

CLINICAL PROTOCOL

Subject: ANTIBIOTIC DOSING PROTOCOL	Page 1 of 4	Protocol # NMH CCP 07.0046
Title: INTRAVENTRICULAR (CENTRAL NERVOUS SYSTEM) & INTRATHECAL ANTIBIOTIC DOSING PROTOCOL	Revision of: 05/15/2015	Version: 2.0
		Effective Date: 07/20/2018
		Removal Date:

SCOPE: Applies to entities indicated below as well as their subsidiaries and affiliates

<input checked="" type="checkbox"/> NM – Northwestern Memorial Hospital	<input type="checkbox"/> NM – Lake Forest Hospital
<input type="checkbox"/> NM – Northwestern Medical Group	<input type="checkbox"/> NM – Central DuPage Hospital
<input type="checkbox"/> NM – Regional Medical Group	<input type="checkbox"/> NM – Delnor Hospital
<input type="checkbox"/> NM – Kishwaukee Hospital	<input type="checkbox"/> NM – Valley West Hospital
<input type="checkbox"/> NM – Marianjoy Rehabilitation	<input type="checkbox"/> NM – Kishwaukee Physician Group
<input type="checkbox"/> NM – Marianjoy Medical Group	<input type="checkbox"/> NM – Home Health & Hospice
<input type="checkbox"/> NM – Other **See “Persons Affected Section below**	

I. PURPOSE:

To provide a safe and standardized approach to the treatment of infectious diseases necessitating the use of intrathecal or intraventricular antibiotics.

II. CLINICAL PROTOCOL:

- A. Nosocomial meningitis and ventriculitis are serious medical complications associated with neurosurgical intervention.
- B. Mortality rates in nosocomial bacterial meningitis are reported to be high.
- C. Antimicrobial penetration into the cerebrospinal fluid and ventricles can be limited and complicate treatment.
- D. One approach to treating nosocomial central nervous system (CNS) infections includes a combination of intravenous and intraventricular/intrathecal antibiotics.
- E. Combination therapy can ensure optimal drug exposure while minimizing systemic adverse effects.

III. PROCEDURE AND THERAPEUTIC GUIDELINES:

Indications

- A. Multi-drug resistant (MDR) organisms necessitating treatment with antibiotics with poor CNS penetration.

- B. *Enterococcus* spp., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Escherichia coli*, and other MDR Gram-negative organisms.
- C. Failure to clear CSF despite systemic therapy for at least 5-7 days of active therapy.

Antibiotic Dose Protocol and Order Set

Antimicrobial Agent	Standard Daily Intrathecal / Intraventricular Dose	High Dose – Daily Intrathecal / Intraventricular Dose	Diluent (preservative-free)	Syringe Volume	Beyond-Use Date
Colistin (CMS)	10 mg or 125,000 units	--	Normal Saline	3 mL	3 hours
Polymyxin B	5 mg or 50,000 units	--	Normal Saline	3 mL	3 hours
Amikacin	20 mg	30 mg	Normal Saline	3 mL	3 hours
Gentamicin	4 mg	8 mg	Normal Saline	3 mL	3 hours
Tobramycin	4 mg	8 mg	Normal Saline	3 mL	3 hours
Vancomycin	10 mg	20 mg	Normal Saline	3 mL	3 hours
Daptomycin	5 mg	--	Normal Saline	5 mL	3 hours
Tigecycline	5 mg	--	Normal Saline	5 mL	3 hours

Operative

Antimicrobial Dose Preparation

- A. Preservative-free drug will be utilized unless unavailable and the risk of untreated infection outweighs the risk of toxicity.
- B. The dispensing pharmacist will prioritize obtaining preservative-free product if available but should not delay preparation for timely administration in cases where such products are not readily available.
- C. Drugs will be diluted in preservative-free normal saline when possible.
- D. Intraventricular medications must be picked up at the pharmacy window by a physician, nurse, or clinical pharmacist given the short beyond-use dating.

Antimicrobial Dosing and Administration

- A. An orderable in EPIC searchable by “Intraventricular Antimicrobials (intrathecal)” should be utilized to order each of the above antibiotics.
- B. Patients should be initially treated with the standard daily intraventricular or intrathecal dose.
- C. Utilization of the high daily intraventricular or intrathecal dose must be evaluated in conjunction with a NSICU pharmacist (1-8069) or ID pharmacist (5-5955).
- D. Intraventricular or intrathecal antibiotic doses may be administered through an external ventricular drain (EVD) or lumbar drain, or possibly via an Ommaya reservoir.

1. Intraventricular or intrathecal doses must be administered by a Neurosurgery physician (resident, fellow, or attending), however, when dose administration is to be through an Ommaya reservoir, the ID Service will consult with the Neurosurgery Service to work out administration responsibilities.
- E. The intraventricular device must be clamped for at least 1 hour or as long as possible after administration.
- F. The bedside nurse will chart when medication doses have been given in the electronic medical record, specifying the name of the physician who administered the dose in the comments field.

Intraventricular/Intrathecal Amphotericin B

- A. Amphotericin B is rarely described in literature for the treatment of cryptococcal meningitis, coccidioidomycosis, or invasive CNS fungal infections that would otherwise likely fail with systemic therapy.
- B. Consensus intrathecal/intraventricular amphotericin B dosing is lacking in human patients.
- C. Due to limitations in available literature, please page an infectious diseases pharmacist to discuss appropriate dose titration at 5-5955.

Therapeutic Drug Monitoring

If CSF antibiotic concentrations are desired please page an infectious diseases pharmacist to discuss the indication, logistics, and interpretation at 5-5955.

IV. CLINICAL PROTOCOL UPDATE SCHEDULE:

Every 3 years or more if appropriate.

V. REFERENCES:

- A. Amod F, Moodley I, Peer A.K.C, et al. Ventriculitis due to a hetero strain of vancomycin intermediate *Staphylococcus aureus* (hVISA): successful treatment with linezolid in combination with Intraventricular vancomycin. *Journal of Infection* 2005; 50:252-257
- B. Bargiacchi O, Rossati A, Car P, et al. Intrathecal/Intraventricular colistin in external ventricular device-related infections by multi-drug resistant Gram negative bacteria: case reports and review. *Infection* 2014; 42:801-809
- C. Bayston R, Hart CA, Barnicoat M. Intraventricular vancomycin in the treatment of ventriculitis associated with cerebrospinal fluid shunting and drainage. *J Neurol Neurosurg Psychiatry* 1987 Nov; 50(11):1419-23
- D. Cascio A, Alfredo C, Sinardi L, et al. Post-neurosurgical multidrug-resistant *Acinetobacter baumannii* meningitis successfully treated with intrathecal colistin. A new case and a systematic review of the literature. *Int J Infect Dis* 2010 Jul; 14(7):e572-9
- E. Cascio A, Mezzatesta ML, Odierna A, et al. Extended-spectrum beta-lactamase-producing and carbapenemase-producing *Enterobacter cloacae* ventriculitis successfully treated with Intraventricular colistin. *Int J Infect Dis* 2014 Mar; 20:66-7
- F. Gilbert DN, Moellering RC, Eliopoulos GM, et al. The Sanford Guide to Antimicrobial Therapy 2014 44th Edition. Table 9A. Antimicrobial Therapy, Inc, Sperryville, VA. Copyright 1969-2014.

- G. Guardado AR, Blanco A, Asensi V, et al. Multidrug-resistant *Acinetobacter* meningitis in neurosurgical patients with Intraventricular catheters: assessment of different treatments. *J Antimicrob Chemother* 2008 Apr; 61(4):908-13
- H. Imberti R, Cusato M, Accetta G, et al. Pharmacokinetics of Colistin in Cerebrospinal Fluid after Intraventricular Administration of Colistin Methanesulfonate. *Antimicrob Agents Chemother* 2012 Aug; 56(8):4416-21
- I. Lauretti L, D'Alessandris QG, Fantoni M, D'Inzeo T, Fernandez E, Pallini R, Scoppettuolo G. First reported case of intraventricular tigecycline for meningitis from extremely drug-resistant *Acinetobacter baumannii*. *J Neurosurg*. 2017 Aug;127(2):370-373
- J. Mei S, Luo X, Li X, Li Q, Huo J, Yang L, Zhu L, Feng W, Zhou J, Shi G, Zhao Z. Development and validation of an LC-MS/MS method for the determination of tigecycline in human plasma and cerebrospinal fluid and its application to a pharmacokinetic study. *Biomed Chromatogr*. 2016 Dec;30(12):1992-2002
- K. Mueller SW, Kiser TH, Anderson TA, Neumann RT. Intraventricular Daptomycin and Intravenous Linezolid for the Treatment of External Ventricular-Drain-Associated Ventriculitis Due to Vancomycin-Resistant *Enterococcus faecium*. *Ann Pharmacother* 2012 Dec; 46(12):e35
- L. Nevrekar S, Cunningham KC, Greathouse KM, Panos N. Dual Intraventricular Plus Systemic Antibiotic Therapy for the Treatment of *Klebsiella pneumoniae* Carbapenemase-Producing *Klebsiella pneumoniae* Ventriculitis. *Ann Pharmacother* 2014 Feb; 48(2):274-8
- M. Pallotto C, Fiorio M, D'Avolio A, Sgrelli A, Baldelli F, Di Perri G, De Socio GV. Cerebrospinal fluid penetration of tigecycline. *Scand J Infect Dis*. 2014 Jan;46(1):69-72
- N. Patel JA, Pacheco SM, Postelnick M, Sutton S. Prolonged triple therapy for persistent multidrug-resistant *Acinetobacter baumannii* ventriculitis. *Am J Health Syst Pharm* 2011 Aug; 68(16):1527-31
- O. Pfausler B, Spiss H, Beer R, et al. Treatment of staphylococcal ventriculitis associated with external cerebrospinal fluid drains: a prospective randomized trial of intravenous compared with Intraventricular vancomycin therapy. *J Neurosurg* 2003 May; 98(5):1040-4
- P. Schwabe M, Juttner E, Blaich A, et al. Cure of ventriculitis and central nervous system shunt infection by *Staphylococcus epidermidis* with vancomycin by Intraventricular injection in a liver transplant recipient. *Transpl Infect Dis* 2007 Mar; 9(1):46-50
- Q. Segal-Maurer S, Mariano N, Qavi A. Successful Treatment of Ceftazidime-Resistant *Klebsiella pneumoniae* Ventriculitis with Intravenous Meropenem and Intraventricular Polymyxin B: Case Report and Review. *Clin Infect Dis* 1999 May; 28(5):1134-8
- R. Soto-Hernández JL, Soto-Ramírez A, Pérez-Neri I, Angeles-Morales V, Cárdenas G, Barradas VA. Multidrug-resistant *Klebsiella oxytoca* ventriculitis, successfully treated with intraventricular tigecycline: A case report. *Clin Neurol Neurosurg*. 2020 Jan;188:105592
- S. 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 Jun; 52(11):1310-6
- T. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice Guidelines for the Management of Bacterial Meningitis. *CID* 2004; 39:1267-1284
- U. Tutuncu EE, Kuscu F, Gurbuz Y, et al. Tigecycline use in two cases with multidrug-resistant *Acinetobacter baumannii* meningitis. *Int J Infect Dis*. 2010 Sep;14 Suppl 3:e224-6
- V. Wu Y, Chen K, Zhao J, Wang Q, Zhou J. Intraventricular administration of tigecycline for the treatment of multidrug-resistant bacterial meningitis after craniotomy: a case report. *J Chemother*. 2018 Feb;30(1):49-52

VI. APPENDICES:

None