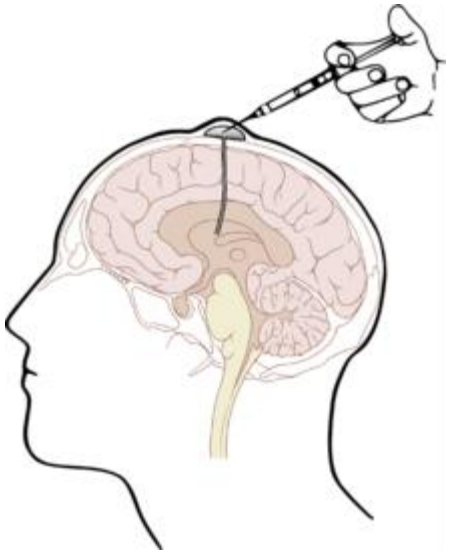
Administración intratecal/intraventricular de antibióticos



Iván Pelegrín

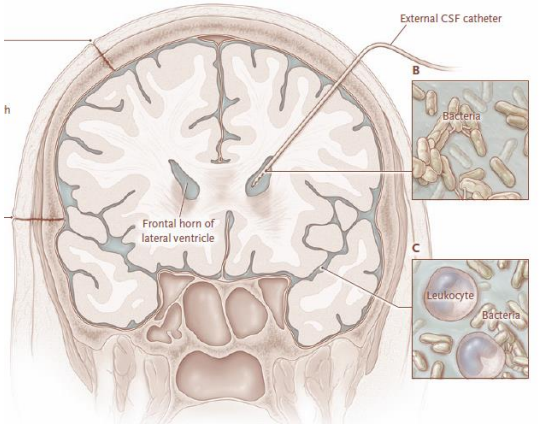
Servicio de Enfermedades Infecciosas

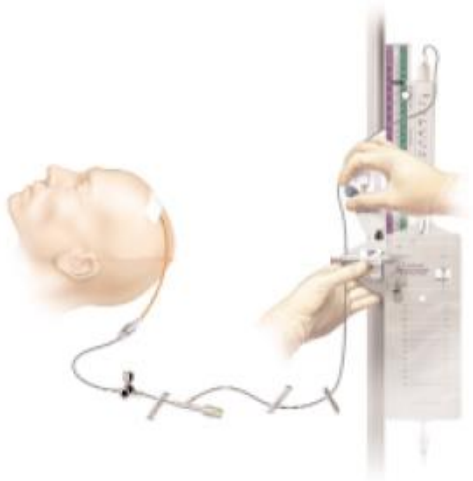
Bellvitge Hospital

Madrid, 22 Junio 2016

Introducción

- Uso: Ventriculitis, meningitis, infecciones de shunt





- Drenajes temporales: DVE/DEL/Ommaya
- Drenajes permanentes: DVP/DVA

Tratamiento recomendado

IDSA GUIDELINES

Practice Guidelines for the Management of Bacterial Meningitis

Allan R. Tunkel,[1] Barry J. Hartman,[2] Sheldon L. Kaplan,[3] Bruce A. Kaufman,[4] Karen L. Roos,[5] W. Michael Scheld,[6] and Richard J. Whitley[7]

Protocolos Clínicos SEIMC

II

Infecciones del sistema nervioso central

Infecciones relacionadas con las derivaciones de líquido cefalorraquídeo (LCR)

b) Infección de las derivaciones externas.

En estos casos, las bases del tratamiento son similares. La medida más aceptada es el tratamiento antibiótico por vía parenteral, manteniendo "in situ" el catéter infectado los primeros 2-5 días, a fin de permitir el drenaje del LCR infectado sin la inserción inmediata de un nuevo drenaje externo. Posteriormente, una vez controlada la infección y sin que pasen más días, la retirada del catéter ventricular es obligada. El mantenimiento del catéter puede dificultar el control de la infección ventricular, por lo que si el paciente empeora o no mejora pronto, deberá procederse a la extracción inmediata del catéter infectado y, si es necesario, a la inserción de un nuevo drenaje externo, sea ventricular o, si el tipo de hidrocefalia lo permite, lumbar, cuya inserción es más simple y conlleva menor riesgo de sobreinfección.

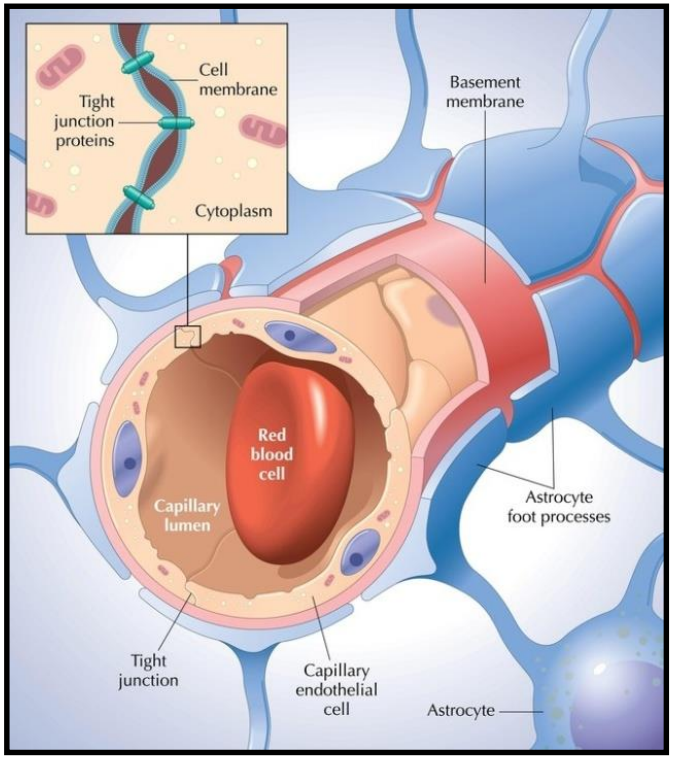
- Antibiótico endovenoso +/- Retirada/recambio del catéter +/-Antibióticio local

Escasa penetración de ATB ev

Table 1. Factors influencing antibiotic concentrations in CSF.

Factor(s) [reference]	Example	Effect
Drug lipophilicity [21–23]	Fluoroquinolones Rifampin	Rapid entry into CSF Relatively good CSF concentrations, $T^{1}/_{2}$ similar to serum
High degree of ionization [21, 23]	β-Lactam antibiotics	Low lipid solubility, poor penetration through BBB
High serum protein binding [24]	Ceftriaxone	Delayed entry into CSF, long CSF and serum $T^{1}/_{2}$
Active transport system [25–27]	Penicillin	Relatively rapid entry into CSF, short duration of effective CSF levels
Inflammation [21–23, 28–30]	Meningitis	Increased penetration of hydrophilic agents (minimal effect on lipophilic agents)
Infecting organism [31, 32]	*Listeria* species, *Haemophilus* species	Greater antibiotic penetration
	Escherichia coli, *Streptococcus pneumoniae*	Lesser antibiotic penetration

NOTE. BBB = blood-brain barrier; $T^{1}/_{2}$ = half-life.



Target: Cmax/ MIC >10

Microbiología

Table 1
Microbiology of ventriculostomy-related infections

Study,[Ref.] Year	Country	No. of Positive Cultures	Coagulase-Negative Staphylococci	*S aureus*	*Acinetobacter*	*Pseudomonas*	Enterobacteriaciae	Other
Camacho et al,[20] 2011	Brazil	22	2 (9%)	1 (5%)	6 (27%)[a]	3 (14%)	7 (32%)	3 (14%)
Chi et al,[8] 2010	Taiwan	35	1 (3%)	2 (6%)	6 (17%)	9 (26%)	7 (20%)	10 (29%)
Scheithauer et al,[14] 2010	Germany	21[b]	9 (43%)	4 (19%)	1 (5%)		6 (29%)	1 (5%)
Lo et al,[11] 2007	Australia	25	4 (16%)	2 (8%)	10 (40%)	1 (4%)	4 (16%)	4 (16%)
Orsi et al,[86] 2006	Italy	11	2 (18%)	1 (9%)		4 (36%)	1 (9%)	3 (27%)
Korinek et al,[10] 2005	France	57	44 (77%)	4 (7%)	1 (2%)	1 (2%)	1 (2%)	6 (11%)
Arabi et al,[18] 2005	Saudi Arabia	22[c]	3 (14%)	1 (5%)	6 (27%)	2 (9%)	4 (18%)	3 (14%)
Bota et al,[87] 2005	Belgium	58	21 (36%)	18 (31%)	2 (3%)	3 (5%)	12 (21%)	2 (3%)
Schade et al,[9] 2005	Netherlands	14	8 (57%)	3 (21%)			1 (7%)	2 (14%)
Flibotte et al,[21] 2004	USA	17[b]	12 (71%)	1 (6%)		1 (6%)	1 (6%)	1 (6%)
Lyke et al,[12] 2001	USA	11	2 (18%)				9 (82%)	
Sundbarg et al,[3] 1988	Sweden	27	16 (59%)	4 (15%)	2 (7%)		1 (4%)	4 (15%)
Mayhall et al,[5] 1984	USA	19	6 (32%)	1 (5%)	2 (10%)		8 (42%)	2 (11%)

[a] One-half were resistant to carbapenem antibiotics.
[b] Induded 1 case of fungal infection.
[c] Included 3 cases of fungal infection.

Stenehjem E. et al. Infect Dis Clin N Am 26 (2012) 89-110.

Nosocomial ventriculitis and meningitis in neurocritical care patients

R. Beer
P. Lackner
B. Pfausler
E. Schmutzhard

J Neurol (2008) 255:1617–1624
DOI 10.1007/s00415-008-0059-8

Table 3 Microbiology of EVD-related ventriculomeningitis

Staphylococcus epidermidis	70%
Staphylococcus aureus	10%
Others (including gram negative bacteria and fungi)	< 20%
– Gram negative rods (Klebsiella spp., E. coli, Pseudomonas spp.)	15%
– Anaerobes	rare
– Candida spp.	very rare

Aumento creciente de infecciones por BGN

DVE (n=35)	DLE (n=11)
12 (34%) Estafilococos	**3 (27%) Estafilococos**
7 *S. epidermidis* 3 *S. aureus* 1 SCN	2 SCN 1 MARSA
13 (37%) Enterobacterias	**2(18%) Enterobactèries**
4 *E.cloacae* 2 ABAU 1 *Klebsiella pneumoniae* 1 *E.coli* 1 *E.cloacae y Klebsiella* *1 Serratia marcenses*	1 *Klebsiella y Proteus* *1 Citrobacter koserii*
7 (20%) *Pseudomonas aeruginosa*	**5 (45%) *Pseudomonas aeruginosa***
2 PAMR	1 PAMR
2 (5%) Estreptococs	**1 (9%) *Propionibacterium acnes***
1 *S.mitis*	
1 *E.faecalis* ***1 (3%) Candida albicans***	

Período Octubre 2010- Octubre 2015

Bellvitge Hospital

¿Cuándo utilizar tratamiento intraventricular?

- En situaciones clínicas especiales (individualizar el caso):

- Fracaso clínico y/o microbiológico.
- Gérmenes multirresistentes que no tengan un buen tratamiento ATB ([ ] no elevadas de ATB frente a una MIC/MBC alta).

SCN: oxa R
BGN: Cef /Carbapenem R

- Uso combinado ev e IV/IT: rápida esterilización y curación microbiológica.

Antibióticos

Uso no aprobado por FDA.

No hay consenso sobre posología

Table 3. Recommended Doses of Selected Antimicrobial Agents Administered by the Intraventricular Route.*

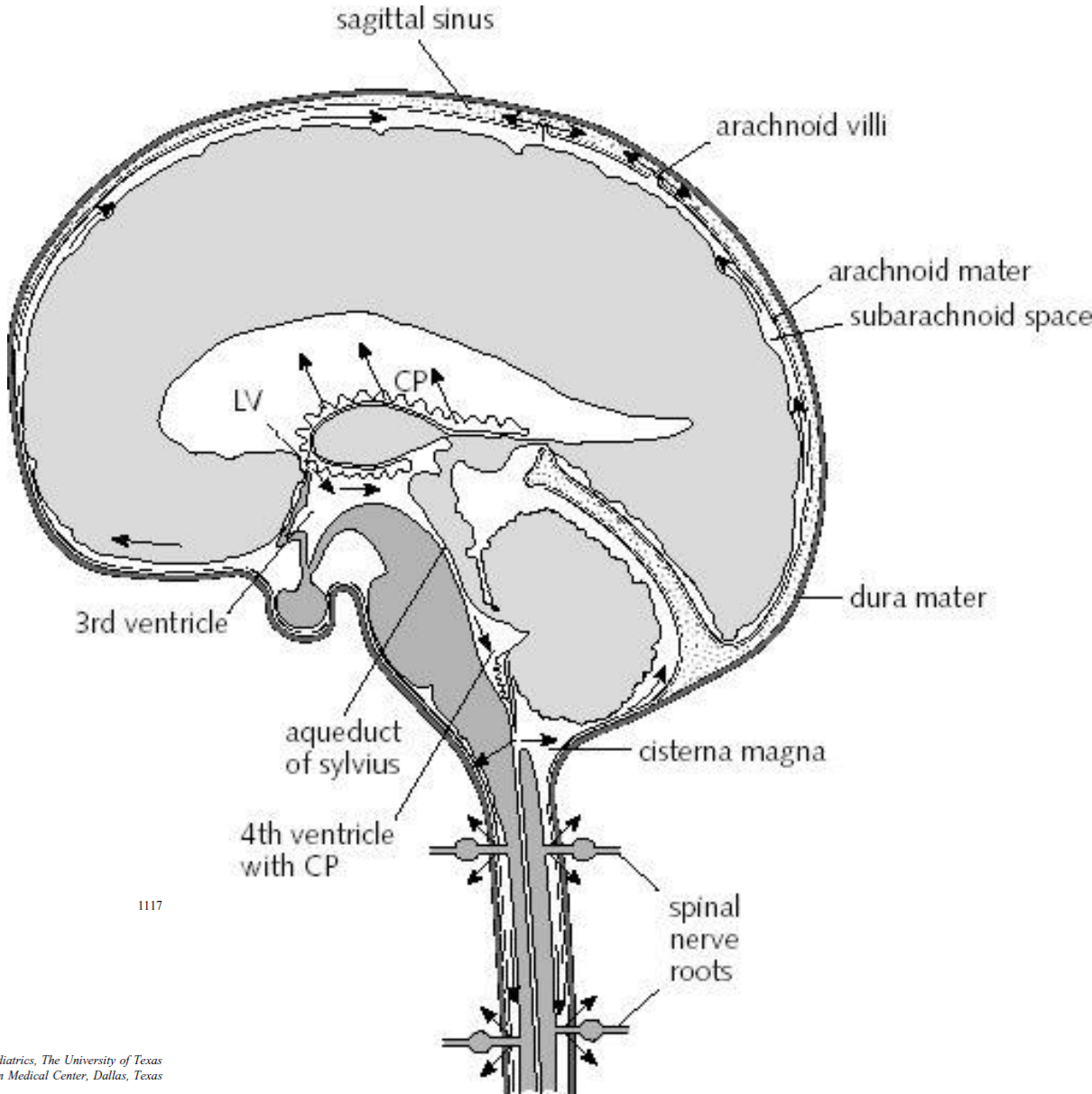
Antimicrobial Agent	Daily Intraventricular Dose
Vancomycin	5–20 mg†
Gentamicin	1–2 mg in infants and children; 4–8 mg in adults
Amikacin	5–50 mg‡
Polymyxin B	2 mg in infants and children; 5 mg in adults
Colistin, usually formulated as colistimethate sodium	10 mg once daily or 5 mg every 12 hr§

* There are no data that define the exact dose of an antimicrobial agent that may be administered by the intraventricular route, but the dose can be estimated through the measurement of the cerebrospinal fluid trough concentration, in the case of agents for which these measurements can be obtained. Medications administered by the intraventricular route should be preservative-free.
† Most studies have used a 10-mg or 20-mg dose.
‡ The usual daily dose is 30 mg.
§ In one study, patients received 10 mg every 12 hours without an increase in side effects.[35]

Van de Beek, et al. *N Engl J Med*. 2010; 362: 146-154.

Fisiopatología LCR

- Producción LCR 20ml/h (500ml/24h).
- Volumen total 120-150ml día (recambio 2-3 veces/día)



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STATE-OF-THE-ART CLINICAL ARTICLE

Antibiotic Pharmacodynamics in Cerebrospinal Fluid

Irja Lutsar, George H. McCracken, Jr., and Ian R. Friedland

From the Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas, Texas

PK/PD ATB intraventriculares

- Diferencia entre administración intratecal/intraventricular

- Extrapolación de PK/PD ATB administrados ev: concentración/tiempo dependiente
  - AG: Cdep>MIC
  - Vancomicina: AUC/MIC
  - Colistina: AUC/MIC

Lutsar, McCracken, and Friedland CID 1998;27 (November)

Forma de administración

- Preparaciones estériles en volúmenes pequeños: 2ml
- Cada 24h si DVE/DLE cerrado
- Cada 12h si DVE/DLE abierto (Pinzar 3h tras administración si el paciente lo tolera)
- Si hay dos accesos ventriculares plantear repartir dosis en función del volumen esperado

British Journal of Neurosurgery 2000; 14(1): 7–12

REVIEW ARTICLE

The management of neurosurgical patients with postoperative bacterial or aseptic meningitis or external ventricular drain-associated ventriculitis

INFECTION IN NEUROSURGERY WORKING PARTY OF THE BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY*

bag. If the causative organism is a CoNS, the patient should be treated by instilling vancomycin (5–20 mg, depending on the ventricular volume, i.e. 5 mg for patients with 'slit' ventricles, 10 mg for those with ventricles of normal size and 15–20 mg for those with greater than normal volumes) directly into the ventricles and clamping the drain for approximately 15 min. If CSF is draining freely (i.e. ≥100 ml/day), a daily dose should be administered, but if there is no or little CSF drainage (<50 ml/day), the dose need be repeated only every third day; patients from whom intermediate volumes of CSF (50–100 ml/day) are draining should be given doses on alternate days and those from whom very large volumes (>200 ml/day) are draining may require higher dosages or twice-daily instillation. The frequency of dosing must be reviewed daily and should be based on the amount of fluid drained since the previous dose. Treatment for 5–7 days is usually adequate.

Ajuste de dosis

- Determinación de niveles (niveles pre y postdosis):
  - Necesario para no sobre/infradosificar
  - Indicador del volumen efectivo IV
  - Riesgo de superinfección por manipulaciones
- Conocer MIC microorganismo y recordar Cmax-MIC > 10

Neurotoxicidad

- No correlación con niveles

- Penicilina/Cefalosporinas: crisis comicial
- AG: Meningitis química, crisis comiciales
- Vancomicina: No neurotoxicidad reportada
- Colistina: apnea respiratoria, bloqueo

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-016-0269-3
CrossMark

REVIEW ARTICLE

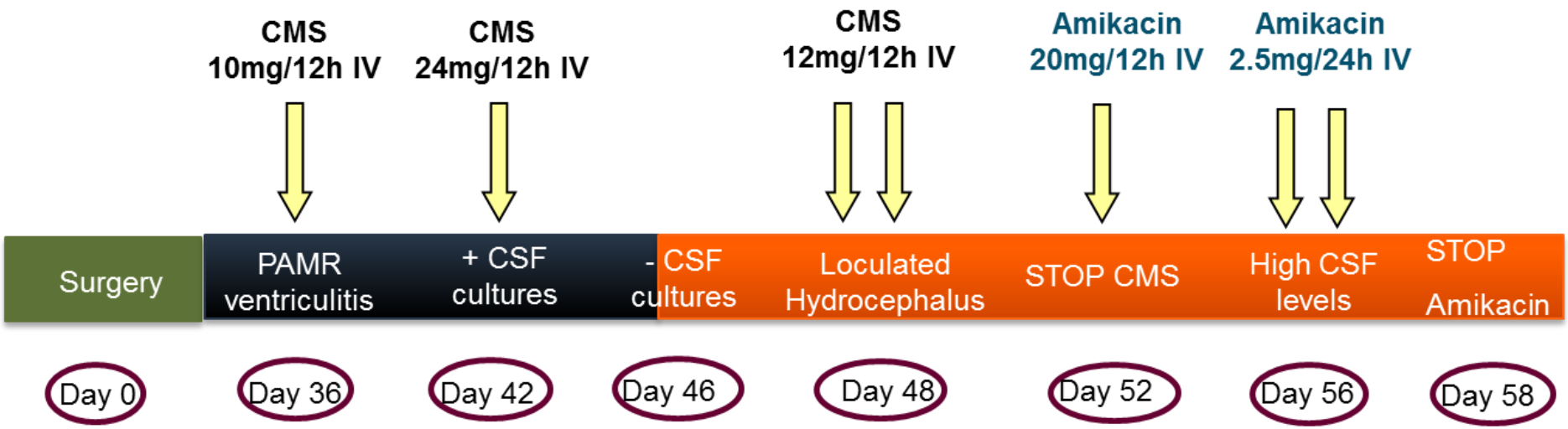
Systematic Review of Efficacy, Pharmacokinetics, and Administration of Intraventricular Aminoglycosides in Adults

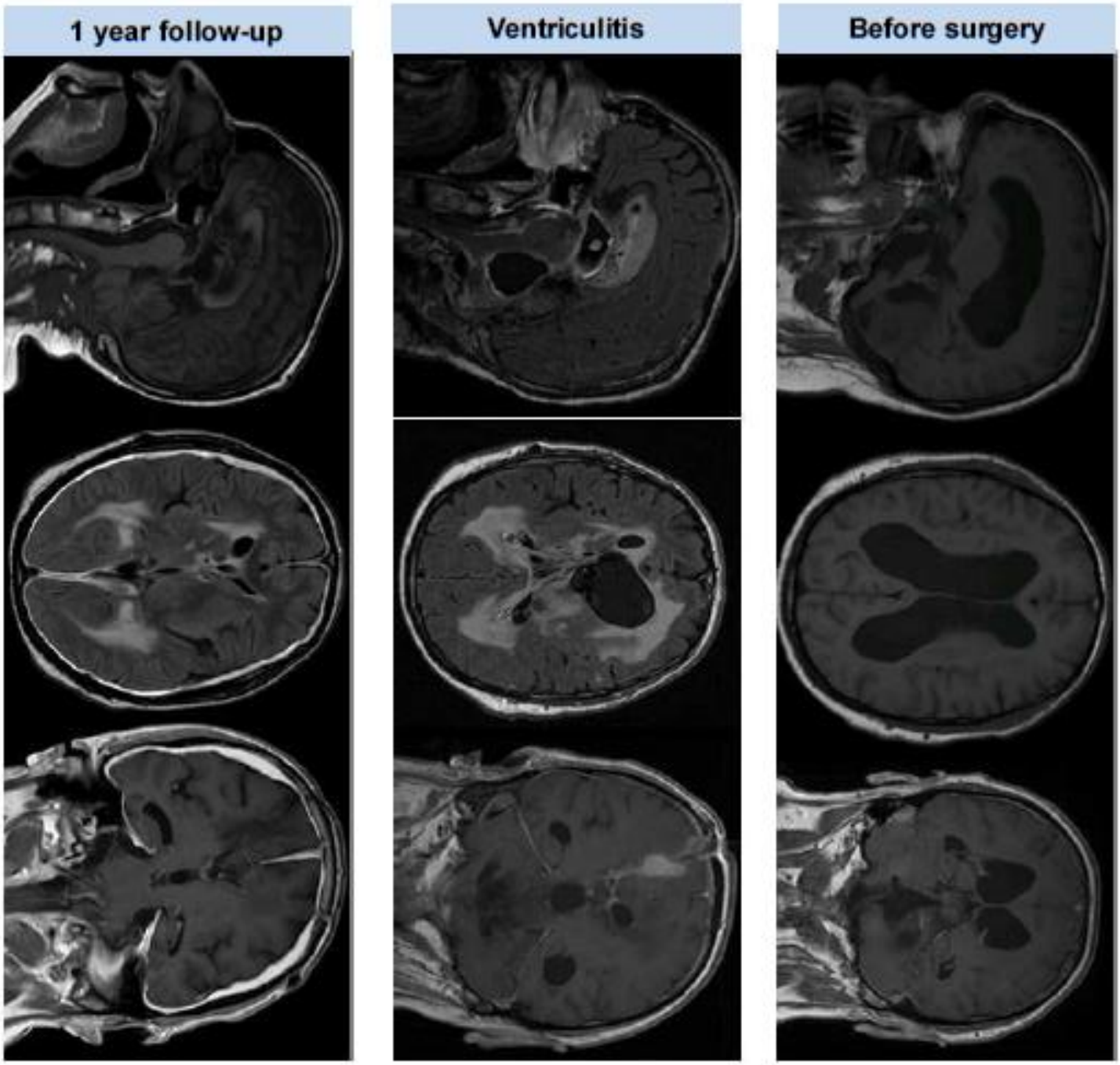
Marlys LeBras[1] · Ivy Chow[2] · Vincent H. Mabasa[2] · Mary H. H. Ensom[1,3]

Caso clínico

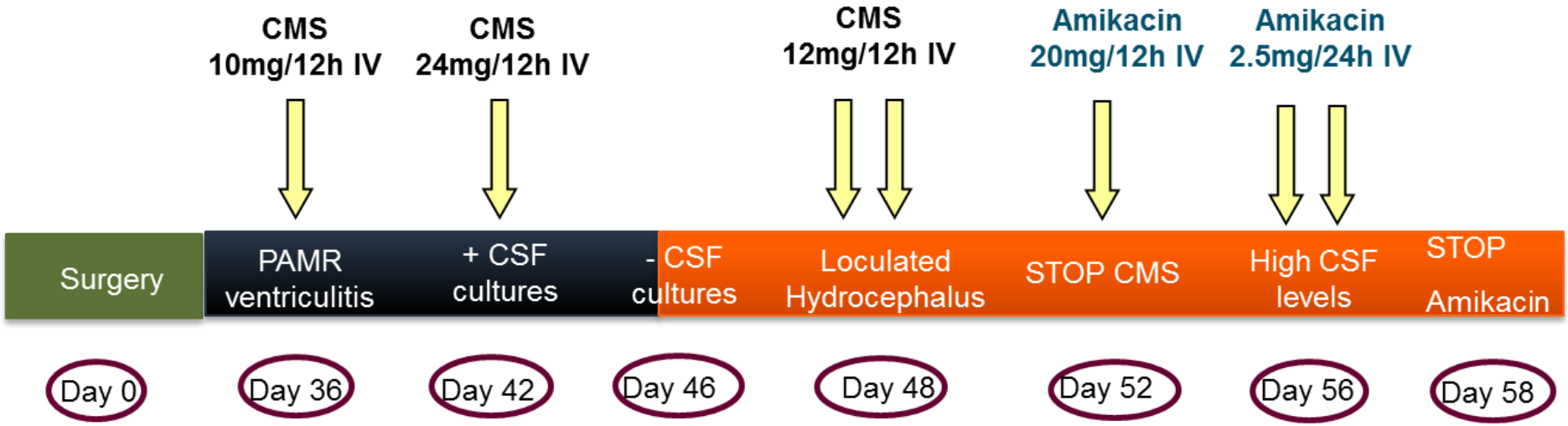
- 58 años IQ craniotomía suboccipital + DVE
- Ventriculitis por PAMR

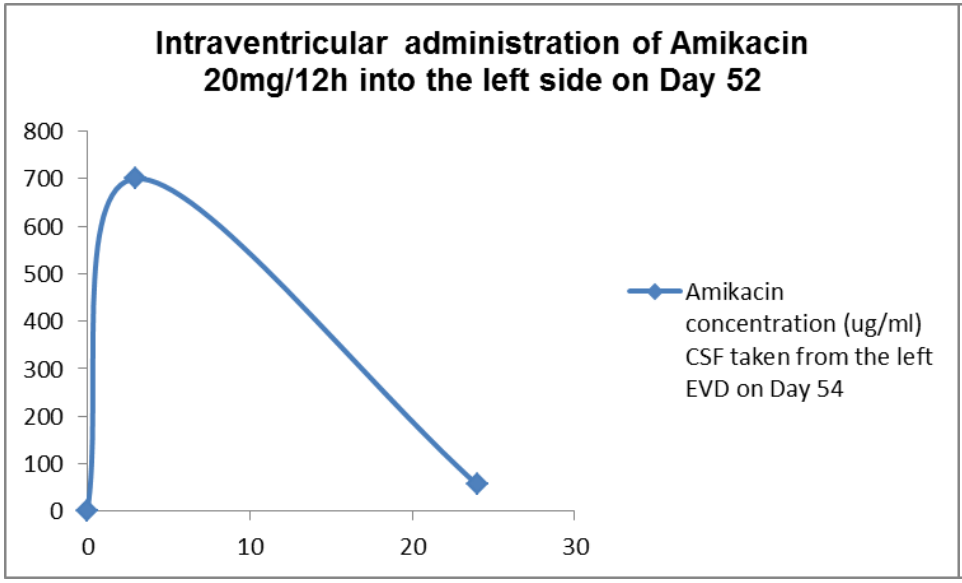
(MIC colistina 2mg/L, Amikacina 16 mg/L)

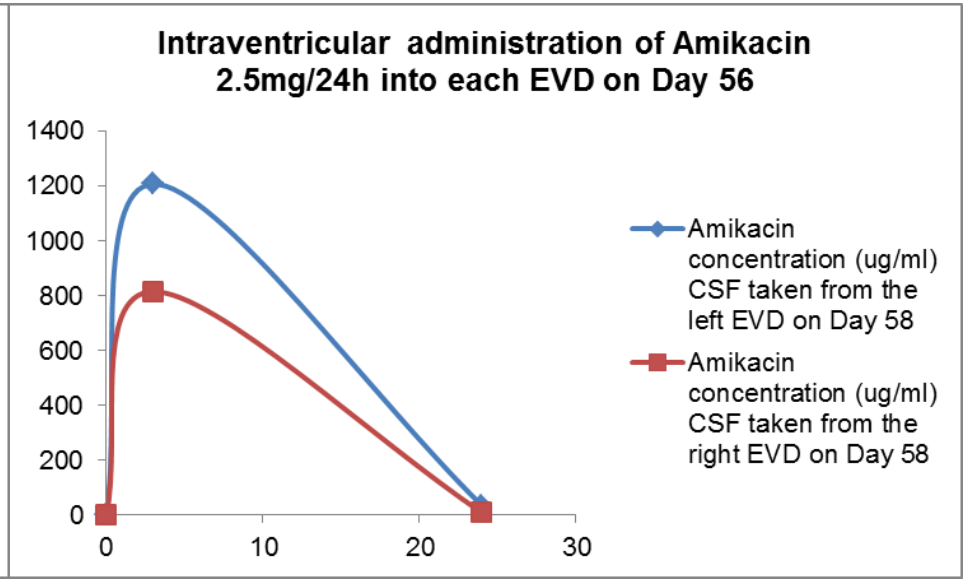



1 year follow-up
Ventriculitis
Before surgery

Caso clínico







Ventajas

- Concentraciones de ATB altas salvando el problema del paso de la BHE
- Evitar toxicidad sistémica
- Única opción en inf multi-R

Inconvenientes

- No aprobado por la FDA
- Posología no establecida
- Manipulación del sistema de drenaje de LCR
- Toxicitad local

Los inicios del tratamiento IV

THE LANCET, APRIL 12, 1980

INTRAVENTRICULAR GENTAMICIN THERAPY IN GRAM-NEGATIVE BACILLARY MENINGITIS OF INFANCY

Report of the Second Neonatal Meningitis Cooperative Study Group*

GEORGE H. MCCRACKEN JR SUSAN G. MIZE
NORMA THRELKELD

Departments of Pediatrics and Medical Computer Science, University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas

- EC con 53 niños meningitis/ventriculitis por BGN (*E.coli i Salmonella spp*)

Mortality rate: grupo **IV** (42,9%) vs grupo tratamiento **sistémic** (12,5%)

Successful Treatment of Ventriculitis Due to Carbapenem-Resistant *Acinetobacter baumannii* with Intraventricular Colistin Sulfomethate Sodium

Table 1. Clinical characteristics of the five patients with carbapenem-resistant *Acinetobacter baumannii* ventriculitis.

Patient no.	Age/sex	Underlying condition	Surgery/ ventricular tube*	Clone	Antibiotic treatment		Infection outcome‡
					Intrathecal colistin†	Intravenous antibiotics†	
1	47/F	Subarachnoid hemorrhage	No/yes (7)	E	No	Mer (2) + Tm (2)	Died (2)
2	61/F	Ependymoma	Yes/yes (11)	E	No	Sulb (7) + Tm (7)	Died (7)
3	64/M	Epidermoid tumor	Yes/yes (21)	E	No	No	Died (1)
4	16/M	Hemangioblastoma	Yes/yes (16)	D	Yes (19)	Sulb (3) + Tm (19)	Cured§
5	34/F	Subarachnoid hemorrhage	No/yes (7)	E	Yes (17)	Tm (17)	Cured

NOTE. Mer = meropenem; Sulb = sulbactam; Tm = tobramycin.
* Parentheses indicate the days from catheter insertion to diagnosis of infection.
† Parentheses indicate the days of treatment.
‡ Parentheses indicate the days from diagnosis of infection to death.
§ The patient died of a noninfectious cause, 66 days after treatment ended.

P. Fernandez-Viladrich, X. Corbella, L. Corral, F. Tubau, and A. Mateu

Departments of Infectious Diseases, Intensive Medicine, and Microbiology, Hospital de Bellvitge, University of Barcelona, Barcelona, Spain

Bellvitge Hospital

MAJOR ARTICLE

Neurosurgical Gram-Negative Bacillary Ventriculitis and Meningitis: A Retrospective Study Evaluating the Efficacy of Intraventricular Gentamicin Therapy in 31 Consecutive Cases

Thomas Tängdén,[1] Per Enblad,[2] Måns Ullberg,[3] and Jan Sjölin[1]

[1]Department of Medical Sciences, Section of Infectious Diseases, [2]Department of Neurosurgery, and [3]Department of Medical Sciences, Section of Clinical Microbiology, Uppsala University, Uppsala, Sweden

Conclusions. Our results support combination treatment with intraventricular gentamicin for postneurosurgical GNB ventriculomeningitis. Meropenem seems to be an effective and safe alternative for the systemic antibiotic treatment of these neurointensive care infections.

- Retrospectivo durante 10 años.
- Meningitis/Ventriculitis BGN
- ev (n: 18) vs IV (n: 13)
- Inicio IV: 8 días (1-23).
- Duración IV: 8 días (4-19)
- Duración tratamiento total: 3 sem

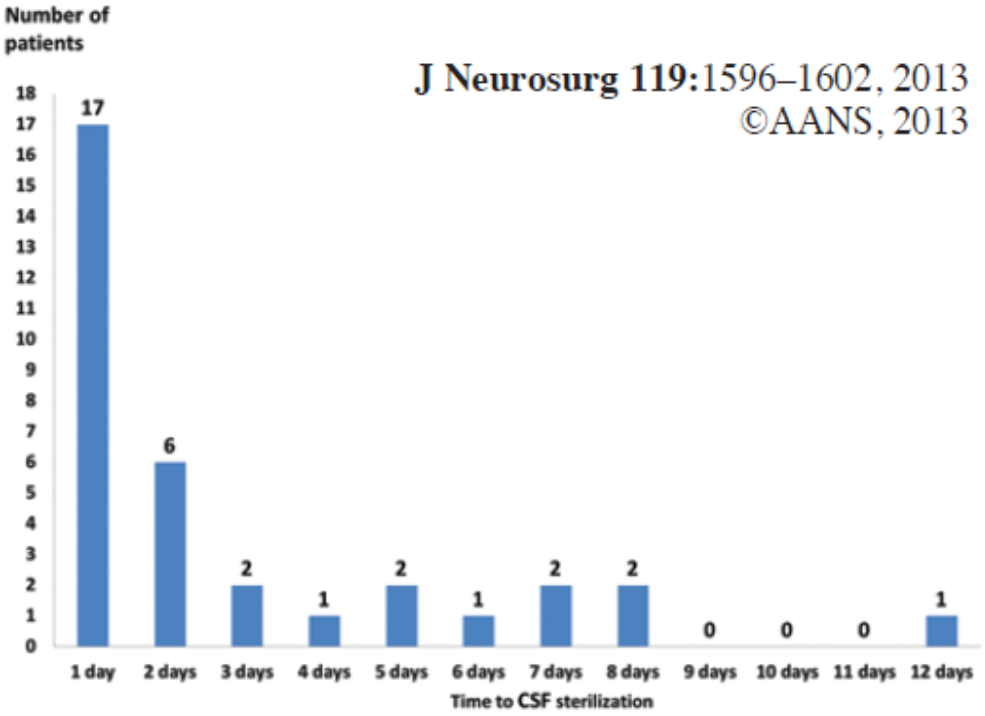
Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state

Clinical article

FRANTIŠEK REMEŠ, M.D.,[1] ROBERT TOMÁŠ, M.D., PH.D.,[1] VLASTIMIL JINDRÁK, M.D.,[2] VÁCLAV VANIŠ, M.D.,[2] AND MICHAL ŠETLÍK, M.D.[1]

Departments of [1]Neurosurgery and [2]Microbiology, Na Homolce Hospital, Prague, Czech Republic

- n = 34 pacientes meningitis/ventriculitis después de 5-8días de tratamiento ev.
- Inicio del tractament IV/IT = 7,2dies.
- Tiempo de esterilització LCR = 2,9 +/- 2,7 días.



J Neurosurg 119:1596–1602, 2013

Conclusiones

- El uso de ATB IV se hace imprescindible cuando hay fracaso clínico/microbiológico y en episodios causados por mo multi-R.

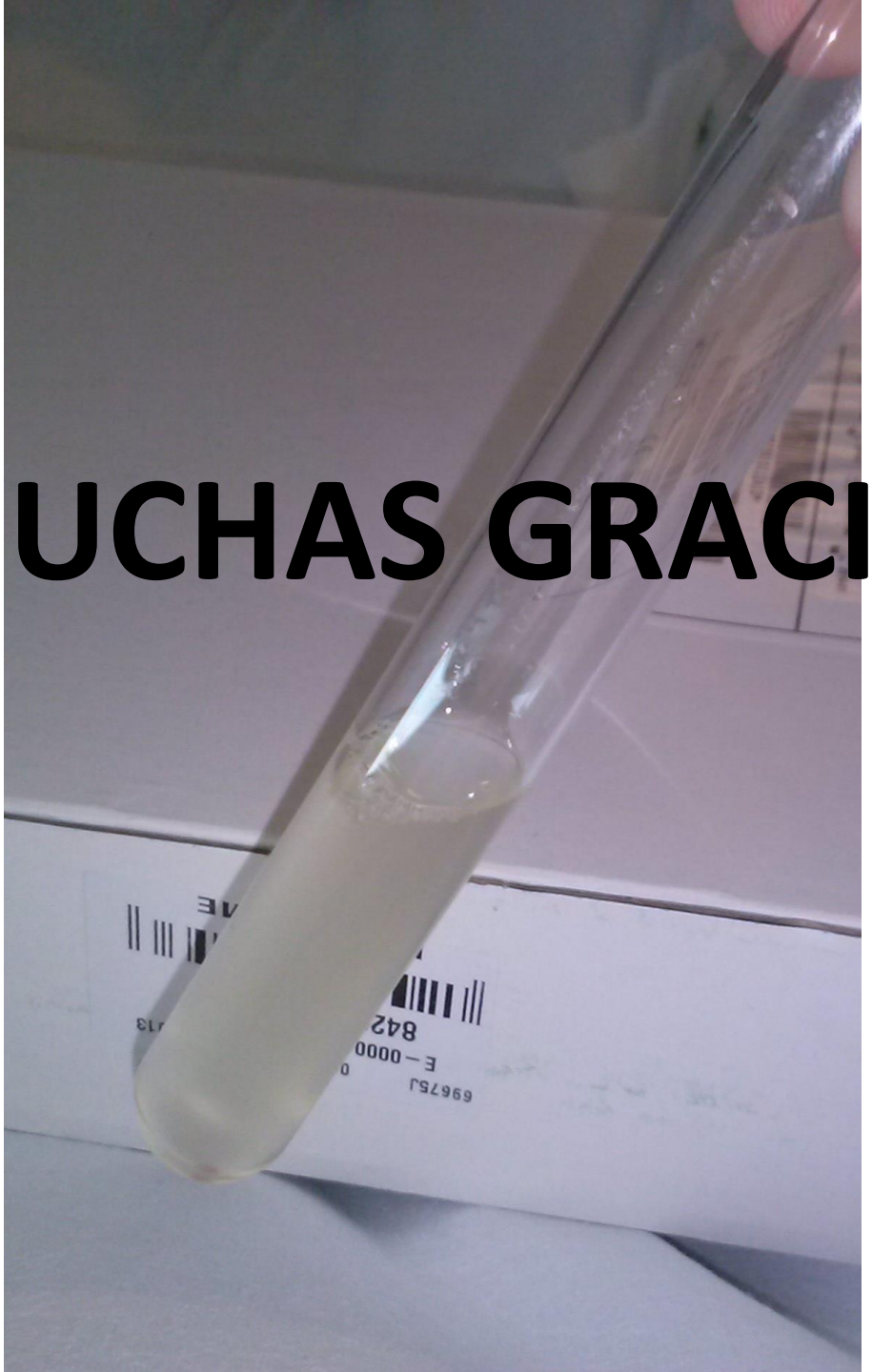
- El uso de ATB IV se ha asociado con mejor pronóstico en estudios retrospectivos.

- Se requieren más estudios para estandarizar la adminsitración de los ATB IV; esto permitiría ampliar su uso.

Posibles aplicaciones

- Tratamiento empírico inicial
- Tratamiento de microorganismos sensibles
- Disminuir la duración de tratamiento
- Tratamiento IT/IVT en solitario (sin sistémico)

MUCHAS GRACIAS



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