

Experience in the treatment of meningitis associated with health care in pediatric patients

Mónica C. Mercado^{1*}, Martín Guerrero-Becerra², Lorelay Gutiérrez-Oliva¹, Pedro A. Martínez-Arce², Mariana Merlo-Palomera², and Luis Á. Arredondo-Navarro¹

¹Pediatric Neurosurgery; ²Pediatric Infectology. Hospital Civil de Guadalajara "Fray Antonio Alcalde", Universidad de Guadalajara, Guadalajara, Mexico

Abstract

Objective: The objective of the study was to describe our clinical experience in meningitis associated with health care (MAHC). **Methods:** A retrospective study included pediatric patients, with MAHC, from 2010 to 2017. Parametric variables were evaluated by media, standard deviation, media and interquartile range. Non-parametric variables were described by reasons and proportions, Chi-square IC 95%. Significant variables ($p < 0.005$) were evaluated by bivariate logistic regression model to identify related risks for adverse evolution. We obtained the approval of the research ethics committee of our hospital for publication of this data. **Results:** A total of 114 cases of MAHC in children were analyzed. There were Gram-negative bacilli (62.6%) and ESBL producers (42.4%). Mortality was higher amongst cases exposed to more than three antibiotics OR = 5.50 (IC 95%, LI 0.996, LS 30.36) sig 0.050 mortality correlation 0.847. **Conclusions:** Gram-negative bacteria are frequent in MAHC, mortality was correlated to exposition more than three antibiotics.

Key words: Meningitis. *Acinetobacter baumannii*. Antibiotics.

Experiencia en tratamiento de meningitis y ventriculitis asociada a los cuidados de la salud en pacientes pediátricos

Resumen

Objetivo: Describir experiencia clínica en tratamiento de MACS. **Métodos:** Estudio retrospectivo en pacientes pediátricos con MACS durante 2010 a 2017. Variables paramétricas evaluadas con medias, desviación estándar y rango intercuartil. Variables no paramétricas por razones, proporciones, Chi cuadrada IC 95%. Variables significativas ($p < 0.005$) evaluadas por modelo de regresión logística bivariada para identificar riesgos de evolución adversa. **Resultados:** 114 casos de MACS en niños con predominio de gramnegativos (62.6%) BLEE (42.4%). Mortalidad mayor entre casos expuestos a más de tres antibióticos OR = 5.50 (IC 95%, LI 0.996, LS 30.36) sig. 0.050, correlación con mortalidad 0.847. **Conclusiones:** Las bacterias gramnegativas son más frecuentes en MACS, con mortalidad correlacionada a exposición con más de tres antibióticos.

Palabras clave: Meningitis. *Acinetobacter baumannii*. Antibióticos.

Correspondence:

*Monica Cecilia Mercado

E-mail: monicauribe_99@yahoo.com.mx

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Introduction

Meningitis associated with health care (MAHC) or nosocomial origin, usually of bacterial etiology, can be a consequence of invasive procedures: craniotomy (0.8-1.5%) internal ventricular catheters (4-17%) or external (8%), lumbar puncture ($\times 1$ every 50,000), intrathecal infusion of medications, spinal anesthesia (0.8-5%), complicated head injury (1.4-25%), or metastatic infection in patients with acquired bacteremia¹⁻³. MAHC episodes can be diagnosed during the hospitalization period and up to one year after its onset. It is often produced by multiresistant bacteria, unlike the bacteria that cause community meningitis⁴.

In recent years, there has been a reported decrease in the incidence of MAHC, although report of permanent sequels and frequent association with coagulase-negative *Staphylococcus* persists; nevertheless, participation of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Acinetobacter baumannii* are relevant; often multidrug-resistant (MDR), especially related to use of broad-spectrum antibiotics⁵⁻⁹.

The term MDR refers to the expression of bacterial resistance to at least one agent in ≥ 3 antibiotic categories. We define a bacterium as extra drug resistant (XDR), when it is not susceptible to more than one antimicrobial agent in at least two antibiotic categories. Resistant broad (PDR) refers to bacterial expression of resistance to all antibiotic categories; particularly, values of minimum inhibitory concentration (MIC) are more useful than category of sensitive, intermediate, or resistant¹⁰.

Mortality related to MAHC ranges from 9% to 33% depending on the causative agent^{11,12}. The objective of this study is to describe our clinical experience in MAHC treatment through the evolution of cases.

Methods

We carried out a retrospective, descriptive study, between 2010-2017. All pediatric patients hospitalized with a diagnosis suggestive of MAHC in the pediatric division of the Civil Hospital of Guadalajara "Fray Antonio Alcalde" were included in a non-randomized sample (for convenience).

Hospital Civil de Guadalajara Fray Antonio Alcalde, a 1000-bed it is a tertiary care teaching hospital. The hospital provides services to the Jalisco state and its capital, Guadalajara, the second-largest city in Western Mexico, as well as to surrounding states. The hospital consists of adult and pediatric beds. All of the pediatric

units are located in one building. There are two neonatal intensive care units (ICUs) and one pediatric ICU. In 2018, there were 7398 patients discharged from the pediatric ward; 300 patients were submitted to neurochirurgical treatment.

Patients who met the clinical and laboratory criteria issued by the Centers of Disease Control and Prevention (CDC)'s National Healthcare Safety Network of 2017 (NHSN), and the official Mexican Standard of Epidemiology for Disease Prevention and Control NOM-026 SSA2-1998 were included in the study.

We review patients from 1 month to 14 years and 11 months of age who, having undergone some neurosurgical procedure such as placement of Ventricular Peritoneal Shunt Valve (VPSV), drainage of hematoma, biopsy or resection of brain tumor, among other procedures without other evident focus of infection. They developed meningitis data in the following 14 days and up to 1 year after placement of cerebrospinal fluid (CSF) drainage devices, which were also accompanied by MAHC definition.

Definition

According to the Meningitis and Ventriculitis Management Guidelines of 2017 CDC/NHSN associated with health care are defined, as a patient with bacterial growth in CSF culture, or a patient with at least two signs and symptoms of fever $> 38^{\circ}\text{C}$ or hypothermia $< 36^{\circ}\text{C}$, headache, apnea, bradycardia, irritability, cranial or meningeal signs, in addition to abnormal analysis of CSF cytochemistry (hyperproteinorrachy, hypoglycorrhachia, and hypercellularity for central laboratory ranges); organisms seen in Gram-stain, bacteria grown in CSF and blood.

Demographic data, comorbidities, clinical manifestation, as well as microbiological and radiological reports of patients, were recorded together with the antibiotic treatment and its duration. Bacterial isolates in blood and CSF as well as the determination of bacterial antibiotics sensitivity were analyzed by antibiogram performed by VITEK 2 automated method. Durham California, based on the Clinical and Laboratory Standards Institute (CLSI) formerly the National Committee for Clinical Laboratory Standards as well as the final evolution of each case such as: therapeutic failure, cure, death, relapse or reinfection, were evaluated by at least two infectious pediatricians and the information of cases was registered on an Excel database and analyzed by means of Statistical Package for the Social Sciences IBM SPSS 23.0

Table 1. Demographic characteristics in 114 episodes of nosocomial meningitis

Variable	Value (%)	Media	Desv. Std.	Inter quartil range
Age months		45.7	31.9	37.5
Male	49 (43)			
Female	65 (57)			
Hospital stay		46	32	35
CVC* time	96 (84.2)	24	21	34
Previous antibiotics	82 (72)	3	3.1	3
VPSV** (days postinsertion)	57 (50)	79	156	90
Ventriculostomy (duration days)	63 (55)	6	8.5	10
Neurochirurgic procedure	60 (52.6)			
CSF fistula [†]	20 (17.5)			
Agents in CSF				
Gram-negative bacteria	59 (51.7)			
Gram-positive bacteria	33 (29)			
Candida	4 (3.5)			
Polymicrobial	7 (6.1)			
Negative	11 (10.5)			
Leucocytes ($\times 10^9$)		14.500	6.869	10610
Plaquetas ($\times 10^9$)		453.254	155.783	256.700
CRP [‡] (mg/dL)		96.6	102.1	144.6
PCT [§] (mmol)		9.3	27.7	3.32
CSF glucose (g/L)		29.6	27.5	39
CSF protein (g/L)		8.1	2.4	0.694
CSF cells		3851	16587	432

*Central venous catheter.

**Ventricular peritoneal shunt valve.

†Cerebrospinal fluid.

‡C-reactive protein.

§Procalcitonin.

Ethics

Standard treatment for nosocomial meningitis was administered to all patients. The study was approved for its execution and publication by the research ethics committee of the Civil Hospital of Guadalajara “Fray Antonio Alcalde” with registration number 026/18.

Statistic analysis

Parametric variables were evaluated with means, standard deviation, and interquartile range. Non-parametric variables were described by means of ratios, proportions, compared with Chi-square 95% CI. All significant variables ($p < 0.05$) were subjected to a bivariate logistic regression model, to identify risk factors related to adverse evolution.

Results

Demographics

Between 2010 and 2017, we collected clinical data from 118 episodes of MAHC from 86 patients. We exclude four cases due to insufficient data.

Included patient's ages were from 1 to 200 months of age in their majority; they were carriers of meningitis associated with VPSV (44/51.7%).

Once the MAHC diagnosis was made, the shunt device was removed within the next 24-72 hours; in each case the patients were subsequently subjected to the placement of an external CSF device.

Change of ventriculostomy was carried out every 7-10 days, until obtaining bacterial negativization, with subsequent resolution of infectious process, for

Table 2. Evolution of 114 cases of MACS according to the type of agents isolated in CSF

Etiology	Healing	Reinfection	Death	Death OR		Total
	n (%)	n (%)	n (%)	IC 95%		
Gram-positive						
CNS	11 (50)	6 (27.3)	3 (13.6)	0.78	0.21 -2.03	22 (19.3)
MSSA	0	1 (25)	3 (75)	5.1	2.50-10.64	4 (3.5)
MRSA	2 (50)	2 (50)	0	0.52	0.08-3.46	4 (3.5)
Enterococcus	7 (63.6)	2 (18.2)	1 (9)			11 (9.7)
Candida	4 (66.6)	1 (16.6)	1 (16.6)	1	0.27-8.78	6 (5.2)
Gram-negative						
GNB MR	16 (50)	11 (34.4)	6 (18.8)	1.18	0.49-2.84	32 (28)
GNB ESBL	13 (46.4)	10 (35.7)	3 (10.7)	0.57	0.18-1.83	28 (24.6)
Other	2 (28.6)	3 (42.9)	2 (28.6)	6.29	0.52-2.68	7 (6.1)
Total	48 (42.1)	36 (31.6)	19 (16.6)			114 (100)

CNS: central nervous system; MSSA: *Staphylococcus aureus* sensitive methicillin; MRSA: methicillin-resistant *Staphylococcus aureus*, GNB MR: gram-negative bacteria meropenem resistant; GNB ESBL: gram-negative bacteria extended-spectrum beta-lactamase producer.

replacement of a new CSF derivation system, when it was necessary.

Two-thirds of patients received antibiotics before admission for their treatment, on average three antibiotics; 80% of children required antibiotics infusion through central venous catheter, 23 days on average (Table 1).

Treatment and evolution

We started an antibiotic scheme guided by a Gram stain of CSF. According to our epidemiology, included for treatment vancomycin and cefepime prescribed at weight and meningeal doses.

In case not having growth in the first CSF culture, treatment was directed based on Gram-stain findings and subsequent CSF cultures, taking into account in addition, results of blood cultures for its final classification as Gram-positive bacterial meningitis, Gram-negative bacterial meningitis, mixed bacterial meningitis or by *Candida* species.

Single or polymicrobial etiology, and consistent on bacterial or yeast growth were obtained from a first CSF culture on 89.5% of the samples.

Bacteremia associated with meningitis was isolated in 28/100 cases, but only 7% (8/28) of those were related to the same causative agent. Bacteremia of a different etiology associated with catheter was considered as a coinfection with meningitis.

We obtained an isolation of 71 Gram-negative strains (62.6%). Derived from antibiotic resistance phenotype

producing extended-spectrum beta-lactamases (ESBL) in Gram-negative bacteria, these strains received meropenem alone or in combination with rifampicin. Two strains of *Elizabethkingia meningoseptica* were resistant to vancomycin and treated with trimethoprim/sulfamethoxazole.

The most common Gram-negative agent in meningitis cases was *A. baumannii* 30 (42.25%), all of these cases were considered as a therapeutic failure secondary to meropenem resistance.

In addition, 15 cases (21.1%) of Gram-negative bacterial infection, among them: *P. aeruginosa*, *K. pneumoniae*, and *E. coli*; they did not show clearing of CSF in more than 10 days of treatment also with clinical symptoms, they were considered with therapeutic failure to cefepime and meropenem, even though the antibiogram showed sensitivity to meropenem.

All these cases received colistimethate intravenously at a dose of 10 mg/kg (125,000 IU), and intrathecal at a dose of 10 mg/kg of impregnation followed by 5 mg/kg (75,000 IU) per day, in addition to oral rifampicin, until CSF clearing.

Among the Gram-positive bacteria, a strain of *Enterococcus faecium* was resistant to vancomycin and linezolid; it received 4 weeks of treatment with daptomycin. Finally, four cases with meningitis due to methicillin-sensitive *Staphylococcus aureus* (MSSA) were treated with vancomycin/rifampicin combination for 20 days, on average 16 days and sensitivity to vancomycin with a MIC < 1 µg/mL, all cases were coinfecting

We suggest that the lack of growth of bacteria in blood and CSF was probably secondary to the previous use of antibiotics, on average three except among episodes of *Candida* etiology that received seven antibiotics as a mean for infectious processes of nosocomial bacterial origin.

Limitations and biases of this study are based on the availability for determination of lactate, procalcitonin, and C-reactive protein in CSF, by our laboratory. Not all bacterial strains could be subjected to a regular determination of sensitivity to bacterial agents, especially colistimethate.

With the exception of colistimethate, all antibiotics used were of generic origin, at appropriate doses, and in duration. We also do not have molecular tools for microbiological diagnosis to determine specifically types of resistance.

In addition, the inability to analyze biofilms in shunts and venous catheters prevents knowing the type of biofilm and the extent of antibiotic therapy as well as the possibility of permanence right there. Moreover, finally, in limitation of hospital resources such as availability of operating rooms, surgical shifts, and access by relatives of patients to pay for VPSV antibiotics impregnated and external drainage systems of CSF.

Conclusions

It was remarkable the participation of *A. baumannii* MDR, especially in cases where the patient was exposed to broad-spectrum antibiotics, for these cases, although colistimethate can be a salvage treatment, it is an option that already shows resistance and has been transferred to other Gram-negative bacteria.

In our population, the etiology of MAHC by Gram-positive bacteria was associated with a higher mortality risk, associated with other nosocomial infections.

To reduce bacterial resistance, in the future, we must adhere to recommendations of management guidelines for meningitis, in particular, shorten the time of exposure to external drains of CSF and use VPSV impregnated with antibiotics to limit re-infection.

It is essential to always count in hospital units with molecular tools to identify antibiotic resistance.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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