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A Review of Safety and Effectiveness of Intravenous and Intraventricular Tigecycline in Healthcare-Associated *Acinetobacter baumannii* Meningitis and Ventriculitis

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Abstract

Objective To review the clinical data on the safety and effectiveness of intravenous (IV) and intraventricular (IVT) tigecycline in healthcare-associated *Acinetobacter baumannii* meningitis and ventriculitis.
Methods A literature search was performed in PubMed (from 2005 to December 2018). The bibliographies of the retrieved articles were searched for additional relevant studies. Articles were included if they described the use of tigecycline (IV and/or IVT) in patients with healthcare-associated *A. baumannii* meningitis or ventriculitis. Clinical studies as well as case series and case reports were included, while animal and in vitro studies were excluded.

Results The use of IV and/or IVT tigecycline was described in 39 patients infected with healthcare-associated *A. baumannii* meningitis or ventriculitis in 14 reports; 12 were case reports, one was case series, and one was retrospective multicenter study evaluating 23 carbapenem-resistant *A. baumannii* healthcare-associated meningitis cases treated with IV tigecycline including regimens. Using tigecycline was successful in most cases. Treatment failed in two patients and two patients died.
Conclusion Despite the limited studies, IV and IVT tigecycline has been used successfully and safely for the treatment of healthcare-associated *A. baumannii* meningitis and ventriculitis. However, large randomized controlled trials are necessary to clearly evaluate the safety and effectiveness of IV and IVT tigecycline in healthcare-associated *A. baumannii* meningitis and ventriculitis.

Introduction

Meningitis is an inflammation of the meninges surrounding the brain and the spinal cord while ventriculitis is an inflammation of the ventricles in the brain. Healthcare-associated meningitis and ventriculitis may result from invasive procedures (e.g., craniotomy, lumbar puncture, placement of external or internal ventricular catheters, intrathecal (IT) infusions of medications, or spinal anesthesia), complicated traumatic brain injury, or sometimes, metastatic infection in patients with hospital-acquired bacteremia [1]. These cases of meningitis and ventriculitis are caused by a different spectrum of pathogens (e.g., carbapenem-resistant Gram-negative bacilli and staphylococci) compared with cases acquired in the community [1]. Carbapenem-resistant *Acinetobacter baumannii* is found in 10% of healthcare-associated meningitis, with mortality ranging from 15 to 71% [2].

Meropenem is currently recommended for treatment of meningitis and ventriculitis caused by *Acinetobacter* species, while colistin or polymyxin B is recommended for carbapenem-resistant strains [2]. Intraventricular (IVT) or IT administration of polymyxin (colistin or polymyxin B) should be considered for patients with healthcare-associated *A. baumannii* meningitis and ventriculitis that are difficult to eradicate with IV colistin or polymyxin B [1, 3, 4]. However, even with the use of IVT/IT colistin or polymyxin B, some cases failed to respond [5], and many cases were infected with colistin-resistant *A. baumannii* [6, 7].

Despite its poor penetration to the cerebrospinal fluid (CSF) [8, 9], many clinical cases have reported the successful use of IV tigecycline, alone or in combination with colistin and other antibiotics, in the treatment of healthcare-associated *A. baumannii* meningitis and ventriculitis [10, 11]. Also, some clinical cases have reported the use of IVT tigecycline in combination IV antibiotics in the treatment of these diseases [6, 12]. The purpose of this review is to evaluate and provide a comprehensive summary of the clinical data on the safety and effectiveness of IV and IVT tigecycline in the treatment of these diseases.

Methods

A literature search was performed in PubMed (from 2005 to December 2018) using the following search terms: "tigecycline" and "meningitis" or "ventriculitis". Publications in languages other than English were excluded. The bibliographies of the retrieved articles were searched for additional relevant studies. Articles were included if they described the use of tigecycline (IV and/or

Table 1. Summary of cases received tigecycline (intravenous and/or intraventricular) for healthcare-associated *Acinetobacter baumannii* meningitis or ventriculitis

Reference	Age, gender	Underlying condition	Foreign body	Days from surgery to diagnosis	Antimicrobial sensitivities	Antimicrobial regimen
[6]	22 years, M	Giant pituitary adenoma	Fibrin glue, dural substitutes	18	S to TGC, (MIC = 2 mg/L)	IV TGC (100 mg q12 h) + IVT TGC at a dose of 2 mg/day (after 10 days, the dose was escalated to 2 mg q12 h). IVT CST (60,000 IU q12 h for 2 days, then escalated to 120,000 IU q12 h) and IV *MEM* (2 g q8 h) were added
[7]	4 months, M	HCP, VPS infection	EVD	NR	S to TGC (MIC = 0.5 mg/L)	IV TGC 1.2 mg/kg/dose q12 h, + IV CST + IT CST
	2 months, F	HCP, MMC, VPS infection	EVD	NR	S to TGC (MIC = 0.5 mg/L)	IV TGC 1.2 mg/kg/dose q12 h + *MEM* + IV CST
[10]	25 years, M	PA grade 4 in the posterior fossa	EVD	11	S only to TGC and CST	IV TGC 100 mg as a loading dose followed by 50 mg q12 h + IV CST (9 MIU/day)
[11]	26 years, M	MVA	LD	14	NR	IV TGC 50 mg q12 h
[12]	55 years, F	Aneurysmal SAH	EVD	21	Borderline S to CST (MIC = 2 mg/L) and TGC (MIC = 2 mg/L)	IV TGC 100 mg q12 h + RIF 600 mg + IV CST 4.5 MIU q12 h. IVT TGC at a dose of 4 mg 12 q24 h was added to IVT CST.
	50 years, M	Third ventricular mass	EVD	20	S to CST (MIC ≤ 0.5 mg/L), TGC (MIC = 1 mg/L), and TOB (MIC ≤ 1 mg/L)	IV CST 4.5 MIU q12 h. + IVT CST 250000 IU q24 h. However, after 15 days of IVT CST infusions, fever persisted, and the CSF remained abnormal. Therefore, IVT TGC 4 mg q24 h was added to IVT CST.
[13]	45 years, F	IVH	EVD	5	S to CST (MIC = 0.5 mg/L) and TGC (MIC = 0.25 mg/L)	IV CST (9 MIU per day in 3 doses without loading dose) + IVT CST (125,000 IU per day) + IV TGC (50 mg q12 h after a loading dose of 100 mg). After 4 days of this regimen, the patient had clinical and bacteriologic failure. So, the dose of IVT CST was doubled to 20 mg per day. Then, given the presence of an infected IVT hematoma, IVT fibrinolysis was performed to dissolve the clot, using 2 injections of alteplase 2 mg, at day 3 and day 4 of antibiotics. IV CST doses were doubled after 9 days to 6 MIU q8 h, because of a low residual

Table 1. (Continued)

Reference	Age, gender	Underlying condition	Foreign body	Days from surgery to diagnosis	Antimicrobial sensitivities	Antimicrobial regimen
						serum concentration of 0.8 mg/L. Three days later, the dose was decreased to the initial regimen (9 MIU per day) because of an episode of ARF. IVT CST was reduced to the initial dose of 10 mg per day from day 10 of antibiotics.
[14••]	39 years, F	Cranial mass	LD	NR	S to TGC, CST	IV TGC 50 mg q12 h
	48 years, M	ICH	LD	NR	S to TGC, CST	IV TGC 50 mg q12 h
	74 years, M	ICH	LD	NR	S to TGC, CST	IV TGC 50 mg q12 h
	53 years, F	TBI	LD	NR	S to TGC, CST	IV TGC 50 mg q12 h
	79 years, M	SAH, shunt infection	LD	NR	S to TGC, CST	IV TGC 50 mg q12 h
	60 years, F	TBI, shunt infection	LD	NR	S to TGC, CST	IV TGC 50 mg q12 h
	75 years, M	SDH	NR	NR	S to TGC, CST, TET, DOX	IV TGC 50 mg q12 h + IV CST 150 mg q8 h
	43 years, M	Subacute hematoma	LD	NR	S to TGC	IV TGC 50 mg q12 h + IV CST 150 mg q8 h
	26 years, M	VPS revision, shunt infection.	VPS	NR	S to TGC, CST	IV TGC 50 mg q12 h + IV CST 150 mg q8 h + IT CST 5 mg q12 h + IV VAN 1 g q12 h
	21 years, F	Nasal encephalocele, LD	LD	NR	S to TGC, AMK, CST	IV TGC 50 mg q12 h + IV CST 150 mg q12 h
	55 years, M	GSI, EVD	EVD	NR	S to TGC, CST, CIP, NET, TET, LVX. I to AMK, IPM, *MEM*	IV TGC 50 mg q12 h, IV CST 150 mg q12 h. CST was switched to *MEM* 2 g q8 h and VAN 1 g q12 h because of ARF on day 5
	23 years, M	EDH and SDH	NR	NR	S to TGC, CST, AMK, NET. I to LVX	IV TGC 50 mg q12 h + *MEM* 2 g q8 h + VAN 1 g q12 h + IV CST 150 mg q12 h
	58 years, F	Aneurysmal SAH	EVD	NR	S to TGC (MIC = 0.5 mg/L), GEN, TOB, NET. I to SXT	IV TGC 50 mg q12 h + IV CST 150 mg q12 h + IT CST 5 mg q12 h
	46 years, F	Aneurysmal SAH	EVD	NR	S to TGC (MIC = 0.5 mg/L), CST GEN, NET. I to AMK	IV TGC 50 mg q12 h + IV CST 150 mg q12 h + RIF 600 mg q24 h
	43 years, M	SDH, shunt infection	NR	NR	S to TGC, CST, GEN, NET. I to DOX, AMK, LVX	IV TGC 50 mg q12 h + IV CST 150 mg q12 h + IT CST 5 mg q12 h
	70 years, F	LSS	NR	NR	S to TGC, SXT, NET. I to DOX	IV TGC 50 mg q12 h + IT NET 150 mg q24 h followed by IV NET 400 mg q24 h. IV NET was switched to IV CST 150 mg q12 h due to microbiological failure.
	68 years, M	SAH, HCP	EVD	NR	S to TGC, CAZ, DOX, NET. I to CPZ/SBT, AMK	IV TGC 50 mg q12 h + NET + linezolid 600 mg q12 h
	M	ICH	LD	NR	S to TGC	IV TGC 50 mg q12 h + IV NET 400 mg q24 h
	48 years, F		NR	NR	S to CST, TGC, NET	

Table 1. (Continued)

Reference	Age, gender	Underlying condition	Foreign body	Days from surgery to diagnosis	Antimicrobial sensitivities	Antimicrobial regimen
		Pituitary gland adenoma, rhinorrhea				IV TGC 50 mg q12 h + IT NET 150 mg q24 h followed by IV NET 400 mg q24 h
	25 years, M	HCP, VPS dysfunction	EVD	NR	S to TGC, AMK, DOX	IV TGC 50 mg q12h + IV AMK 500 mg q12h
	47 years, M	ICH, VPS infection, HCP	VPS	NR	S to TGC, NET, CPZ/SBT	IV TGC 50 mg q12 h + IV AMK 500 mg q12 h + RIF 300 mg q12 h
	59 years, M	Cerebral abscess	EVD	NR	S to TGC, CST. I to IPM, *MEM*, AMK.	IV TGC + *MEM* + IT AMK (dose and frequency were NR)
	37 years, M	SDH, cervical 3–4 fracture, HCP, EVD	EVD	NR	S to TGC, CST	IV TGC 50 mg q12 h + *MEM* 2 g q8 h
[15•]	55 years, M	ICH	EVD	25	Resistant to TGC	IV TGC (100 mg q12 h) + IV CPZ/SBT (2 g q8 h) + CVI TGC (10 mg/500 mL saline q12 h, in from the right occipital horn and out from the left horn). After 12 days, IV TGC was reduced to 50 mg q12 h, whereas CVI TGC was adjusted to IVT TGC (2 mg q12 h).
[16]	57 years, M	Severe TBI	EVD	8	S to polymyxin (MIC = 1 mg/L) and TGC (MIC ≤ 1 mg/L).	IVT polymyxin B (50,000 U q24 h) + IV polymyxin B (450 000 U q12 h) + TGC (50 mg q12 h). Then switched to IVT polymyxin B (25,000 U q12 h), IV polymyxin B (475 000 U q12 h), and IV TGC (50 mg q12 h). Finally, IVT polymyxin B was stopped and IV polymyxin B (500 000 U q12 h) and IV TGC (50 mg q12 h) administration for was continued another 14 days until the patient's clinical conditions were stable
[17]	48 years, M	MVA	Spinal instrumentation	7	S to TGC (MIC = 0.38 mg/L) and NET	*MEM* 2 g q8 h + IV NET 400 mg q24 h + IV TGC was added at 50 mg q12 h following a loading dose of 100 mg.
	52 years, M	Lumbar disk herniation	None	8	S to TGC (MIC = 0.38 mg/L) and NET	*MEM* 2 g q8 h + IV NET 400 mg q24 h + IV TGC was added at 50 mg q12 h following a loading dose of 100 mg.
[18]	70 years, F	SAH	EVD	5	S to TGC (MIC ≤1 mg/L) and CPZ/SBT. Polymyxin sensitivity was not tested	IV TGC (100 mg first then 50 mg q12 h) + IV CPZ/SBT (3 g q8 h). After 6 days,

Table 1. (Continued)

Reference	Age, gender	Underlying condition	Foreign body	Days from surgery to diagnosis	Antimicrobial sensitivities	Antimicrobial regimen
						IVT TGC 2 mg q12 h was started.
[19]	42 years, M	Low-grade ependymoma	EVD	17	S to aminoglycosides, CST (MIC <0.5 mg/L) and TGC (MIC = 0.5 mg/L).	IV CST (2 MIU q6 h) + AMK (1250 mg IV q24 h and 20 mg IVT q24 h). After 3 days, AMK was stopped and IV TGC was started (50 mg every 12 h after a loading dose of 100 mg). After 12 days, the antimicrobial regimen was changed by stopping TGC and starting IT CST (75,000 IU q24 h, increased 3 days later to 150,000 IU q24 h).
[20]	75 years, M	Small right SDH	EVD	4	S to CST and TGC	IV CST was started at the dose of 2 MIU q8 h together with 200,000 IU through IVT q24 h. IV TGC was given at a loading dose of 100 mg followed by 50 mg q12 h.
[21]	50 years, M	Craniocerebral injury from a falling accident.	EVD	NR	S to TGC (MIC = 2 mg/L)	Initially, IV TGC (50 mg q12 h). Then his body temperature became 40 °C; his CSF analysis was abnormal, and CSF culture showed *A. baumannii*. IVT TGC (3 mg q24 h) was added + IV TGC dose increased (100 mg q12 h) + CPZ/SBT (3 g q12 h). His fever improved 6 days later but the CSF culture was still positive, so IVT TGC dose was increased to 4 mg q12 h.

Reference	Duration of therapy	Days to sterilize the CSF	Infection outcome	Survival
[6]	IV TGC (> 75 days), IVT TGC (75 days), IVT CST (14 days), MEM (44 days)	68 after IVT TGC	Cured	Yes
[7]	IV TGC and IV CST (14 days), IT CST (10 days)	6	Cured	NR
	IV TGC and IV CST (12 days), *MEM* (10 days)	7	Cured	NR
[10]	21 days	NR	Cured	Yes
[11]	21 days	14	Cured	Yes
[12]	IVT TGC (15 days), IVT CST (22 days). IV was NR	4 after IVT CST and IVT TGC	Cured	NR
	IVT TGC (15 days), IVT CST (30 days). IV was NR	3 after IVT CST	Cured	NR
[13]	IV therapy (21 days), IVT CST (16 days)	7	Cured	Yes
[14••]	16 days	3–5 days of therapy	Cured	Yes

Table 1. (Continued)

Reference	Duration of therapy	Days to sterilize the CSF	Infection outcome	Survival
	13 days	3–5 days of therapy	Cured	Yes
	21 days	3–5 days of therapy	Cured	Yes
	12 days	3–5 days of therapy	Cured	Yes
	5 days	NR	NR	Died
	11 days	3–5 days of therapy	Cured	Yes
	IV TGC (54 days), IV CST (13 days)	NR	NR	Yes
	IV TGC and IV CST (23 days)	Was not achieved	Treatment failed	Died
	IV TGC (24 days), IV CST (29 days), IT CST (20 days), VAN (19 days)	3–5 days of therapy	Cured	Died
	IV TGC and IV CST (26 days)	3–5 days of therapy	Cured	Yes
	IV TGC (7 days), IV CST (5 days) *MEM* (12 days), VAN (3 days)	NR	NR	Died
	IV TGC (16 days), *MEM* (14 days), VAN (18 days), IV CST (24 days)	3–5 days of therapy	NR	Yes
	IV TGC (67 days), IV CST (63 days), IT CST (19 days)	Achieved at the end of treatment	Cured	Yes
	IV TGC (68 days), IV CST (14 days), RIF (54 days)	3–5 days of therapy	Cured	Yes
	IV TGC and IV CST (24 days), IT CST (22 days)	Achieved at the end of treatment	Cured	Yes
	TGC (18 days), IT NET (3 days), IV NET (6 days), IV CST (9 days)	Achieved at the end of treatment	Cured	Died
	All for 14 days	3–5 days of therapy	NR	Died
	IV TGC and IV NET (18 days)	3–5 days of therapy	Cured	Yes
	IV TGC (8 days), NET (5 days), IT NET (3 days)	NR	Cured	Yes
	IV TGC and IV AMK (25 days)	Achieved at the end of treatment	Cured	Yes
	All for 14 days	CSF culture showed *P. aeruginosa* at end of treatment	*Acinetobacter* was eradicated but CSF was positive for *Pseudomonas*	Yes
	IV TGC (26 days), *MEM* (33 days), IT AMK (23 days)	3–5 days of therapy	Cured	Died
	IV TGC and MEM (21 days)	3–5 days of therapy	Cured	Yes
[15•]	IV TGC (17 days), CVI TGC (12 days), IVT TGC (5 days)	12 days	Cured	Yes
[16]	NR	5 days	Cured	Yes
[17]	IV TGC *and MEM* (21 days), IV NET (14 days)	NR	Cured	Yes
	IV TGC *and MEM* (21 days), IV NET (14 days)	NR	Cured	Yes
[18]	IVT TGC (10 days). IV was NR	16 days (10 days after IVT TGC)	Cured	Yes
[19]	IV CST (40 days), AMK (3 days), IV TGC (12 days), IT CST (25 days)	7 days (4 days after IV TGC)	Cured	Yes
[20]	IV TGC and IV CST (14 days), IVT CST (8 days)	3 days	Cured	NR
[21]	IV TGC (27 days), IVT TGC (12 days), CPZ/SBT (17 days).	19 days, 3 days of high-dose IVT TGC	Cured	Yes

AMK, amikacin; *ARF*, acute renal failure; *CAZ*, ceftazidime; *CIP*, ciprofloxacin; *CSF*, cerebrospinal fluid; *CPZ/SBT*, cefoperazone/sulbactam; *CST*, colistin; *CVI*, continuous ventricular irrigation; *DOX*, doxycycline; *EDH*, epidural hematoma; *EVD*, extraventricular drainage; *GEN*, gentamicin; *GSI*, gunshot injury; *h*, hours; *HCP*, hydrocephalus; *I*, intermediate; *ICH*, intracerebral hemorrhage; *IPM*, imipenem; *IT*, intrathecal; *IU*, international units; *IV*, intravenous; *IVT*, intraventricular hemorrhage; *LD*, lumbar drainage; *LSS*, lumbar spinal stenosis; *LVX*, levofloxacin; *MEM*, meropenem; *MIC*, minimum inhibitory concentration; *MMC*, myelomeningocele; *MVA*, motor vehicle accident; *NET*, netilmicin; *NR*, not reported; *PA*, pilocytic astrocytoma; *RIF*, rifampicin; *S*, sensitive; *SAH*, subarachnoid hemorrhage; *SDH*, subdural hematoma; *SXT*, cotrimoxazole; *TBI*, traumatic brain injury; *TET*, tetracycline; *TGC*, tigecycline; *TOB*, tobramycin; *VAN*, vancomycin; *VPS*, ventriculoperitoneal shunt

IVT) in patients with healthcare-associated *A. baumannii* meningitis or ventriculitis. Clinical studies as well as case series and case reports were included, while animal and in vitro studies were excluded. Articles that described the use of tigecycline (IV and/or IVT) in patients with healthcare-associated meningitis or ventriculitis caused by pathogen other than *A. baumannii* were excluded. Also, articles that described the use of tigecycline in infections other than meningitis or ventriculitis were excluded.

Results

The search strategy retrieved 44 citations (43 citations from PubMed and one from the bibliographies of the retrieved articles); only 14 citations met the inclusion criteria. Among the identified articles, 12 were case reports, one was case series, and one was a retrospective multicenter study that evaluated 23 carbapenem-resistant *A. baumannii* healthcare-associated meningitis cases treated with IV tigecycline including regimens. The search did not reveal any randomized controlled trials evaluating the use of tigecycline in patients with healthcare-associated *A. baumannii* meningitis or ventriculitis. Table 1 gives data regarding the demographic characteristics, underlying condition, presence of foreign bodies, susceptibilities to antimicrobial agents, antimicrobial and therapeutic schedules, dosages, CSF sterilization, and survival of the patients included in this review.

Use of tigecycline for *A. baumannii* control

Wadi and Al Rub [11] described the first use of tigecycline in a patient with multidrug-resistant (MDR) *Acinetobacter* healthcare-associated meningitis (secondary to head trauma after a motor vehicle accident). Once the patient had meningeal signs, CSF culture was sent and showed MDR *Acinetobacter* (sensitivity to antibiotics was not reported). The patient was started on IV tigecycline monotherapy (50 mg q12 h). He showed significant improvement with subsidence of fever, headache, and confusion. Tigecycline was continued for 21 days until a week after the last sterile CSF culture.

The use of IV and/or IVT tigecycline was described in 39 patients infected with healthcare-associated *A. baumannii* meningitis or ventriculitis in 14 reports [6, 7, 10–13, 14••, 15•, 16–21]. Thirty-seven patients were adults (mean age, 49.14 years; ± 16.40 SD), while the remaining 2 were infants (2 and 4 months old). Most patients were male (27 of 39, 69%). In most cases, meningitis or ventriculitis was developed post-neurosurgical procedures for the management of different central nervous system diseases. The presence of a foreign body was reported in 34 cases; 19 cases had external ventricular drain, 10 cases had lumbar drain, and 2 cases had ventriculoperitoneal shunt. The sensitivity of *A. baumannii* was reported in 38 cases; 37 cases were sensitive to tigecycline while one case was resistant (MIC = 16 mg/L). Sensitivity to colistin or polymyxin B was reported in 27 cases; 24 cases were sensitive while 3 were resistant. No MIC breakpoints exist for tigecycline to *A. baumannii*. The common practice is to use the same Food and Drug Administration (FDA) breakpoints that were set for *Enterobacteriaceae* for *A. baumannii* as well (an isolate with an MIC of ≥ 4 mg/L was considered non-susceptible).

IV administration of tigecycline

IV tigecycline monotherapy was used in 7 patients [11, 14••]. Six of 7 patients were cured and survived. The duration of IV tigecycline monotherapy ranged from 5 to 21 days (mean, 14.14 days; ± 5.72 SD), while CSF sterilization was achieved in 3–5 days up to 14 days of tigecycline therapy. All seven patients received a regular dose of tigecycline (50 mg q12 h). High-dose IV tigecycline (100 mg q12 h) was used in four patients only [6, 12, 15•, 21]. In these cases, it was used in combination with other antibiotics and all patients were cured. Thirty-two patients received IV tigecycline in combination with other antibiotics (IV and/or IVT/IT) to treat healthcare-associated *A. baumannii* meningitis or ventriculitis [6, 7, 10, 12, 13, 14••, 15•, 16–21]. Other antibiotics used for the same diseases included IV colistin (18 cases), IVT/IT colistin (10 cases), IV polymyxin B (1 case), IVT polymyxin B (1 case), meropenem (8 cases), rifampicin (3 cases), IV netilmicin (5 cases), IT netilmicin (2 cases), IV amikacin (3 cases), IVT/IT amikacin (2 cases), and cefoperazone/sulbactam (3 cases). One patient received netilmicin as part of therapy but the route of administration was not reported [14••]. Patients who received IV tigecycline in combination with other antibiotics had a duration of IV tigecycline therapy ranging from 7 to 68 days (average, 26.12 days; ± 18.77 SD), while CSF sterilization was achieved in 3–5 days up to 68 days.

IVT administration of tigecycline

IVT tigecycline was never used alone and it was always used in combination with IV antibiotics or IV antibiotics plus IVT polymixin. Six adult patients received IVT tigecycline as part of treatment for healthcare-associated *A. baumannii* meningitis or ventriculitis [6, 12, 15•, 18, 21]. One patient received initially high-dose IV tigecycline (100 mg q12 h) plus meropenem (2 g q8 h) and vancomycin (1 g q12 h). Because CSF cultures remained positive for *A. baumannii* (only sensitive to tigecycline), IVT tigecycline at a dose of 2 mg/day (after 10 days, the dose was escalated to 2 mg q12 h) was added. Also, IVT colistin (60,000 IU q12 h for 2 days, then escalated to 120,000 IU q12 h) was added for this patient [6]. The second patient received initially IV colistin (4.5 MIU q12 h) plus IVT colistin (250,000 IU q24 h); the *A. baumannii* strain in the CSF was sensitive only for colistin and tigecycline. However, after 15 days of IVT colistin infusions, fever persisted, and the CSF analysis remained abnormal. Therefore, IVT tigecycline (4 mg q24 h) was added to IVT colistin [12]. The third patient received high-dose IV tigecycline (100 mg q12 h) plus rifampicin (600 mg) and IV colistin (4.5 MIU q12 h) and IVT colistin (250,000 MIU q24 h); the *A. baumannii* strain in the CSF was sensitive only for tigecycline (MIC = 2 mg/L). Because the patient did not improve, IVT tigecycline (4 mg q24 h) was added to IVT colistin [12]. The fourth patient had an extensively drug-resistant (XDR) *A. baumannii* (tigecycline MIC = 16 mg/L). He was administered high-dose IV tigecycline (100 mg q12 h), IV cefoperazone/sulbactam (2 g q8 h), and continuous ventricular irrigation of tigecycline (10 mg/500 mL saline twice daily, in from the right occipital horn and out from the left horn). After 12 days, IV tigecycline was reduced to 50 mg q12 h, while continuous ventricular irrigation of tigecycline was modified to IVT tigecycline (2 mg q12 h) [15•]. The fifth patient received IV tigecycline (100-mg loading then

50 mg q12 h) plus IV cefoperazone/sulbactam (3 g q8 h). After 6 days, the same *A. baumannii* strain sensitive only to tigecycline (polymyxin sensitivity was not tested) was still isolated from the CSF, so IVT tigecycline (2 mg q12 h) was started [18]. The last patient received initially IV tigecycline (50 mg q12 h) for 10 days. Then, his body temperature raised to 40 °C and his CSF culture was abnormal showing *A. baumannii*. Thus, IVT tigecycline (3 mg q24 h) and cefoperazone/sulbactam (3 g q12 h) were added with an increase of IV tigecycline dose (100 mg q12 h). His fever improved 6 days later but the CSF culture was still positive, and an IVT tigecycline dose was increased to 4 mg q12 h [21]. The duration of IVT tigecycline ranged from 10 to 75 days. None of the patients experienced any side effect from IVT tigecycline, and all patients were cured.

Concerning the technical aspects of IVT tigecycline administration, Lauretti et al. [6] closed the CSF drain temporarily for 2 h after every injection to prevent untimely washout of the drug. While Tsolaki et al. [12] withheld the CSF diversion for 4 h, this additional time might enhance IVT tigecycline effect by leaving it to equilibrate better throughout the CSF compartment. Long et al. [15•] described a treatment that involved continuous ventricular irrigation (CVI) of 10 mg of tigecycline in 500-mL saline twice daily, in from the right occipital horn and out from the left horn. After 12 days of CVI of tigecycline, ventriculitis signs resolved, and the load of *Acinetobacter* in the CSF decreased until CSF sterilization. At that moment, CVI of tigecycline was adjusted to IVT tigecycline (2 mg twice daily). Lastly, Fang et al. [21] administered tigecycline in the ventricular system, closing the drainage tube for almost 1 h.

Regarding outcome after treatment with IV and/or IVT tigecycline, treatment failed in two patients; the CSF of one of them was cleared from *A. baumannii* but it showed positive growth of *Pseudomonas* at the end of treatment [14••]. The outcome was not reported in 5 patients while 32 patients were cured. Survival was reported in 34 cases [6, 10, 11, 13, 14••, 15•, 16–19, 21] and only 5 patients died (mortality rate = 14.71%). Only two patients developed side effects from receiving IV tigecycline, resulting in an elevation of liver enzymes but tigecycline was continued for them on top of this side effect [14••].

Discussion

A. baumannii is a strict aerobic Gram-negative bacillus that has been increasingly involved as an important cause of healthcare-associated infections and resulted in high mortality rate reaching up to 35% depending on type of infection and Acinetobacter strain [22]. The incidence of MDR and pandrug-resistant *A. baumannii* has recently increased because of the abuse of antibiotics and the development of various mechanisms of antibiotic resistance [23]. Post-neurosurgical *A. baumannii* infection is common in healthcare settings [24]. Treatment of such infections is challenging because of the presence of antibiotic resistance and poor penetration of antibiotics through the blood-brain barrier.

Tigecycline, a glycylcycline antibiotic, has an excellent activity against species of MDR Gram-positive and Gram-negative bacteria including *Acinetobacter* species [25]. In 2005, the US FDA approved the clinical use of IV tigecycline for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia. Its CNS penetration is low (around 11%) [8] and thus, it is not currently recommended

for the treatment of *Acinetobacter*-caused meningitis [2]. Polymixin use as a therapy of healthcare-associated *A. baumannii* meningitis and ventriculitis was not successful in many cases [5], and because of antimicrobial resistance (mainly colistin and carbapenem resistance) [6, 7], IV and/or IVT tigecycline was considered as a salvage therapy in many cases of healthcare-associated *A. baumannii* meningitis and ventriculitis.

The use of tigecycline in the treatment of healthcare-associated *A. baumannii* meningitis and ventriculitis was successful in most cases as detailed in this study. Treatment failed in two patients and two patients died. Even using IV tigecycline monotherapy was successful in treating patients with healthcare-associated *A. baumannii* meningitis or ventriculitis [11, 14••], despite having low CNS penetration [8]. Regarding safety, only two cases experienced side effects from IV tigecycline [14••]; both cases had elevation in liver enzymes but tigecycline was not held for them. None of the cases that received IVT tigecycline had side effects.

Only four patients with healthcare-associated *A. baumannii* meningitis or ventriculitis received high-dose IV tigecycline [6, 12, 15•, 21]. It was used in combination with other antibiotics and all patients were cured. High-dose tigecycline is associated with better outcomes compared with conventional dose in non-approved indications like ventilator-associated pneumonia due to Gram-negative MDR bacteria including carbapenem-resistant *A. baumannii* [26]. In the literature, tigecycline (IV and/or IVT/IT) has been proven to be effective for treating healthcare-associated meningitis or ventriculitis caused by other Gram-negative and Gram-positive pathogens including *Klebsiella pneumoniae*, *Elizabethkingia meningoseptica*, and *Enterococcus faecium* [27–30].

Due to its excellent effectiveness against XDR bacteria, its preservative-free formulation, its safety profile, and limited CNS penetration, tigecycline is an ideal candidate for IVT use. In the six patients who received IVT tigecycline for healthcare-associated *A. baumannii* meningitis or ventriculitis, the dose of IVT tigecycline ranged from 2 to 8 mg/day [6, 12, 15•, 18, 21]. Wu et al. [27] evaluated the IVT administration of tigecycline for the treatment of MDR bacterial meningitis caused by MDR *K. pneumoniae*. They analyzed the pharmacokinetics of tigecycline and measured tigecycline trough concentrations for the three different dosages of IV and IVT tigecycline. The results of this study showed levels of 0.313, 1.290, and 2.886 mg/L for 49 mg IV plus 1 mg IVT q12 h, 45 mg IV plus 5 mg IVT q12 h, and 40 mg IV plus 10 mg IVT q12 h, respectively. The highest IVT tigecycline dosage achieved the optimal trough concentration, which was higher than the MIC for *K. pneumoniae* (2 mg/L). Although the level of tigecycline in the CSF was not measured for patients with healthcare-associated *A. baumannii* meningitis or ventriculitis who received IVT tigecycline, 4 mg/day of IVT tigecycline was sufficient in five cases. Only one patient required a high-dose IVT tigecycline (8 mg/day) [21].

Conclusion

Post-neurosurgical *A. baumannii* infection is common in healthcare settings. Treatment of such infections is challenging because of the presence of antibiotic resistance and poor penetration of antibiotics through the blood-brain barrier. IV and IVT tigecycline has been used successfully for the treatment of healthcare-

associated *A. baumannii* meningitis and ventriculitis. IV and IVT tigecycline might be considered in cases with healthcare-associated *A. baumannii* meningitis and ventriculitis when initial therapy with polymyxin fails, when polymyxin resistance appears, and when patients develop side effects (mainly neurotoxicity) from IVT/IT polymixin. However, large randomized controlled trials are necessary to clearly evaluate the safety and effectiveness of IV and IVT tigecycline in healthcare-associated *A. baumannii* meningitis and ventriculitis.

Compliance with ethical standards

Conflict of interest
Mohammad Abdallah declares that he has no conflict of interest. Hamzeh Alsaleh declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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