidence of surgical site infection or meningitis and was discharged from the hospital without any sequelae.

2.2. Case 2

A 52-year-old man had undergone surgery twice in the previous two months for lumbar disk herniation at the L2–L3 level. Four days after the second surgical intervention, he was diagnosed with a surgical site infection by his surgeon. Local wound care was taken and no systemic antibiotics were applied.

On the eighth day his condition had deteriorated. On physical examination, neck stiffness, unconsciousness, and fever were noted. CSF obtained via lumbar puncture showed 1930×10^6/l white blood cells (95% polymorphonuclear leukocytes), glucose of 29 mg/dl, and total protein of 136 mg/dl; a simultaneous blood glucose level was 177 mg/dl. Following CSF and blood cultures, vancomycin 2×1 g/day IV and meropenem 3×2 g/day IV were initiated empirically with the diagnosis of post-neurosurgical meningitis.

On the second day, CSF culture yielded *A. baumannii*. Netilmicin 1×400 mg/day IV was added to the empirical regimen. The following day, the isolate was found to be MDR by the disk diffusion method and it was only sensitive to tigecycline and netilmicin. The MIC for tigecycline was 0.38 μg/ml by Etest (AB Biodisk). Vancomycin was stopped and tigecycline 2×50 mg/day IV, following a loading dose of 100 mg IV, was added to the combination therapy.

At follow-up, the patient's mental status improved and his fever gradually subsided. Netilmicin was stopped at the end of the second week and meropenem and tigecycline were continued for three weeks. The patient was discharged at the end of therapy without any evidence of infection.

3. Discussion

Nosocomial meningitis following neurosurgical procedures is relatively uncommon.[5,6] The epidemiology of post-neurosurgical meningitis has changed in the last decade and Gram-negative bacillary meningitis has become increasingly important.[7,8] The emergence of MDR strains in recent years has complicated therapy. As a consequence, carbapenems have been recommended as part of the initial choice of empirical therapy for post-neurosurgical meningitis.[7,9]

A. baumannii rarely causes community-acquired infections. Invasive neurosurgical procedures constitute one of the major risk factors for *Acinetobacter spp* meningitis. Krol et al. reviewed the literature recently and reported that almost all *A. baumannii* meningitis reports since 1962 have been related to invasive procedures such as craniotomy or ventriculostomy.[2] Deep and superficial surgical site infections have also been reported to cause nosocomial meningitis.[6]

A. baumannii is characterized by frequent multidrug resistance. Carbapenems have been regarded as the agents of choice for *A. baumannii* infections for a long time, but resistance rates have risen substantially in some areas.[10] The carbapenem susceptibility of Acinetobacter isolates in patients with nosocomial meningitis was found to be only 55% in the study by Metan et al.[7] The high incidence of carbapenem-resistant strains narrows the therapeutic options and complicates empirical therapy.

Colistin is one of the few alternatives for treating MDR *A. baumannii* infections. There are numerous reports regarding the use of intravenous and intrathecal colistin for MDR *A. baumannii* meningitis.[11,12] The use of colistin in Turkey is hindered by the unavailability of this drug in the market. On the other hand, clinical experiences with the use of sulbactam for treating MDR *A. baumannii* meningitis are limited and rather inconclusive.[10]

Tigecycline is the first commercially available agent of a new class of antimicrobials, the glycylcyclines. It has been licensed for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections. It has been shown to have good in vitro activity against carbapenem-resistant *A. baumannii* isolates.[13] A comprehensive review by Karageorgopoulos et al. provides information regarding the use of tigecycline in various clinical conditions, such as ventilator-associated pneumonia, bacteremia and urinary tract infections due to MDR *A. baumannii*. Tigecycline has been used mainly as part of a combination regimen for the treatment of these infections and most patients included in these reports had good clinical outcomes.[14]

However clinical experience in patients with meningitis is very limited. There is one case report regarding the use of tigecycline in a patient with meningitis secondary to an external shunt infection.[15] In addition, a review of 34 patients by Gordon and Wareham included a patient who had *A. baumannii* meningitis treated with tigecycline and had a favorable clinical response.[16] Also, in a rabbit model of penicillin-resistant pneumococcal meningitis, tigecycline was found to be effective in reducing colony counts in CSF in combination with vancomycin.[17]

Herein, we have reported two cases of MDR *A. baumannii* meningitis secondary to surgical site infections. Both patients had surgical site infections following neurosurgical procedures and consequently developed meningitis. The diagnosis was based on clinical and CSF findings, as well as positive CSF cultures. Both *A. baumannii* isolates recovered from the CSF of these patients were resistant to carbapenems, piperacillin/tazobactam, ceftazidime, and quinolones and showed susceptibility only to tigecycline and netilmicin.

Although tigecycline is not approved for central nervous system infections, it was the best available option for the treatment of these two cases according to the antibiotic susceptibility results. Considering the information available regarding the enhanced therapeutic effect that might result from the use of tigecycline in combination with other agents, even in cases of resistance to other antibiotics, meropenem was not discontinued.[18] The clinical condition of both patients improved only after tigecycline was added to the regimen.

In conclusion, MDR *A. baumannii* meningitis is a rare complication of neurosurgical procedures. Treatment of these infections is a challenge for physicians and experience is limited. Central nervous system infections due to MDR *A. baumannii* will not respond to empirical treatment and special attention must be given in accordance with the local surveillance findings in hospitals where *A. baumannii* is prevalent.

To the best of our knowledge, this is the first report of tigecycline therapy in combination with meropenem and netilmicin for MDR *A. baumannii* meningitis secondary to surgical site infections. Further research is necessary to determine the role of tigecycline in the treatment of MDR *A. baumannii* infections.

Conflict of interest: No conflict of interest to declare.

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