

Original Article

Intrathecal and intraventricular antibiotics for postoperative Gram-negative meningitis and ventriculitis

Saad Akhtar Khan, Muhammad Waqas¹, Usman T. Siddiqui¹, Muhammad Shahzad Shamim¹, Karim Rizwan Nathani¹, Rashid Jooma¹, Faisal Mehmood²

Section of Neurosurgery, The Memon Medical Institute, ¹Section of Neurosurgery, ²Department of Medicine, The Aga Khan University Hospital, Karachi, Pakistan

E-mail: Saad Akhtar Khan - drsaadkhan84@gmail.com; Muhammad Waqas - shaiq_waqas@hotmail.com; Usman T. Siddiqui - usmansiddiqui@hotmail.com;

*Muhammad Shahzad Shamim - shahzad.shamim@aku.edu; Karim Rizwan Nathani - karim.rizwan.n@gmail.com; Rashid Jooma - rashid.jooma@aku.edu;

Faisal Mehmood - faisal.mehmood@aku.edu

*Corresponding author

Received: 21 February 17 Accepted: 01 June 17 Published: 26 September 17

Abstract

Background: Postoperative meningitis is a growing cause of concern, especially with the evolution of multidrug-resistant organism. The authors evaluate the use of intraventricular/intrathecal (IVT/IT) antibiotics for postoperative gram-negative meningitis in patients whom intravenous antibiotics were ineffective.

Methods: Medical records were retrospectively reviewed and neurosurgery patients with gram-negative postoperative infection meningitis/ventriculitis were enrolled in the study. Their demographics, hospital course, and outcomes were recorded in a pro forma and analyzed using Statistical Package for the Social Sciences, version 19.

Results: The review identified 21 patients with postneurosurgical gram-negative meningitis/ventriculitis who were treated with IVT or IT antibiotics. The most common organism was *Acinetobacter species* ($n = 14$; 66%). Amikacin was used in 7 patients, polymyxin B in 9 patients, and colistin in 5 patients. A combination of antibiotics was used in one patient. Cerebrospinal fluid sterility was achieved in all patients with no incidence of relapse. There was a single death, though that was not related to the infectious process as the patient had a massive pulmonary embolism.

Conclusion: The findings of this study suggest that IVT and IT antibiotic therapy is a useful option in patients who are nonresponsive to standard intravenous therapy with little or no side effects.

Key Words: Antibiotics, gram negative, intrathecal, intraventricular, meningitis, postoperative, ventriculitis

Access this article online

Website:

www.surgicalneurologyint.com

DOI:

10.4103/sni.sni_81_17

Quick Response Code:

INTRODUCTION

Postoperative meningitis and ventriculitis are one of the grave delayed complications of neurosurgical procedures. Recently, an increase in incidence of postoperative meningitis has been observed.^[26] The concern is further aggravated by rising incidence of multidrug-resistant organisms in such infections^[11,22] that makes their treatment a daunting challenge. The most common

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Khan SA, Waqas M, Siddiqui UT, Shamim MS, Nathani KR, Jooma R, et al. Intrathecal and intraventricular antibiotics for postoperative Gram-negative meningitis and ventriculitis. *Surg Neurol Int* 2017;8:226. <http://surgicalneurologyint.com/Intrathecal-and-intraventricular-antibiotics-for-postoperative-Gram-negative-meningitis-and-ventriculitis/>

causative agents are gram-positive organisms, such as *Staphylococcus aureus*;^[6] however, in case of gram-negative organisms the prognosis is much poor.^[6]

Intraventricular (IVT) and intrathecal (IT) antibiotics were reported to be used as back as a century ago.^[4] However, still there exist concerns regarding its indications, efficacy, and even safety. The primary advantage for this route is that it provides a direct path for antibiotic delivery bypassing the blood–brain barrier, providing larger effective concentration of antibiotics at the infected site with reduced, if any, systemic side effects.^[19] The disadvantages are limited data available for calculation of effective dosage, and the risk for infection due to access to the subarachnoid space and ventricles. The two common routes of access for administration include ventricular access devices such as external ventricular drain (EVD) and lumbar drain (LD), both of which carry minimal procedure-related complications.^[20,27]

The use of IVT and IT antibiotic therapies has recently regained interest. An earlier infantile randomized control trial identified a three-fold increased relative risk of mortality with the use of IVT/IT and intravenous^[1] antibiotics compared to IV antibiotics only. The trial was subjected to significant criticism due to the duration of IV antibiotics and the route of administration of IT antibiotics, which in this case was serial lumbar puncture.^[13] Recent studies on using IVT polymyxin and IVT gentamycin in adults have reported much higher cure rates.^[7,23]

Most papers addressing this very important neurosurgical topic share the common limitations of small sample size, heterogeneity of patient population, and treatment plans.^[16,18,23,25] We, therefore, retrospectively analyzed our own results with the management of such patients to contribute to the existing body of literature. We have analyzed and shared clinical features, hospital course, treatment plans, and eventual outcomes of patients treated for postoperative gram-negative meningitis/ventriculitis with IVT/IT antibiotic therapy.

MATERIALS AND METHODS

The Aga Khan University Hospital is an ISO certified tertiary care hospital with Joint Commission International Accreditation (JCIA) and established Neurosciences program. The hospital maintains a vigorous medical recording system based on electronic as well as manually compiled patient records, logged through International Classification of Diseases (ICD) coding. We reviewed our medical records for all patients admitted to the hospital from January 2008 to December 2012, with a history of neurosurgical procedure performed within 2 weeks of presentation and later presenting with “culture proven” gram-negative ventriculitis/meningitis. Patients who

responded to IV antibiotic therapy alone, not requiring IVT or IT antibiotics were excluded. The study was exempted by the Ethics Review Committee as it was a retrospective chart review.

IV antibiotics were started in all patients as soon as a diagnosis was made on cerebrospinal fluid (CSF) analysis. All patients underwent CSF analysis once at least every third day until the CSF culture was negative or the patient was discharged. Patients were started on IVT/IT antibiotics only in cases where IV antibiotics were ineffective despite 5 days of IV therapy, or if the first CSF analysis showed frank pus. IVT/IT antibiotics were administered either through EVD or LD. Dosages were based on available literature on the respective minimum inhibitory concentrations (MICs). IVT/IT antibiotics were continued until three consecutive CSF cultures were negative.

Data were collected on a standardized pro forma for all relevant clinical, laboratory, and radiological variables. Data were analyzed on Statistical Package for the Social Sciences, version 19 (SPSS IBM v 19). Continuous variables with normal distribution were expressed with mean and standard deviation, while continuous data without normal distribution were expressed with median and range. Categorical data were expressed as percentage and proportions. Mann–Whitney U-test was applied to compare nonparametric numerical data. Categorical data were compared using Chi-square test. A *P* value of 0.05 was regarded as significant.

Biochemical outcomes were based on the concepts of cure, relapse, and failure. “Cure” was defined as three consecutive negative CSF culture results and no relapse after withdrawal of antibiotics; “Relapse” was defined as isolation of the same organism from the CSF or central nervous system (CNS) lesion within 3 weeks of completing therapy; and “Failure” was defined as no biochemical response to treatment. Clinical outcomes were reported as pretreatment and posttreatment Glasgow Coma Scale (GCS) score. We further classified the standard GCS.^[14] GCS score of 3 or less was classified as unfavorable and 4 or more as favorable. Outcomes of the patients were determined from medical records and were based on the detailed assessment of the patient made and documented on the last clinical follow-up by the attending physician.

RESULTS

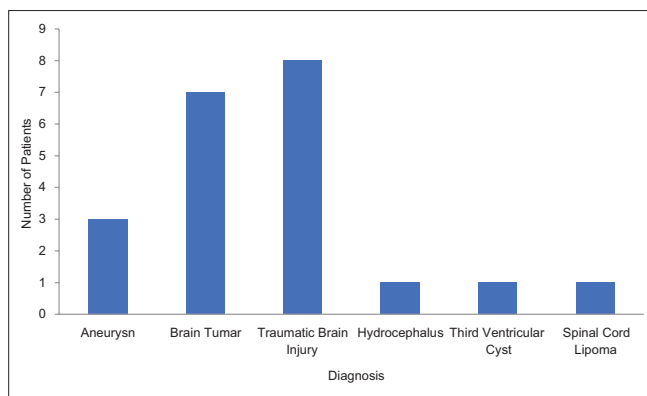
During the study period, 94 cases were reported of postoperative meningitis/ventriculitis at our institution. Of these, 63 were culture proven gram positive and hence excluded from our study. The remaining 31 patients either had isolated gram-negative meningitis/ventriculitis or mixed gram-positive/negative infection,

with 21 patients out of these requiring treatments with IVT/IT antibiotics.

Out of the total 21 patients enrolled in the study, 16 were males and 5 were females. Their mean age was 41.7 ± 11 years (range: 26–58 years). All except one of these patients had cranial surgery. Details of individual cases are shown in Table 1. Of the total, 8 patients were admitted with a GCS of >12 , while the remaining had a GCS ≤ 12 . In our setting, postoperative gram-negative meningitis/ventriculitis was most commonly found in patients of traumatic brain injury ($n = 8$), followed by brain tumor ($n = 7$). The primary diagnosis of the patients can be observed in Graph 1.

Acinetobacter species was the most common organism isolated on CSF culture ($n = 14$) followed by *Klebsiella pneumoniae* ($n = 3$), *Pseudomonas aeruginosa* ($n = 1$), and *Enterobacter cloacae* ($n = 1$). One patient had polymicrobial growth. Three antibiotics were used in the IVT/IT treatment group: Amikacin, polymyxin B, and colistin. The indication was primarily based on the sensitivity of pathogenic organisms cultured on CSF of individual patients; Table 2 shows the resistance pattern of the organism. Amikacin was used in 7 patients, polymyxin B in 9 patients, and colistin in 5 patients. A combination of two IVT/IT antibiotics, polymyxin B and amikacin, was used in one patient. An EVD was used as the route of administration in 13 cases (62%), while a LD was used in 8 (38%) patients. Median duration between starting of IT/IVT after being diagnosed with postneurosurgical meningitis/ventriculitis was 3 days (range 0–7 days). Median duration of IVT/IT therapy was 15 (9–25) days. CSF sterility was achieved in all patients, with a median time to sterility being 7.1 ± 3.8 (range 2–16) days (EVD 7.08 ± 3.37 days vs. LD 7.1 ± 4.6 days, P value 0.176). Only two patients achieved CSF sterility within 48 hours.

Discharge GCS improved in 2, remained the same in 7, and deteriorated in 12 patients. Median hospital stay was 38 days (20–257 days), with the EVD group [46 (29–72)] having a longer stay than LD group [32.5 (20–76) days].



Graph 1: Primary diagnosis of the patients who developed Gram Negative Meningitis/Ventriculitis

At 6 months follow-up, favorable outcomes were seen in 14 (66.7%) patients and 7 (33.3%) patients remained in an unfavorable state. One (5%) patient died during treatment and although the patient had *Acinetobacter species* infection, the cause of death was found to be a massive pulmonary embolus. No adverse effects attributable to IVT/IT therapy were noted in the study.

DISCUSSION

Management of hospital acquired meningitis and/or ventriculitis is a daunting challenge for clinicians.^[24] The increasing incidence of multidrug-resistant organism has further worsened the situation.^[5] In neurosurgical postoperative patients the complexity is compounded even further as the underlying CNS pathology causes disruption of the blood–brain barrier and in-turn alters both pharmacokinetics and drug penetration.^[25] This has been shown in patients with traumatic brain injury who were administered intravenous vancomycin, but the drug consistently failed to achieve concentrations above the MIC.^[3] In these circumstances, IVT/IT provides a direct access, which can potentially overcome these issues. High CSF sterility rates along with relatively short time needed to achieve sterility in recent reports has supported the use of IVT/IT therapy in both bacterial and fungal infections.^[28]

We herein report one of the largest series of patients with gram-negative CNS infections treated with IVT or IT therapy [Table 3]. We achieved 95% sterility rate in our study with one patient continuing extended IV course after completing IVT therapy. Time to achieve CSF sterility ranged from 2 to 16 days. Additionally, there was no relapse in our study. These findings are consistent when compared from the international data. In a recent study on postoperative meningo-ventriculitis by Remes *et al.*,^[18] the time to achieve CSF sterility ranged from 1 to 12 days and there was just one case of relapse. Tangden *et al.*^[23] reported their data of 13 patients with gram-negative meningo-ventriculitis treated with IT antibiotics and achieved CSF sterility of all patients without relapse. Though our experience was favorable for both IVT and IT approach, however, we do prefer IT over IVT due to the convenience of the procedure and lower comparative risk of complications.

Earlier studies have debated the use of LD as the route for antibiotic administration as there remained speculations with regards to effective delivery of administered antibiotic into the ventricular cavity and CSF cistern. Kaiser *et al.* demonstrated that a 5–10 mg injection of antibiotic via lumbar route showed significantly lower ventricular CSF drug level when compared to lumbar CSF, while with ventricular drug injection the levels in the lumbar CSF were comparatively much higher.^[7] We, however, did not see a significant difference in the CSF

Table 1: Clinical parameters of individual patients

Case no	Age/Gender	Pathology	Primary surgery	Organism	IVT/IT antibiotic	IVT/IT route	Antibiotic dosage	CSF negativity	Days to sterility	Biochemical outcome	Clinical outcome	Admission GCS	Discharge GCS	Length of hospital stay
1	51/M	SAH, anterior circulation aneurysm	Craniotomy	ATSP	PMB	LD	50000 units OD	Yes	4	Cure	F	10	9	48
2	44/M	SAH, anterior circulation aneurysm	Craniotomy	ATSP	PMB	EVD	50000 units OD	Yes	2	Cure	UF	14	14	36
3	35/M	SAH, anterior circulation aneurysm	Craniotomy	ATSP	COL	EVD	10 mg OD	Yes	7	Cure	UF	4	6	46
4	61/F	Supratentorial primary brain tumor	Craniotomy	ATSP	AMK	LD	30 mg OD	Yes	10	Cure	F	15	14	76
5	45/F	Supratentorial primary brain tumor	Craniotomy	PSAE	AMK	LD	30 mg OD	Yes	2	Cure	F	15	15	33
6	26/M	Supratentorial primary brain tumor	Craniotomy	ATSP	PMB	EVD	50000 units OD	Yes	3	Cure	F	5	6	41
7	29/M	Supratentorial primary brain tumor	Craniotomy	ATSP	PMB	EVD	50000 units OD	Yes	7	Cure	UF	15	9	42
8	58/M	Supratentorial primary brain tumor	Craniotomy	ATSP/ENCL	PMB	LD	50000 units OD	Yes	16	Cure	F	10	9	77
9	33/M	Supratentorial primary brain tumor	Craniotomy	ENCL	AMK	EVD	40 mg OD	Yes	14	Cure	UF	15	10	72
10	36/M	Supratentorial primary brain tumor	Craniotomy	ATSP	PMB + AMK	EVD	50000 units OD (PMB) 30 mg OD (AMK)	Yes	5	Cure	UF	12	9	51
11	26/M	Traumatic brain injury	Craniotomy	ATSP	PMB	EVD	50000 units OD	Yes	8	Cure	F	12	11	69
12	43/M	Traumatic brain injury	Craniotomy	ATSP	PMB	EVD	50000 units OD	Yes	13	Cure	F	10	12	38
13	29/M	Traumatic brain injury	Craniotomy	PM	PMB	LD	50000 units OD	Yes	6	Cure	F	10	10	25
14	47/F	Traumatic brain injury	Craniotomy	ATSP	COL	EVD	10 mg OD	Yes	7	Cure	UF	3	7	56
15	60/F	Traumatic brain injury	Craniotomy	ATSP	COL	LD	10 mg OD	Yes	4	Cure	In hospital mortality	14	-	20

Contd...

Table 1: Contd...

Case no	Age/Gender	Pathology	Primary surgery	Organism	IVT/IT antibiotic	IVT/IT route	Antibiotic dosage	CSF negativity	Days to sterility	Biochemical outcome	Clinical outcome	Admission GCS	Discharge GCS	Length of hospital stay
16	55/M	Traumatic brain injury	Craniotomy	ATSP	COL	EVD	10 mg OD	Yes	6	Cure	UF	4	5	29
17	44/M	Traumatic brain injury	Craniotomy	KLPN	AMK	LD	30 mg OD	Yes	10	Cure	UF	10	7	32
18	44/F	Traumatic brain injury	Craniotomy	PSAE/ KLPN	COL	EVD	10 mg OD	Yes	8	Cure	F	11	11	56
19	34/M	Third ventricle colloid cyst	Craniotomy	KLPN	AMK	EVD	10 mg OD	Yes	7	Cure	F	15	14	34
20	57/M	Hydrocephalus	EVD	KLPN	AMK	EVD	10 mg OD	Yes	5	Cure	F	12	10	257
21	36/M	Spinal cord lipoma	Laminectomy	ATSP	PMB	LD	50000 units OD	Yes	5	Cure	F	15	15	23

ATSP=Acinetobacter species; ENCL=Enterobacter cloacae; LD=Lumbar drain; EVD=External ventricular drain; PSAE=Pseudomonas aeruginosa; KLPN=Klebsiella pneumoniae; PM=Polymicrobial; AMK=Aminikacin; PMB=Polymyxin B; COL=Colistin; F= Favorable; UF=Unfavorable

sterility rates when comparing the two routes in our study. Remes *et al.* drew the same conclusions in their study and even though lumbar and ventricular CSF drug levels were not measured, the CSF sterility rates showed no significant difference either using IT or IVT therapy.^[18]

Postneurosurgical meningitis and/or ventriculitis have a critically high mortality rate, ranging from 3 to 33%.^[2,12,15,17] The fact that it is a relatively uncommon phenomenon has precluded it from undergoing any prospective data collection or randomized controlled trials. In our study, the mortality rate was 5%, which suggests that IT/IVT has valuable potential, especially in patients who can be started early and have a good baseline GCS as has been suggested by previous authors.^[25]

In our series, Acinetobacter species was the most commonly encountered gram-negative organism which makes this series differ from other reports, looking specifically at gram-negative meningitis/ventriculitis, where Pseudomonas species is usually more common.^[25] We have previously reported the relatively high incidence of Acinetobacter at our institution.^[21] It is becoming a growing concern in patients with nosocomial meningitis especially as most cultured organisms are resistant to third and fourth-generation cephalosporins, and some carbapenems.^[9] It has been shown to be an independent predictor of unfavorable outcomes in neonates and children^[10,16] and is the major cause of mortality in adults in one report.^[25] The single mortality in our series also had Acinetobacter species infection though the cause of death was a pulmonary embolism.

The major reason for the cautioned use of IVT/IT therapy has been the significant toxicity that was reported by earlier studies.^[8,14] These included seizures in up to 20% of the patients and chemical ventriculitis in as high as 60% of the patients,^[8,14] though those were considered to be dose related. Few papers have also reported side effects such as transient hearing loss and seizures using gentamicin and vancomycin, though most recent studies have shown little or no serious adverse effects with the use of polymyxin B, colistin, and vancomycin.^[18,25,28] Meropenem and netilmicin which were used by Remes *et al.* for the first time also showed no adverse effects.^[18] In our study, we did not encounter any patient with any serious adverse effects which supports the safety of IVT/IT therapy if used in the correct dosage.

CONCLUSION

The study describes the clinical outcomes of patients with gram-negative meningitis and/or ventriculitis being treated with IVT/IT antibiotics. In our study, there was good CSF sterility rate with no relapse. This, along with minimal side effects, makes IVT/IT an effective and relatively safe treatment option, especially in patients

Table 2: Antimicrobial resistance of causative organisms from CSF in 21 episodes of postneurosurgical gram-negative meningitis treated with IVT/IT therapy. Patient 8 and 18 had two causative organisms as shown in Table 1. Patient 13 has not been included in the table

Antimicrobial agent	<i>Acinetobacter</i> species n=14	<i>Enterobacter</i> species n=2	<i>Klebsiella pneumoniae</i> n=4	<i>Pseudomonas aeruginosa</i> n=2	Total n=22 ^a
Amikacin	10	1	1	1	13 (59.1%)
Carbapenem	11	0	0	0	11 (50%)
Cephalosporin	14	1	4	0	19 (86.4%)
Clotrimoxazole	10	0	4	0	14 (63.6%)
Gentamycin	12	1	3	0	16 (72.7%)
Polymyxin B	0	1	3	0	4 (18.2%)
Quinolone	9	0	1	0	10 (45.5%)

Table 3: Previous studies with postneurosurgical gram-negative meningitis treated with IVT/IT therapy

Author	Year of study	Number of patients	Route used			Outcome	CSF sterility (%)	Most common organism	Most common antibiotic	Major adverse effect of IVT/IT
Our study	2014	21	13	8	0	F: 11 (52.3%) UF: 9 (42.9%) D: 1 (4.8%)	100	ATSP	Polymyxin B	None
Wang <i>et al.</i>	2012	14	14	0	0	F + UF: 11 (73.3%) D: 4 (26.67%)	73.3	ATSP	Amikacin	None
Remes <i>et al.</i>	2013	16	5	10	1	F: 1 (11.1%) UF: 6 (66.67%) D: 2 (22.2%)	100	KLPN	Gentamycin	None

ATSP=*Acinetobacter* species; ENSP=*Enterobacter* species; KLPN=*Klebsiella pneumoniae*; NA=Not available; F=Favorable; UF=Unfavorable; C=Cure; D=Death

nonresponsive to standard intravenous therapy. However, prospective randomized trials with high sample size are needed to validate the findings.

Competing Interest

The authors declare that they have no financial or nonfinancial competing interest.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Bhutia S, Srinivasan K, Ananthkrishnan N, Jayanthi S, Ravishankar M. Blood utilization in elective surgery—requirements, ordering and transfusion practices. *Natl Med J India* 1996;10:164-8.
- Briggs S, Ellis-Pegler R, Raymond N, Thomas M, Wilkinson L. Gram-negative bacillary meningitis after cranial surgery or trauma in adults. *Scand J Infect Dis* 2004;36:165-73.
- Caricato A, Pennisi M, Mancino A, Vigna G, Sandroni C, Arcangeli A, *et al.* Levels of vancomycin in the cerebral interstitial fluid after severe head injury. *Intensive Care Med* 2006;32:325-8.
- Clifford HE, Stewart GT. Intraventricular administration of a new derivative of polymyxin B in meningitis due to *Ps. pyocyanea*. *Lancet* 1961;2:177-80.
- Falagas ME, Bliziotis IA, Tam VH. Intraventricular or intrathecal use of polymyxins in patients with Gram-negative meningitis: A systematic review of the available evidence. *Int J Antimicrob Agents* 2007;29:9-25.
- Federico G, Tumbarello M, Spanu T, Rosell R, Iacoangeli M, Scerrati M, *et al.* Risk factors and prognostic indicators of bacterial meningitis in a cohort of 3580 postneurosurgical patients. *Scand J Infect Dis* 2001;33:533-7.
- Kaiser AB, McGee ZA. Aminoglycoside therapy of gram-negative bacillary meningitis. *N Engl J Med* 1975;293:1215-20.
- Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Intrathecal colistin for drug-resistant *Acinetobacter baumannii* central nervous system infection: A case series and systematic review. *Clin Microbiol Infect* 2010;16:888-94.
- Kim BN, Peleg AY, Lodise TP, Lipman J, Li J, Nation R, *et al.* Management of meningitis due to antibiotic-resistant *Acinetobacter* species. *Lancet Infect Dis* 2009;9:245-55.
- Krcmery V, Ondrusova A, Bucko L, Kalavsky E. Predictors of mortality in paediatric nosocomial meningitis: Results from 12 years national survey. *Scand J Infect Dis* 2006;38:744-5.
- Lu CH, Chang WN, Chuang YC. Resistance to third-generation cephalosporins in adult gram-negative bacillary meningitis. *Infection*. 1999;27:208-11.
- Mancebo J, Domingo P, Blanch L, Coll P, Net A, Nolla J. Post-neurosurgical and spontaneous gram-negative bacillary meningitis in adults. *Scand J Infect Dis* 1986;18:533-8.
- McCracken GH, Jr., Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. *Lancet* 1980;1:787-91.
- Ng J, Gosbell IB, Kelly JA, Boyle MJ, Ferguson JK. Cure of multiresistant *Acinetobacter baumannii* central nervous system infections with intraventricular or intrathecal colistin: Case series and literature review. *J Antimicrob Chemother* 2006;58:1078-81.
- O'Neill E, Humphreys H, Phillips J, Smyth EG. Third-generation cephalosporin resistance among Gram-negative bacilli causing meningitis in neurosurgical patients: Significant challenges in ensuring effective antibiotic therapy. *J Antimicrob Chemother* 2006;57:356-9.
- Ondrusova A, Kalavsky E, Rudinsky B, Freybergh FP, Bauer F, Miklosko J, *et al.* *Pseudomonas aeruginosa* causing nosocomial meningitis in neonates and children: Overview of 15 cases within 10 years. *Neuro Endocrinol Lett* 2007;28(Suppl 2):20-1.
- Parodi S, Lechner A, Osih R, Vespa P, Pegues D. Nosocomial enterobacter meningitis: Risk factors, management, and treatment outcomes. *Clin Infect Dis* 2003;37:159-66.

18. Remes F, Tomas R, Jindrak V, Vanis V, Setlik M. Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state. *J Neurosurg* 2013;119:1596-602.
19. Rodriguez Guardado A, Blanco A, Asensi V, Perez F, Rial JC, Pintado V, et al. Multidrug-resistant *Acinetobacter* meningitis in neurosurgical patients with intraventricular catheters: Assessment of different treatments. *J Antimicrob Chemother* 2008;61:908-13.
20. Roitberg BZ, Khan N, Alp MS, Hersonskey T, Charbel FT, Ausman JJ. Bedside external ventricular drain placement for the treatment of acute hydrocephalus. *Br J Neurosurg* 2001;15:324-7.
21. Saleem AF, Ahmed I, Mir F, Ali SR, Zaidi AK. Pan-resistant *Acinetobacter* infection in neonates in Karachi, Pakistan. *J Infect Dev Ctries* 2010;4:30-7.
22. Talon D, Bailly P, Bertrand X, Thouverez M, Mulin B. Clinical and molecular epidemiology of chromosome-mediated resistance to third-generation cephalosporins in *Enterobacter* isolates in eastern France. *Clin Microbiol Infect* 2000;6:376-84.
23. Tangden T, Enblad P, Ullberg M, Sjolín J. Neurosurgical gram-negative bacillary ventriculitis and meningitis: A retrospective study evaluating the efficacy of intraventricular gentamicin therapy in 31 consecutive cases. *Clin Infect Dis* 2011;52:1310-6.
24. van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med* 2010;362:146-54.
25. Wang JH, Lin PC, Chou CH, Ho CM, Lin KH, Tsai CT, et al. Intraventricular antimicrobial therapy in postneurosurgical gram-negative bacillary meningitis or ventriculitis: A hospital-based retrospective study. *J Microbiol Immunol Infect* 2014;47:204-10.
26. Wang KW, Chang WN, Huang CR, Tsai NW, Tsui HW, Wang HC, et al. Post-neurosurgical nosocomial bacterial meningitis in adults: Microbiology, clinical features, and outcomes. *J Clin Neurosci* 2005;12:647-50.
27. Wiesel J, Rose DN, Silver AL, Sacks HS, Bernstein RH. Lumbar puncture in asymptomatic late syphilis. An analysis of the benefits and risks. *Arch Intern Med* 1985;145:465-8.
28. Ziai WC, Lewin JJ, 3rd. Improving the role of intraventricular antimicrobial agents in the management of meningitis. *Curr Opin Neurol* 2009;22:277-82.