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Research Article

Neonatal Bacterial Meningitis in a Third Level Hospital in Mexico City during a 32 Years Period: Clinical Characteristics and Risk Factors for Mortality and Neurologic Sequelae

Mercedes Macías-Parra[1]*, Patricia Saltigeral-Simental[1], Miguel Ángel Rodríguez-Weber[2], Silvestre García de la Puente[3] and Virginia Díaz -Jiménez[1]

[1]*Department of Pediatric Infectious Disease National Institute of Pediatrics (INP), Mexico City, Mexico*

[2]*Neonatal Intensive Care Unit INP, Mexico City, Mexico*

[3]*Department of Pediatric Nephrology INP, Mexico City, Mexico*

***Corresponding Author**: Mercedes Macías-Parra, Department of Pediatric Infectious Disease National Institute of Pediatrics (INP), Mexico City, Mexico.

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Abstract

Objective: Neonatal bacterial meningitis (NBM) remains an important cause of death and major neurological sequelae especially in developing countries, where information is limited.

Methods: This retrospective study describes the epidemiological, clinical findings and risk factors for death and neurodevelopmental sequelae in neonates diagnosed with bacterial meningitis at the Instituto Nacional de Pediatria (INP) in Mexico City between1980 and 2012.

Inclusions criteria were neonates (≤ 28 days of age) with 1. Confirmed bacterial meningitis: a) positive cerebrospinal fluid (CSF) culture, b) positive peripheral blood culture and positive CSF culture, c) positive blood culture with CSF pleocytosis, d) CSF pleocytosis and positive Gram stain and 2. Probable meningitis a) CSF pleocytosis and clinical features of meningitis. Neonates with any of the following conditions were excluded: viral meningitis, fungal meningitis, intraventricular hemorrhage, congenital anomalies of the central nervous system, genetic abnormalities, metabolic diseases or perinatal asphyxia.

Results: 136 cases fulfilled the criteria of NBM, (95 confirmed and 41 probable cases), with an incidence of 14 cases/1000 neonatal hospital discharges. CSF cultures were positive in 60% of cases and *Klebsiella pneumoniae* was the most frequent pathogen (18% of patients). Neurological complications occurred in 40%, mortality was 38% and neurological sequelae were observed in 67% of survivors. Low hemoglobin, neurologic complications and generalized seizures were associated with a greater risk of disability which could be predicted in 75% of cases. Use of inotropes, central venous catheter, early- onset meningitis, altered consciousness at admission and low birth weight were significantly associated with mortality which could be predicted in 94%.

Conclusions: Prevention strategies and treatment guidelines area required to improve the outcome of NBM.

Keywords: *Bacterial; Neonatal Meningitis, Outcome, Risk Factors*

Introduction

Bacterial meningitis is more frequent in the neonate that in any other age group [1]. According to the World Health Organization (WHO), approximately 88,500 to 126,000 cases of neonatal bacterial meningitis (NBM) occur each year in developing countries [2]. The incidence of NBM has remained stable in the last 30 years and worldwide it is estimated to be 0.22 to 2.66 cases per 1000 live births [3-6].

Low birth weight and prematurity are associated with a tenfold higher incidence reaching 2.5/1000 live births [7] and this figure may be higher in underdeveloped countries [8,9]. In Mexico, its incidence has been reported from 2.6 to 17/per 1000 live births [10].

The etiology of NBM in the neonate is more diverse than the etiology of meningitis in other age groups. In industrialized countries, the etiology of this entity has remained stable in the last decades, with group B *Streptococcus* (GBS) and *Escherichia* coli being the most frequent pathogens in Europe, Australasia and North America [4]. Although data from developing countries is scarce, the etiological agents differ from those of industrialized regions, and gram-negative bacteria such as *Klebsiella* spp. and *E. coli* have been found in 63.5% of the cases [11].

In developed countries, mortality of NBM caused by GBS and *E. coli* has decreased from 50% in 1970 to less than 10% in the 90s [3,4]; in less industrialized regions mortality continues to be 20% to 30% [12]. Likewise, the incidence of long-term neurodevelopmental sequelae remains unacceptably high and unchanged between 1970 and 1990: 50% in NBM caused by GBS or *E. coli*, and up to 78% in patients with meningitis caused by other gram-negative bacteria [3-5]. In a study carried out in the United States on GBS meningitis, 44% of infants were shown to have long term sequelae [13]. However there is limited data on risk factors for death and neurodevelopmental sequelae in children who suffered from NBM, and the information derives mainly from developed countries [14].

Aim of the Study

The aim of this study is to describe epidemiological, clinical findings and risk factors for neurological sequelae and mortality in NBM among new borns admitted to the Instituto Nacional de Pediatría in Mexico City between 1980 and 2012. Information from this study will be useful to establish protocols for early detection to allow timely interventions with the potential to prevent complications and sequelae.

Materials and Methods

In this retrospective study, we reviewed the hospital discharge records of patients admitted to the Instituto Nacional de Pediatria from January 1980 to December 2013 with diagnosis of meningitis, neonatal meningitis or bacterial meningitis. The microbiologic records of the cerebrospinal fluid (CSF) and blood culture at the Microbiology Laboratory Department were also reviewed. There were no cases of NBM in 2013 so the analysis was considered from 1980 to 2012 period. The INP is a tertiary referral pediatric hospital in Mexico City. The neonates are referred from other hospitals or their own communities; 48% of patients come from other states of Mexico.

Inclusion criteria were: neonates (defined as a chronological age up to 28 days of life), with diagnosis of bacterial meningitis. An analytical case definition was used to classify confirmed or probable cases using strict criteria. The CSF white cell count cutoffs used, were based on published normal values according to gestational age [15-17], with no adjustment for traumatic lumbar punctures [18].

NBM cases were classified as confirmed if patient fulfilled any of the following criteria: a) positive peripheral blood culture and positive CSF culture, b) positive CSF culture, c) positive blood culture with CSF pleocytosis, d) CSF pleocytosis with positive CSF Gram stain. NBM were classified as probable cases if CSF pleocytosis was present, and clinical features of meningitis were present, in the absence of positive blood and CSF cultures. The following clinical findings were considered for the diagnosis of meningitis: fever, hypothermia, or temperature instability plus two or more neurological findings (coma, lethargy, seizures, bulging fontanelle, neck stiffness, irritability, poor feeding, or spasticity). Exclusion criteria were: viral meningitis, fungal meningitis, intraventricular hemorrhage, congenital anomalies of the central nervous system, genetic abnormalities, perinatal asphyxia and congenital metabolic diseases. A neonate was considered premature when the gestational age was < 37 weeks. Cases were further classified as early-onset meningitis when the symptoms started on the first seven days from birth or late-onset when they started after seven days of life [1]. Infection related to health care was defined as the appearance of signs and or symptoms of bacterial meningitis after 72 hrs of admission if vertical transmission was ruled out [19].

Neurological complications were documented by brain ultrasound from 1980 to 1989 and by cranial CT scan from 1990 to 2012. All patients with seizures had an electroencephalogram performed. Neurodevelopmental sequelaes were assessed at discharge and during follow up (range 2 to 192 months). Psychomotor development was assessed by the Gesell method: global development of 86% to 100% was considered normal, 85% was considered as mild delay, 65% - 84% as moderate, and ≤ 64% as severe developmental delay [20]. Hearing was assessed by brainstem auditory evoked responses (BAER), hearing impairment was defined as mild for an auditory threshold of 22 - 42 dB, moderate 42 - 62 dB, severe 62 - 92 dB, and profound 93 dB or more [21].

The frequency and mortality of NBM over hospital neonatal discharges were estimated for the period between January 1992 and December 2012, since there was no available data before 1992. There were no significant differences in demographic characteristics, neurologic complications, deaths, and sequelae between probable and confirmed cases, therefore, all cases were analyzed together.

The protocol was approved by the Institute Research Committee and the information was obtained from the medical records keeping the confidentiality of the patients.

Statistical analysis

Descriptive statistics were used to analyze the clinical characteristics and laboratory results. Median (min-max) was used to describe numerical variables. Frequencies or percentages were used to describe categorical variables. To determine the association between clinical and laboratory data with neurodevelopmental sequelae and mortality, Mann-Whitney U test was used for numerical variables and Pearson $\chi 2$ or Fisher exact test for categorical variables, where $p < 0.05$ was considered as significant. To assess the risk factors associated with mortality and neurological sequelae we conducted a multivariable logistic regression analysis, with inclusion in the model the variables that had potential association on bivariable analysis ($p<0.10$). We assessed the model fit using the Hosmer-Lemeshow goodness-of-fit-test. All analyses was conducted using SPSS version 22.

Results

During this 32 years study period, 681 records had the discharge diagnosis of bacterial meningitis. Among these, 139 cases were ≤ 28 days old, including three patients with a positive CSF culture for whom no clinical information was available, therefore, 136 new born infants met the inclusion criteria and were included for the analysis. The diagnosis of confirmed NBM was made in 95 cases (70%) and probable NBM in 41 (30%) (Figure 1). The overall incidence from 1992 to 2012 of NBM confirmed and probable cases was 14 cases per 1000 neonatal hospital discharges (CI95% 8 - 23); for the period of 1992-1999 the incidence was 23 per 1000 neonates, (CI95% 14 - 34) and 7/1000 for the period 2000-2012 (CI95% 3 - 14). No seasonal pattern was observed.

The median gestational age was 38 weeks (range 28 - 41), 35 (26%) were premature. The median birth weight was 3000g (range 900g - 5000g), the birth weight was < 2000g in 25/132 neonates (19%), without significant differences between the study periods. There was a male predominance (n = 94 (69%)). The median age at presentation was 9.3 days (range 1 to 28 days). Early-onset NBM was identified in 67 (49%) cases, with a median age at onset of 3.7 days (range 1 - 6 days); in 22/67 (33%) neonates, the onset was in the first day of life. Late-onset occurred with a median age of 17 days (range 7 - 28 days). Twenty three cases (17%) were identified as bacterial meningitis

Year		1980 - 1989	1990 - 1999	2000 - 2012	*P*
Characteristics	**Number of patients**	**n = 34**	**n = 74**	**n = 28**	* **
Age at admission (days) (ranges)	136	14.5 (1 - 28)	7 (1 - 28)	10.5 (1 - 28)	0.043
Gestational age < 37 weeks	131	37.8 (34 - 40)	36.8 (28 - 41)	37.3 (28 - 41)	NS
Birth weight (Kg) (ranges)	132	3.0 (1.5 - 5.0)	3.0(0.9 - 4.3)	3.0 (1.1 - 3.9)	NS
Gender Male/Female	136	6 / 28	26 / 48	10/18	NS
Duration of symptoms prior to admission (days) (ranges)	134	2.0 (1 - 6)	2.0 (1 - 7)	3.0 (1 - 10)	0.016
Early Onset (< 7 days) (%)	136	13 (38)	40(54)	14 (50)	NS
Tx with TGC*** or Carbapenems (%)	136	3 (9)	53 (72)	25 (89)	< .000001
Tx with aminoglycosides (%)	136	31 (91)	21 (28)	3(11)	< .000001
Neurologycal complications (%)	130	15 (44)	2 5(34)	15 (54)	NS
Sequelae (%)	85	14/16 (87)	29/51 (57)	14/18 (78)	0.042
Deaths (%)	136	22 (65)	23 (31)	6 (21)	0.001

Table 1: *Demographic and Clinical features among 136 patients with confirmed and probable Neonatal Bacterial Meningitis in three decades*

** Kruscal-Wallis test; ** Pearson Chi square; *** Third generation cephalosporins.*

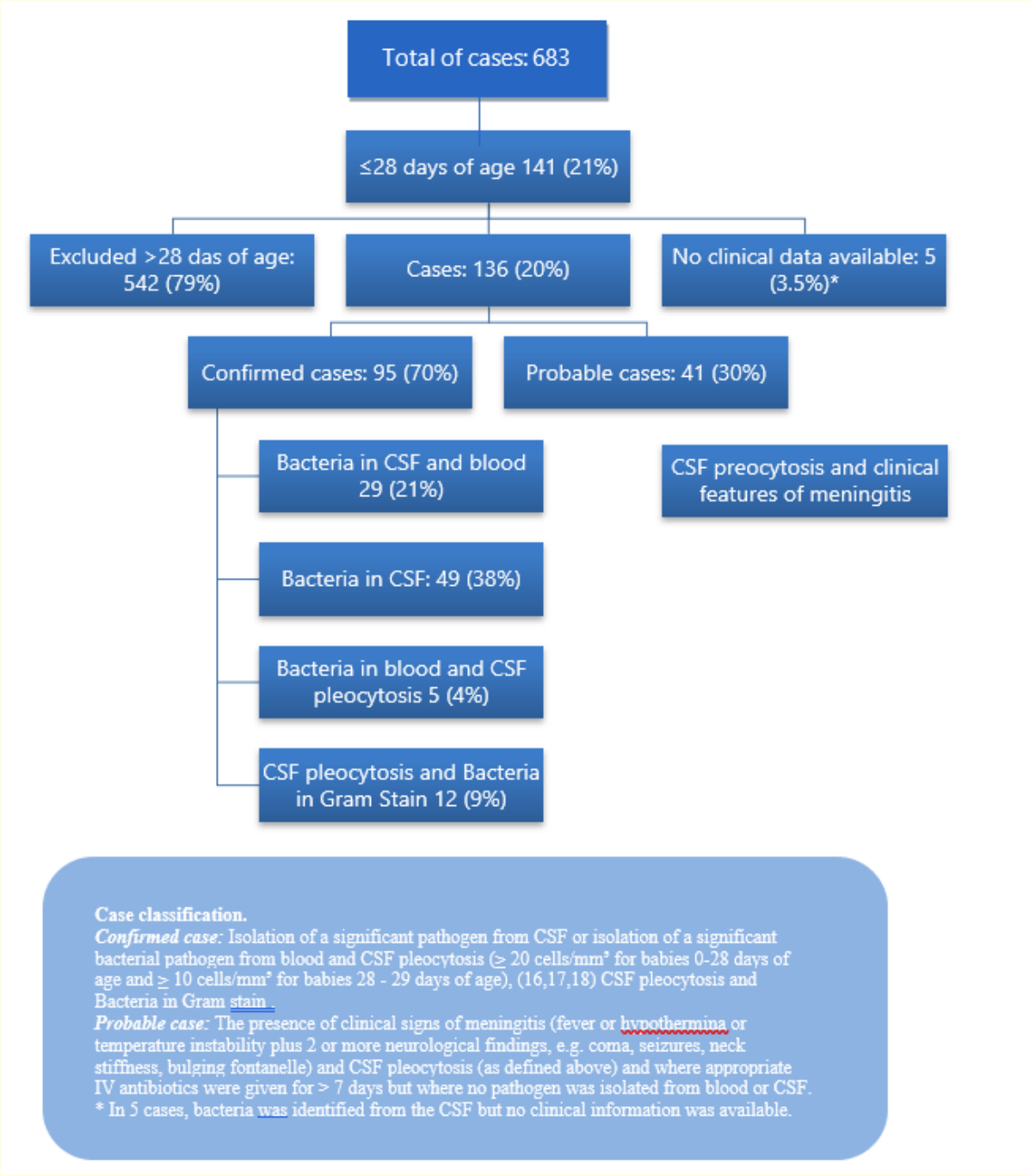

Figure 1: *Flowchart of bacterial meningitis diagnosed during the study. *Excluded as did not meet case definition.*

Abbreviations: CSF: Cerebrospinal Fluid; GBS: Group B Streptococcus; IV: Intravenous

associated to health care. In the last two decades, the mean age of admission was significantly lower with a higher incidence of early-onset meningitis compared with the first study period (Table 1). In contrast, the time of evolution in the last decade was longer than in previous years (3[1 - 10] vs 2 [1.7] days, p = 0.016) (Table 1).

The possible source of infection was identified in 107/135 cases (79%), without statistical difference between the 3 study periods (82%, 81%, 70% respectively). Septicemia was the most frequent source (n = 69), followed by pneumonia (n = 21), gastroenteritis (n = 11), skin (n = 4), soft tissue infection (n = 4) and urinary tract infection (n = 2).

The most common clinical features were: fever and poor feeding (Table 2). Seizures were present at onset of illness in 75 cases (55%), and were generalized in 51 (68%); one patient had status epilepticus on admission. A bulging fontanelle was found in 47 cases (35%), without correlation with the time to diagnosis or the presence of hydrocephalus, four infants (3%) were in coma at admission. Symptoms that were significantly more frequent in term infants compared to preterm infants were: fever (83% vs 57%, p = 0.002), bulging fontanelle (41% vs 17%, p = 0.012), abdominal distention (59% vs 40%, p = 0.047) and vomiting (27% vs 11% p = 0.047) (Table 2).

Clinical features	Term n = 101 (%)	Premature n = 35 (%)	p	Odds Ratio (IC95%)
Fever	84 (83)	20 (57)	0.002	3.7 (1.6 - 8.7)
Poor feeding	78 (77)	23 (66)	0.18	1.8 (0.8 - 4.1)
Seizures	57 (56)	18 (51)	0.61	1.2 (0.7 - 2.6)
Abdominal Distention	60 (59)	14 (40)	0.047	2.2 (1.0 - 4.8)
Bulging Fontanella	41 (41)	6 (17)	0.012	3.3 (1.3 - 8.7)
Hipertonicity	32 (32)	7 (20)	0.19	1.9 (0.7 - 4.7)
Vomiting	27 (27)	4 (11)	0.06	2.8 (0.9 - 8.8)
Hypotermia	17 (17)	7 (20)	0.67	0.8 (0.3 - 2.2)
Neck stiffness	20 (20)	4 (11)	0.26	1.9 (0.6 - 6)
Somnolence or letargy	67 (66)	24 (69)	0.81	0.9 (0.4 - 2.1)
Coma	2 (0.02)	2 (0.06)	0.27	0.3 (.05 - 2.5)

Table 2: *Comparison of signs and symptoms between term and premature new born with bacterial meningitis.*

Sixty two patients (46%) required central venous catheter and 61 (45%) mechanical ventilation for a median of four days (range 1 - 51 days). Inotropes were used in 52 cases (38%).

On admission, 14/134 patients (10%) had hemoglobin less than 10g/dL with a median of 14.1 g/dL. (range 5.8 g/dL - 25 g/dL), 21 patients (16%) had leucopenia, in 57 cases (43%) the platelet count was ≤ 150 x 103/mL. and nine neonates (7%) had platelet count above 450 x 103/mL. Thirty two patients (24%) had CSF proteins ≥ 500 mg %, and glucose of ≤ 10 mg was observed in 41 cases (30%). The CSF cell count was significantly higher in neonates with gram-positive than with gram-negative organisms (median 514 [range 26 - 1539] vs. median 244 [range 2 - 1500]; p = .046) (Table 3). Five neonates (4%) with a positive CSF culture had normal CSF cytology.

A pathogen was identified in 78/131 CSF cultures available (60%), with a significant improvement in microorganism isolation in the third period compared to the first decade (73% vs 50%). In twelve infants in whom the CSF culture was negative, the CSF Gram stain was positive.

Blood cultures were positive in 35/110 samples (32%), with concordance with the organism isolated from CSF in 29 cases (83%). Overall, *K. pneumoniae* remained as the main causative agent in 24/78 (31%) of CSF isolated bacteria, with an increase in detection rate during the second and third periods compared to the first period (20/97 [21%] vs 4/34 [12%]). Gram-positives were detected in 14 (11%) cases including (GBS) in 8 patients (Table 4). The median age at admission was significantly lower in NBM caused by Gram-negative bacteria when compared to NBM caused by Gram-positive organism (6 vs. 14.5 days p = 0.03).

Type of study	Median(min-max)
Biological parameters	
Hemoglobin (g/dL)	14.1 (5.8 - 25)
Leukocyte count (X10^3 µL)	11.6 (1.5 - 42.05)
Neutrophil count (%)	53.5 (7 - 91)
Lymphocytes count (%)	32 (5 - 92)
Platelets (X10^3 µL)	203 (2 - 800)
Cerebrospinal fluid parameters	-
Proteins (mg/dL)	241.5 (35 - 5200)
Cells (mm^3)	300 (2 - 16200)
Neutrophils (%)	75 (2 - 100)
Glucose (mg/dL)	24 (0 - 188)

Table 3: *CSF and blood parameters in 136 new born with confirmed and probable neonatal bacterial meningitis.*

Isolated organism	1980-1989	1990-1999	2000-2012	
	n = 34	n = 71	n = 26	
	(%)	(%)	(%)	(%)
Gram negatives				**Total**
K. pneumoniae	4 (12)	14 (20)	6 (23)	24
E. coli	2 (6)	8 (11)	5 (19)	15
E. cloacae	2 (6)	4 (6)	1 (4)	7
P. aeruginosa	2 (6)	2 (3)		4
Salmonella group D	2 (6)	1 (1)		3
Salmonella sp.	1 (3)			1
Haemophilus influenzae type *b*		3 (4)		3
Neisseria meningitidis		1 (1)		1
Citrobacter sp.			1 (4)	1
Enterococcus fecalis			1 (4)	1
Serratia marcescens		2 (3)		2
K.oxitocca			1 (4)	1
Actinobacter iwoffi			1 (4)	1
Total	13/34 (38)	35/71 (49)	16/26 (61)	64/131 (49)
Gram positives				
Streptococcus group B	1/34 (3)	5/71 (7)	2/26 (8)	8/131 (6)
Staphylococcus epidermidis	1/34 (3)	1/71 (1)		2/131 (2)
Listeria monocytogenes	1/34 (3)			1/131 (1)
Streptococcus pneumoniae		1/71 (1)	1/26 (4)	2 (2)
Streptococcus sp	1/34 (3)			1 (1)
Total	4/34 (12)	7/71 (10)	3/26 (11)	14/131 (11)
Negative culture	17 (50)	29/71 (39)	7/26 (27)	53/131 (40)

Table 4: *Distribution of Pathogens isolated in three decades in 131 CSF* of patients with neonatal bacterial meningitis.*

**CSF: Cerebrospinal Fluid.*

Neurologic complications were present in 55 cases (40%): ventriculitis in 17 (13%), parenchymal hemorrhage 10 (7%), ventriculomegaly 8 (6%), subdural effusion 5 (4%), brain abscess 2 (1%), syndrome of inappropriate antidiuretic hormone secretion 1 (0.7%); 12 patients (9%) had 2 or more complications.

Empiric antimicrobial treatment included an aminoglycoside in 60 (44%) cases, mainly amikacin in addition to ampicillin in 52 cases. Seventy-three patients (54%) received third-generation cephalosporins (TGC) mainly ceftriaxone; all of them also received ampicillin. Three children received carbapenems (2%). Those differences in treatment were mainly due to changes in hospital recommended schemes in the tree periods studied, with an increasing tendency toward the use of cephalosporins. There were significantly more changes in antimicrobial therapy when aminoglycosides were initially given compared with those infants with TGC or carbapenems (35/60 vs. 22/76; p = 0.001). Dexamethasone was administered to 56 cases (41%), with a median of 3 days (range 1 - 6 days).

Overall mortality (1980 - 2012) was 38% (51 children), with a mortality rate for the period of 1992 - 2012 of 70/1000 neonates discharged, and was three and two times higher in the first decade compared with the second and third periods respectively (65% vs 31% and 21% p = 0.001). Five children (10%) died during the first 24h after admission, and 6 (12%) during the first 48h. The median duration of hospitalization was 21 days (min 1 day- max 127 days). There were no relapses.

There were no significant differences in mortality between confirmed NBM and those with probable NBM (35/95 vs. 16/41; p = 0.761), or between cases with gram-negative or gram-positive bacteria (30/64 vs. 5/14; p = 0.447). The mortality was significantly higher in patients treated with aminoglycosides compared with those treated with TGC or carbapenems (84% vs 59% p = 0.007). There was a significant higher mortality in infants treated with dexamethasone than in those who did not received it (28/56 (50%) vs 23/80 (29%) p = 0.012).

Among 85 survivors, 57 infants (67%), developed neurological sequelae during a mean follow-up of 12 months (range 2 - 192 months [only 4 patients had follow up 2 months after discharge]). Most of these infants (86%) had 2 or more disabilities. Mental retardation and motor impairment were the most frequent, in 48 (56%) and 20 (24%), respectively. Mental retardation was severe in 20 cases (42%), moderate in 13 (27%), and mild in 15 (31%). Spastic quadriparesia was present in 13 infants (65%), hemiparesia in four (20%), monoparesia in two (10%) and paraparesia in one (5%). There were 33 cases with epilepsy (39%), with poor control of the crisis in 14 cases (42%). Any degree of hearing loss was documented in 32/34 BAER studies. It was mild in 12 cases, moderate in 12, and profound in 8.

The risk factors for death were determined for the years 1990 - 2012 due to improvements in standard neonatal intensive care, changes in antimicrobial regimens, and availability of CT scan in the institute from 1990. During this period, there were 29/102 (28%) deaths.

Table 5 shows the risk factors significantly associated with an increase in mortality in the bivariate analysis.

The logistic regression multivariate analysis showed that onset during the first 7 days of life, low birth weight, altered consciousness on admission, use of inotropes and central venous catheter, were significant risk factors for death. According to this model, the outcome could be predicted in 94% of cases; the Hosmer-Lemeshow test had a significance of 0.945, indicating, very good model fit as risk factor for death (Table 6).

There were no significant differences in the risk factors for neurodevelopmental sequelae between the three periods; therefore, all patients with factors associated with sequelae in the bivariate analysis were included in the multivariate analysis (Table 7).

In the multivariate analysis the presence of neurologic complications, generalized seizures, and low hemoglobin values remained as risk factors with statistical significance for the development of neurologic sequelae. The model was highly significant to predict the presence or not of neurodevelopmental sequelae in 76.5% of the cases; the Hosmer-Lemeshow test had a significance of .909, indicating, very good model fit (Table 8).

Variable	Dead No.29	Alive No.73	P*
Age (days)	5 (1,23)	12 (1,28)	0.002
Birth weight	2500 (900, 4000)	3150 (1260,4150)	0.000
Admission weight (g) (n = 136)	2240 (900, 3700)	3200 (1360,4500)	0.000
Gestational age	37 (28, 40)	38 (30, 41)	0.01
Sistolic Blood pressure	65 (20, 90)	80 (50, 110)	0.000
WBC Polymorphonuclear %	62 (16, 83)	49 (9, 88)	0.026
Lymphocytes %	29 (5, 64)	40(9, 87)	0.042
Platelet count $x10^3$	90 (2, 372)	232 (6, 576)	0.001
Early Onset < 7 Days	23 (79%)	31 (42%)	0.001
Gestational Age (< 32 weeks)	7 (24%)	2 (3%)	0.002**
Prematurity	16 (55%)	17(23%)	0.031
Previous Hospitalization	22 (76%)	31 (42%)	0.002
Alterations in consciousness	27 (93%)	44 (60%)	0.001
Fever	15 (52%)	59 (81%)	0.003
Hypothermia	13 (45%)	6 (8%)	0.000
Source of Infection	27 (33%)	52 (71%)	0.017
Bacteriemia	12 (41%)	17 (23%)	0.014
Ventilation required	27 (93%)	19 (26%)	0.000
Use of Inotropics	25 (86%)	11 (15%)	0.000
Use of central venous cathether	25 (86%)	24 (33%)	0.000
Positive CSF Culture	23 (88.5%)	37 (52.1%)	0.001
TGC or carbapenem	17 (58.6%)	61 (83.6%)	0.007

Table 5*: Bivariate Analysis of Risk Factors Associated with Mortality among 102 patients with neonatal bacterial meningitis.*

** U of Mann-Whitney or Pearson χ^2 Test. ** Fisher exact Test CVC central venous catheter, CSF cerebrospinal fluid, TGC third generation cephalosporins.*

Risk Factors	B	Odds Ratio	(CI 95%)*	p
Use of Inotropic	3.186	24.181	(4.885, 119.7)	0.00009
Early onset	1.867	6.469	(1.237, 33.841)	0.027
CVC**	1.846	6.337	(1.253, 32.05)	0.026
Weight at admission	-.001	.999	(.998, 1)	0.046
Altered consciousness	1.951	7.037	(1.015, 48.771)	0.048
Constant	-3.65	.026		0.053

Table 6: *Multivariate Analysis of Risk Factors Associated to Mortality in neonatal bacterial meningitis.*

**Confidence Intervals 95% of odds ratio, **central venous catheter.*

Risk Factor	With Sequelae No. 57	Withouth Sequelae No. 28	p *
Hospital stay	25 (9,127)	23 (8,48)	0.028
Seizures Duration (days)	1 (0, 10)	0 (0, 2)	0.000
Assisted Ventilation (days)	0 (0, 51)	0 (0, 16)	0.028
LCR polymorphonuclears %	80 (4, 100)	54 (5, 100)	0.011
Hemoglobin (g/dL)	13 (5.8, 20)	15.6 (10, 24)	0.000
Seizures	40 (70.2%)	9 (32.1%)	0.001
Generalizaded Seizures	29 (50.9%)	5 (17.9%)	0.003
Persistence of crisis to 72h	13 (22.8%)	1 (3.6%)	0.029***
Neurological Complications	35 (61.4%)	6 (21.4%)	0.001
Hydrocephalus	14 (24.6%)	1 (3.7%)	003***
Assisted Ventilation	18 (31.6%)	3 (10.7%)	0.036
Use of Inotropic	12 /21.4%)	1(3.6%)	0.033

Table 7: *Bivariate analysis of risk factors for neurodevelopmental sequelae in neonatal bacterial meningitis.*

** U Mann-Whitney or Pearson χ^2, *** Fisher exact test.*

Prognostic Factors	B	Odds Ratio	IC 95%*	p
Hemoglobin	-.335	.716	(.573 - .894)	0.003
Neurologic Complications	1.623	5.07	(1.54 - 16.71)	0.008
Generalized Seizures	1.467	4.336	(1.24 - 15.2)	0.022
Constant	4.761	116.89		0007

Table 8: *Multivariate analysis of prognostic factors for neurodevelopmental sequelae in neonatal meningitis.*

** Confidence Intervals 95% of Odds ratio.*

Discussion

Neonatal meningitis remains as a substantial cause of morbidity and mortality in the new born, and tends to be higher in less industrialized countries. In this study the overall incidence of NBM was 14/1,000 neonates discharged from INP between January 1992 to December 2012, with a significant decrease between the study period, with an incidence of 23/1,000 neonatal discharges for the 1992 - 1999 period to 7/1000 for years 2000-2012, probably related to an early diagnosis and management of sepsis. The incidence found in this study is lower than the 32.3/1,000 intensive care neonatal discharges reported from Hospital Infantil de México (a referral institute similar to INP), between years 1990-1995 [9]. These differences may be related to the denominator, since our study takes into account all neonatal discharges and the study from Hospital Infantil de Mexico considered the intensive care neonatal discharges; another factor that could contribute to these differences, is the study period with a higher incidence in the 1990s, and a hospital referral bias. In Mexico there is not an active national surveillance program of NBM and it was not a diagnosis of mandatory notification. The Dirección General de Epidemiología from 2000 to 2012 reported 356 cases of NBM and no information is available before the year 2000. Due to this lack

of information it is not possible to compare the incidence of NBM at a community level with that notified in developed countries which have reported over the years 1996-1997 an incidence of 0.21 cases/1,000 live births, or reports with less developed countries with a high variability which ranges from 0.08 in the first week of life to 6.1 per 1000 live births. Community based studies in Pakistan showed an incidence of 0.81/1000 new born infants in the first week of life [22] which contrasts with a higher incidence of 4.9/1000 live births reported in some areas in India [23], but similar to 4.2/1,000 live births reported in Brazil [24] and 6.1/1,000 live births, observed in a rural community in Guatemala [25].

Low birth weight has been considered as a risk factor for the development of NBM and it has been reported to be six to ten times more frequent in infants with low birth weight < 2000g [4]. In this study 19% of patients were less than 2000g. The association between low birth weight and NBM could be explained by an immature immune system [26] or greater exposure to other risk factors, such as prolonged hospitalization and use of intravascular catheters [27].

The pathogens responsible for NBM remained with little changes over the three decades, with *Klebsiella pneumoniae* and *E. coli* accounting for 61% of cases. In 87% *Klebsiella pneumoniae* and 94% of *E. coli* cases, meningitis were of early onset, with no correlation with gestational age or birth weight.

The predominance of gram negative organism has also been documented in other studies from less developed countries with *K. pneumoniae*, *E. coli* and other gram negative bacteria identified as the main pathogens of NBM [11,28,29].

Group B *Streptococcus* ranges from 17% to 30% across the studies in industrialized countries; in our study represented 0.06 % of cases with no significant differences in the study periods. It is not know why in Mexico there is a low prevalence of neonatal infections due GBS. It has been suggested that ethnic, genetic factors [30] or that the immune status of the mothers colonized with GBS [29] might play a role in rates of neonatal infections with GBS. It has also been suggested that this finding may be related to differences in the virulence of GBS strains [31], since there is a low prevalence of GBS serotype III in Mexican women and there is a predominance of non-typeable strains, this could account for the low incidence of GBS neonatal infections in Mexico, since serotype III strains cause most of the serious infections among US infants [32]. It remains unclear how age or parity affect GBS carriage. In this report other gram negative and gram positive were isolated less frequently.

In our study, 50% of cases presented with clinical manifestations starting during the first week of life, suggesting a vertical transmission. The other half had a late onset where the infection could have been acquired in the community as a result of bacterial colonization from a maternal source, or by horizontal transmission from a family contact [1,11]. Twenty three cases (17%) were infection associated to health care and four of them were of early onset.

The initial clinical manifestations of meningitis in the neonate are subtle, nonspecific, and indistinguishable from those of neonatal sepsis or metabolic conditions. In our study, fever and poor feeding were the most frequent manifestations; seizures were present at onset of illness in 55% of the cases, a feature that helped to suspect the diagnosis. Seizures have been reported to be among the first clinical manifestations of NBM in 20 - 50% of cases, this higher incidence found in this study may be associated to a higher rate of gram-negative isolates as has been suggested by other authors [1,4]. A bulging fontanelle was found in 30% of cases, similar compared to the 15% - 35% reported by other authors, the importance of this finding is that its presence suggests the diagnosis but its absence does not rule it out [33,34], there was no correlation between this finding and the duration of illness or the presence of hydrocephalus. Fever, a bulging fontanelle, abdominal distention and vomiting were significantly more frequent in term infants, as well as abdominal distention and vomiting. It is worthwhile to point out that the presence of symptoms suggesting meningitis as spasticity or neck stiffness often appears late in the course of the disease and their presence therefore predicts worse prognosis.

During the first decade the treatment was in almost all cases with an aminoglycoside combined with ampicillin. The rationale for the declining use of aminoglycosides as empiric antimicrobial treatment in our institute in the 90s, was the increased frequency of detection of gram negative organisms resistant to ampicillin and aminoglycosides, the potential for ototoxicity and the availability of newer antibiotics with broader spectrum. The use of TGC was one of the factors that in the bivariate analysis was associated with a significant decrease in mortality compared to aminoglycosides (84% vs 59% p = 0.007); however, this parameter was not significant in the multivariate analysis, probably because for this analysis only cases diagnosed after1990 where included and aminoglycosides were used only in 30% of these cases. This lower mortality has also been observed in studies where the use of TGC correlates with a decrease in mortality but not in long-term morbidity [4]. Some factors that could contribute to this differences in mortality is that CSF aminoglycosides concentrations are minimally above their minimal inhibitory concentrations (MIC) [5,35] and CSF cultures remains positive longer compared with those treated with TGC with greater bactericidal activity in CSF (5-7 days vs. 1 - 2 days; p = 0.05) [36]. The narrow therapeutic index of aminoglycosides and there is impaired efficacy at a low pH of purulent CSF, makes bactericidal levels in CSF difficult to achieve [37,38].

Three patients were treated with meropenem and the experience with this antibiotic for the treatment of NBM is limited, nevertheless when an extended spectrum of beta lactamase producing organism is identified this carbapenem is recommended with an aminoglycoside [5].

There were no relapses in this study. Relapse of meningitis has been reported in up to 8% of cases and sometimes this has been attributed to inadequate dosage or duration of antibiotic therapy [39].

There was no significant difference in mortality between infections with gram-negative or gram-positive organisms. Previous studies have reported a higher mortality with gram negative organism [4], although this finding is difficult to compare due to the small number of gram-positive infections that we observed. In our study, 42.4% of cases received dexamethasone, with a significantly higher mortality compared with those cases that did not received it. However, this difference may be related to a more severe disease rather than a direct effect of the steroid, which should be explored in future studies since there is inconclusive information on the role of dexamethasone in neonatal meningitis [4,5,26].

Predictors of death were early onset, low birth weight, use of inotropes, central venous catheter, and somnolence or coma, factors that are probably related to the disease severity and could -predict death in 94% of cases; with a Hosmer-Lemeshow test significance of .616. This results are similar to those described in industrialized countries where the use of inotropes, presence of coma, seizures lasting >72h, and leukopenia ≤ 5000 x 109 in the first 96h of admission were predictors of death, with an 88% sensitivity and 99% specificity [14]. Leukopenia in this study was highly associated to death in the bivariate analysis; however it was not identified as a risk factor in the model [39,40]. The model in this study may be used to stratify the severity of the illness at admission of patients with characteristics similar to our population.

Neurologic sequelae developed in 67% of survivors. In one-third they were severe, mainly motor impairment or mental retardation. Sequelae were more frequent in the last study period, probably related to a higher survival rate among severely ill children who might have died in previous periods.

Low hemoglobin, generalized seizures, probably due to the effect of hypoxia in the central nervous system and neurologic complications were significant risk factors for the development of neurologic sequelae (OR .776, 4.34, and 5.07 respectively). The B coefficient for hemoglobin is less than 1 indicating that as hemoglobin increases less risk to develop neurological sequelae. Seizures have clearly been associated in other studies with adverse outcomes; however anemia and neurologic complications have not been reported.

The improvement in survival may be reflect an improvement in supportive care and change in antibiotics; therapy however this has been associated with a higher incidence of neurological sequelae.

This is the first report exploring the risk factors for mortality of new born infants with bacterial meningitis mainly due to gram negative organisms.

This report will contribute to expand the knowledge of the etiology of NBM and risk factors for morbidity and mortality in areas with similar conditions to ours. In addition it provides information to help identify interventions, new treatments, antibiotics and molecular target therapies to reduce the complex inflammatory response in these infections to improve the outcome of patients. Finally it highlights the need for vaccines and other interventions to prevent these infections.

Conclusion

The main risk factors for NBM death were: early onset, low birth weight, altered consciousness at admission, use of inotropes and central venous catheter.

The main risk factors for neurodevelopment sequelae were: low hemoglobin, generalized seizures during hospitalization, and the presence of neurologic complications.

The observed mortality reduction trough the three periods studied can be possibly attributed to the use of more efficacious antibiotics, improved intensive care management, and use of medical technologies for early diagnosis and management of neurological complications.

The use of TGC was associated with a significant decrease in mortality but not in morbidity.

In this study, TGC appears to be the most appropriate antibiotics for the initial treatment of NBM where gram negatives organism with sensitivity to these antibiotics are predominant.

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