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ORIGINAL ARTICLE

Invasive meningococcal disease in children and adults in a tertiary level hospital. Recent epidemiology and prognostic factors☆,☆☆

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Neisseria meningitidis;
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Abstract
Introduction: Invasive meningococcal disease (IMD) has a high morbidity and mortality in children and adults. The aim of this study was to describe the clinical and epidemiological characteristics of patients with IMD, to compare them among children and adults, and to determine prognostic factors and changes in epidemiology during a 14-year period.
Methods: A retrospective study was conducted on patients admitted to a third level hospital with IMD between 2004 and 2017. An analysis was made of the clinical, epidemiological and microbiological data.
Results: A total of 84 patients were diagnosed with IMD, of which 50 (59.5%) were children. Median age was 2 years (IQR 0.7–7.5) for children and 41.2 years (IQR 26.4–69.3) for adults. Diagnosis was bacteraemia in 47 patients (56%), meningitis in 24 (28.6%), and both in 13 (15.5%). Serogroup B (MenB) was the most common cause of IMD (40.5%), followed by serogroup C (MenC) in 15.5%, which was more common among adults (26.5% vs 8%, $P = .022$). Incidence rate decreased between 2004–2010 and 2011–2017, from 3.14 to 1.33 cases/100 000 emergencies attended in the study hospital ($P < .001$). Eighty-four percent of children had received ≥1 dose of vaccine against MenC, with none against MenB. Children had higher proportion of ICU admissions

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◊ Appendix A lists the members of the Study Group on Invasive Meningococcal Disease and the institutions they are affiliated to.

(78% vs 44.1%, *P* = .001). Mortality was slightly higher in adults (11.8% vs 2.0%, *P* = .153). Adverse outcomes (sequelae or mortality) were independently associated with intubation and thrombocytopenia, while disease severity with leukopenia and purpuric rash.
Conclusions: IMD incidence has decreased in our setting, with MenB being the most common serogroup. The higher prevalence of MenC in adults was probably related to lower vaccination coverage. According to this study, thrombocytopenia, leukopenia, and purpuric rash were parameters associated with worse outcome.

PALABRAS CLAVE
Neisseria meningitidis;
Sepsis;
Meningitis;
Morbilidad;
Epidemiología

Enfermedad meningocócica invasiva en niños y adultos en un hospital terciario: epidemiología reciente y factores pronósticos

Resumen
Introducción: La enfermedad meningocócica invasiva (EMI) supone una causa importante de morbimortalidad en niños y adultos. Objetivo principal: describir las características clínicas y epidemiológicas de los pacientes con EMI. Objetivos secundarios: describir las diferencias entre niños y adultos, factores pronósticos y cambios epidemiológicos en los últimos 14 años.
Métodos: Estudio retrospectivo realizado en un hospital terciario. Se incluyeron los pacientes diagnosticados de EMI entre 2004 y 2017, recogiéndose datos epidemiológicos, clínicos y microbiológicos.
Resultados: Fueron diagnosticados 84 pacientes con EMI, 50 (59,5%) niños. Edad mediana en niños 2 años (RIC: 0,7-7,5) y adultos 41,2 años (RIC: 26,4-69,3). Bacteriemia en 47 casos (56%), meningitis en 24 (28,6%) y ambas en 13 (15,5%). Predominio del serogrupo B (MenB), en el 40,5%, seguido del serogrupo C (MenC), en el 15,5%, con mayor proporción de MenC en adultos (26,5 vs. 8%; p = 0,022). Disminución en la incidencia de 2004-2010 a 2011-2017, pasando de 3,14 a 1,33 casos/100.000 urgencias en el centro de estudio (p < 0,001). El 84% de los niños había recibido ≥ 1 dosis de vacuna frente a MenC, ninguno frente a MenB. Mayor proporción de ingreso en UCI en niños (78 vs. 44,1%; p = 0,001). Tendencia a mayor letalidad en adultos (11,8 vs. 2%; p = 0,153). La intubación y la trombocitopenia fueron factores de riesgo independientes de desenlace adverso, y la leucopenia y el exantema purpúrico de gravedad.
Conclusiones: Se objetivó un descenso en la incidencia de EMI, siendo MenB el mayoritario. El mayor porcentaje de MenC en adultos probablemente esté relacionado con una menor cobertura vacunal. La trombocitopenia, la leucopenia y el exantema purpúrico fueron factores de riesgo relacionados con peor pronóstico.

Introduction

Invasive meningococcal disease (IMD), despite advances in its prevention and treatment, continues to be a serious health problem due to its high morbidity and mortality.[1] The main preventive strategy that has achieved a reduction in mortality due to IMD is vaccination. In Spain, immunisation with the meningococcal group C (MenC) conjugate vaccine has resulted in a substantial decrease in the incidence of IMD,[2] and group B meningococcus (MenB) is the most prevalent serogroup at present.[2] The MenB and MenACWY vaccines have been recently included in the immunisation schedule for use in the general population, and are expected to further reduce the incidence of IMD in Spain.[3,4]

The primary objective of our study was to describe the clinical and epidemiological characteristics of patients admitted to a tertiary care hospital due to IMD, as well as the microbiological characteristics of isolates obtained in these patients. The secondary objectives were to assess the differences between the paediatric and the adult populations, identify predictors for poorer clinical outcomes and describe epidemiological trends in the past 14 years.

Methods

We conducted a retrospective study in a tertiary care hospital in Madrid that has 120 paediatrics beds (age <17 years) and 1100 adult beds that manages an average of 60 000 paediatric emergency visits and 160 000 adult emergency visits a year.

We included patients with a final diagnosis of confirmed or probable IMD admitted to hospital between January 1, 2004 and December 31, 2017. We classified cases based on the definitions established by the Centers for Disease Control and Prevention[5]:

- Confirmed IMD: isolation of *Neisseria meningitidis* in culture or its detection by polymerase chain reaction (PCR) in a sample of fluid from a normally sterile site.
- Probable IMD: presence of compatible clinical picture (e.g. purpura fulminans) in the absence of microbiological confirmation.

We classified patients based on age as children (<17 years) or adults (≥17 years). We identified cases using the register of isolates of *N. meningitidis* of the Laboratory of Microbiology and the discharge summary database of the hospital, searching for patients with a discharge diagnosis of meningococcal infection documented with codes 036.0 to 036.9 of the International Classification of Diseases, Ninth Revision (ICD-9).[6] For each case, we reviewed the health records to collect data on demographic variables, clinical presentation, laboratory results at admission, admission to the intensive care unit (ICU), microbiological results, length of stay and outcomes, including the presence of sequelae at discharge or identified during the outpatient followup.

We classified the clinical presentation as (a) meningitis, (b) bacteraemia/sepsis or (c) a combination of both. We defined meningitis as detection of *N. meningitidis* in cerebrospinal fluid (CSF) by culture or PCR or pleocytosis in CSF based on normal ranges applicable to the patient's age (>20 polymorphonuclear white blood cells [WBCs]/μL in patients <1 month and >5 polymorphonuclear WBCs/μL in patients >1 month). We defined bacteraemia/sepsis as isolation of *N. meningitidis* in blood culture or presence of purpura fulminans in a patient with compatible manifestations and sterile cultures. Last of all, we defined severe disease as need of invasive ventilatory and/or haemodynamic support, and adverse outcome as death or development of sequelae.

N. meningitidis isolates were identified by standardised techniques (biochemical tests and/or MALDI-TOF mass spectrometry) and typed by means of the kit BD Directigen Meningitidis Combo Test (BectonDickinson; Sparks, MD, USA) in the Microbiology Laboratory of our hospital. In addition, the laboratory subsequently submitted all isolated strains to the reference laboratory of the Centro Nacional de Microbiología (National Centre of Microbiology) to confirm the capsular serotype. The antimicrobial susceptibility was assessed by the broth microdilution method using commercially available Sensititre STRHAE2 plates (ThermoScientific, West Sussex, United Kingdom) in cation-adjusted Mueller-Hinton broth supplemented with 5% horse blood lysate. We applied the susceptibility cut-off points recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[7] Production of β-lactamase was assessed with nitrocefin disks (Cefinase, BectonDickinson; Sparks, MD, USA). Direct detection in CSF by PCR was performed using the RealCycler Universal kit (Progenie Molecular; Valencia, Spain).

Statistical analysis

We performed a descriptive analysis, summarising categorical variables as absolute frequencies and percentages and continuous variables as median and interquartile range (IQR). We compared categorical variables by means of the χ^2 or Fisher test and continuous variables with the Mann–Whitney *U* test after determining by means of the Kolmogorov–Smirnov test that the data distributions were not normal. We assessed the association of clinical, laboratory and demographic variables with patient outcomes (disease severity and poor outcome) with univariate analyses. In the analysis of sequelae, we excluded patients that died. We fitted a multivariate logistic regression model with the variables included in the univariate analyses to predict the risk of severe disease and adverse outcome. We included in the model the variables corresponding to *P*-values of less than .10 in the univariate analysis or that we considered likely to have an effect based on biological principles and the previous literature.[8] We included variables in the predictive model by a stepwise method, successively eliminating those with weaker associations (likelihood of outcome determined by applying a level of significance of 0.10 in the Wald test). We performed the statistical analysis with the software SPSS® version 22 (Chicago, USA). We defined statistical significance as a *P*-value of less than .05.

Results

During the period under study, 84 patients received a final diagnosis of IMD, confirmed in 72 cases (85.7%) and probable in 12 (14.3%). Fifty patients (59.5%) were children and 34 (40.5%) adults, with an overall predominance of the male sex (56%), although with a higher proportion of female patients in the adult subset compared to the paediatric subset (58.8% vs 34%; *P* = .024). Thus, there was a predominance of boys in the paediatric subset (1.9:1) compared to a mild predominance of women in the adult subset (1:1.4). Of all cases of IMD, 28.6% occurred in children aged less than 2 years. The median age was 2 years in paediatric patients (IQR, 0.7–7.5) and 41.2 years in adult patients (IQR, 26.4–69.3). Figs. 1 and 2 show the age distribution of the total sample and the paediatric subset.

The mean annual incidence of IMD was 2.24 cases per 100 000 visits managed in the emergency department of our hospital. However, we found a progressive decline in the annual absolute frequency of IMD (mean of 8.2 cases/year in 2004–2010 vs 3.14 cases/year in 2011–2017) and its incidence when comparing the first period (2004–2010) with the second (2011–2017), as it decreased from 3.14 cases to 1.33 cases per 100 000 visits managed in the emergency department (*P* < .001).

The most frequent serogroup was MenB (40.5%), followed by MenC (15.5%), with a higher proportion of MenC in the adult subset (26.5% vs 8%; *P* = .022). The serogroup was not identified in 44% of cases. Out of all confirmed cases, 69 (95.9%) were confirmed by culture, 2 (2.8%) by PCR (negative CSF cultures in both cases, with blood culture negative in 1 and not performed in the other) and 1 (1.4%) by both techniques. Table 1 shows the serogroup distribution by age group, and Fig. 3 the annual distribution of cases in the total sample by serogroup.

Of the 64 isolates that were available for antimicrobial susceptibility testing, 43 (67.2%) were fully susceptible to penicillin (minimum inhibitory concentration [MIC] ≤0.06 mg/L). The MICs for penicillin in the remaining isolates ranged between 0.12 and 1 mg/L. None of the isolates tested positive for β-lactamase production and all

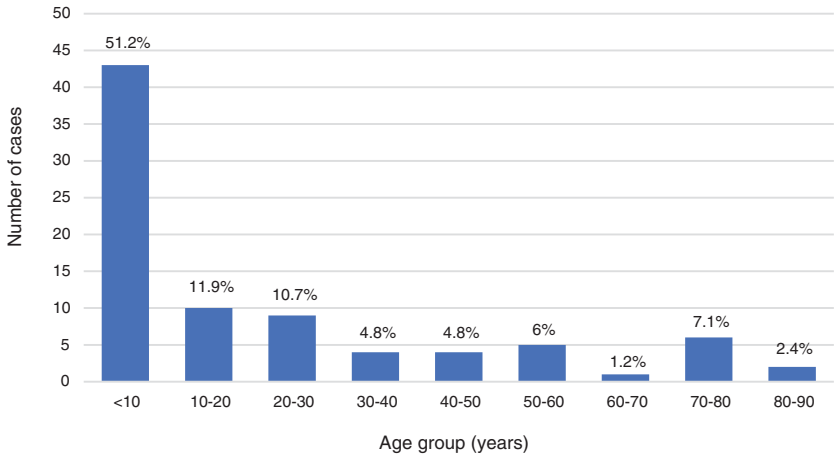

Figure 1 Age distribution (age in years) in the total sample. Proportions calculated over the total sample.

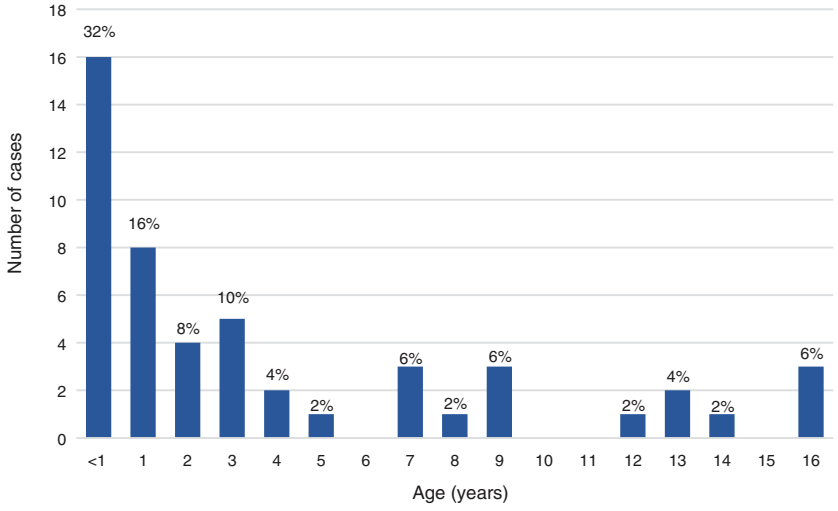

Figure 2 Age distribution (age in years) in the paediatric subset of the sample (age <17 years). Proportions calculated over the total paediatric subset.

Table 1 Serogroup distribution by age group.

Serogroup	Children($n = 50$)	Adults($n = 34$)	Total($n = 84$)	*P*
Group B	25 (50%)	9 (26.5%)	34 (40.5%)	.031
Group C	4 (8%)	9 (26.5%)	13 (15.5%)	.022
Nontypeable/untyped	21 (42%)	16 (47.1%)	37 (44%)	.647

were fully susceptible to cefotaxime, ciprofloxacin and rifampicin.

When it came to vaccination against MenC, of all children with a known vaccination status, 26/32 (81.3%) were correctly vaccinated for their age, 4/32 (12.5%) had incomplete vaccination and 2/32 (6.2%) had not received any of the doses scheduled for their age. None were vaccinated against MenB. Information on vaccination in adult patients was only available in 2 cases, and 1 of these patients had been vaccinated.

The diagnosis was bacteraemia/sepsis in 47 cases (56%), meningitis in 24 (28.6%) and both in 13 (15.5%), without significant differences between children and adults. Table 2 compares the clinical presentation and laboratory findings of IMD in both age groups. Most patients presented with fever (96.4%). Purpuric rashes were more frequent in children (69% vs 29.4%; $P = .006$). A higher proportion of children required inotropic agents (42% vs 20.6%; $P = .041$).

When we compared confirmed and probable cases (Table 3), the only difference we found was the higher proportion manifesting with a purpuric rash in the subset of patients with probable IMD (75% vs 43.1%; $P = .040$) and a higher prevalence of fever before admission in confirmed cases (98.6% vs 83.3%; .052).

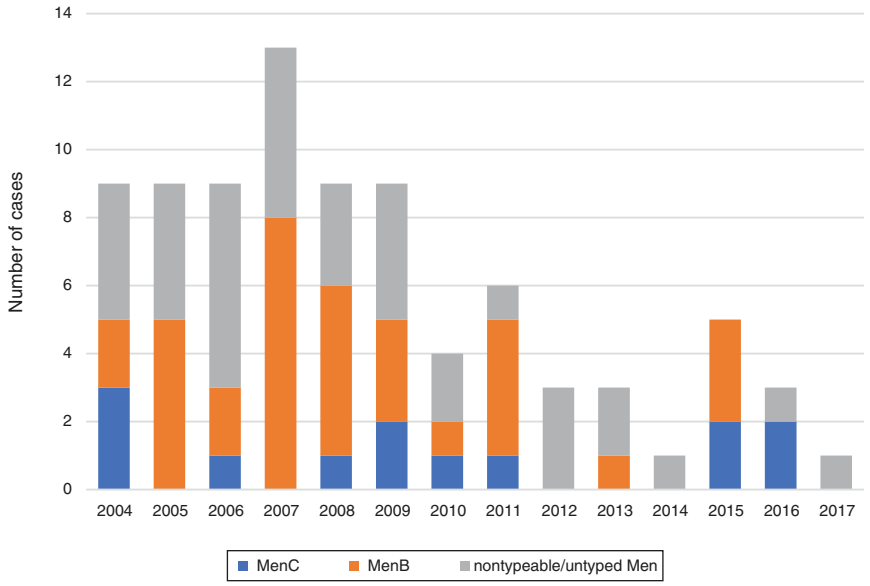

Figure 3 Annual distribution of cases by serotype.

A higher proportion of children required admission to the ICU compared to adults (78% vs 44.1%; $P = .001$). The mean duration of antibiotherapy was 9.8 days (IQR, 7–11 days), the mean length of stay was 10 days (IQR, 7–13 days), and the mean length of stay in the ICU was 2 days (IQR, 1–3.7 days), with no differences between children and adults. In the total sample, 34.5% of patients received dexamethasone as adjuvant therapy. There were 5 deaths (6% of the total sample). All of these patients died within 24 h of admission. Mortality was higher in adult patients, although this difference was not statistically significant (4/34 [11.8%] vs 1/50 [2%], $P = .153$). Of these 5 patients, 3 had infection by MenB and 1 by a nontypeable strain, while *N. meningitidis* was not isolated in the remaining patient.

Of all survivors, 12/79 (15.2%) had sequelae after discharge, including 8/49 children (16.3%) and 4/30 adults (13.3%), with no differences based on age. The sequelae were cosmetic in 7 patients (8.3%), orthopaedic in 7 (8.3%), neurologic in 3 (3.6%) and renal in 3 (3.6%), and 1 patient had hearing loss (1.2%). In the subset of survivors, there were no significant differences in the development of sequelae between those infected by MenC (4/13; 30.8%) and those infected by MenB (7/31; 22.6%), while sequelae were significantly less frequent in patients with infection by untyped/nontypeable strains (1/35; 9%; $P = .015$ and 0.021 for the comparison with MenC and MenB, respectively).

In the univariate analysis, the presence at diagnosis of a purpuric rash, a low WBC count, a high activated partial thromboplastin time or thrombocytopaenia were risk factors for severe disease and adverse outcome (Tables 4 and 5). Furthermore, isolation of *N. meningitidis* in blood culture and the need of inotropic therapy or ventilatory support were also risk factors for an adverse outcome. Severe disease was associated with an increased risk of sequelae (OR, 33.69; $P < .001$). In the multivariate analysis, a WBC count of less than $<5 \times 10^9$ cells/L (OR, 15.64; 95% confidence interval [CI], 1.68–145.8; $P = .016$) and the presence of a purpuric rash (OR, 3.42; 95% CI, 1.02–11.51]; $P = .047$) were independent risk factors for severe disease, while the need for endotracheal intubation (OR, 73.02; 95% CI, 8.08–659.8; $P < .001$) and thrombocytopaenia with a platelet count of less than 150×10^9/L (OR, 24.66; 95% CI, 2.77–219.28; $P = .004$) were independent risk factors for adverse outcome.

Discussion

Our study, conducted in a tertiary care hospital, reflects the shift in the epidemiology of IMD in Spain in the past few decades and has been the first in our country comparing the characteristics of IMD in children and adults. Between 2004 and 2017, the incidence of IMD in the population under study decreased by 50% in both children and adults. Of all cases, 59.5% occurred in the paediatric population, mainly in children aged less than 2 years, and MenB was the most prevalent serotype in children, compared to MenC in adults. The criteria for severe disease were met by 40.5% of cases, while 20.2% had an adverse outcome. The mortality was higher in the adult subset. The presence of purpuric rash, low WBC count and thrombocytopaenia at diagnosis were risk factors for having an adverse outcome.

The inclusion of vaccination against MenC in the routine immunisation schedule has played an essential role in the reduction of the incidence of IMD in Spain. In our sample, MenB was the predominant serogroup, although the proportion of cases of MenC was higher in adults (26.5% vs 8%; $P = .022$). Most children in the sample (84%) had received at least 1 dose of MenC vaccine. On the other hand, we were unable to determine the vaccination status of most of the adults. The higher incidence of MenC in the adult subset could be explained by a lower vaccination coverage in this age group. However, we could not test this hypothesis because the documentation of the vaccination history in most of the adult patients in the sample was incomplete.

The serogroup involved in most of the cases detected in our case series was MenB (40.5%). As observed in other studies,[9] the decline in the number of cases caused by this serogroup occurred before the introduction of the vaccine in the immunisation schedule in 2015. This situation has

Table 2 Comparison of characteristics in children and adults.

	Total $n = 84$ (100%)	Children $n = 50$ (59.5%)	Adults $n = 34$ (40.5%)	*P*
Demographic data				
Age (years)	41.2 (26.4–69.3)	2 (0.7–7.5)	41.2 (26.4–69.3)	
Sex (male)	47 (56%)	33 (66%)	14 (41.2%)	**.024**
Confirmed cases	72 (85.7%)	41 (82%)	31 (91.2%)	.238
Clinical manifestations				
Diagnosis				
Meningitis	24 (28.6%)	15 (30%)	9 (26.5%)	.942
Bacteraemia	47 (56%)	26 (52%)	21 (61.8%)	
Meningitis and bacteraemia	13 (15.5%)	9 (18%)	4 (11.8%)	
Fever	81 (96.4%)	49 (98%)	32 (94.1%)	.347
Purpuric rash	40 (47.6%)	30 (69%)	10 (29.4%)	**.006**
Meningeal signs	25 (29.8%)	15 (30%)	10 (29.4%)	.954
Altered mental status	37 (44%)	22 (44%)	15 (44.1%)	.991
Low blood pressure	36 (42.9%)	24 (48%)	12 (35.3%)	.248
Hypoxaemia	23 (27.4%)	11 (22%)	12 (35.3%)	.230
Vomiting	33 (39.3%)	22 (44%)	11 (32.4%)	.283
Headache	25 (29.8%)	12 (24%)	13 (38.2%)	.161
Painful swallowing	8 (9.5%)	4 (8%)	4 (11.8%)	.564
Cough	5 (6.0%)	0 (0%)	5 (14.7%)	**.005**
Seizures	2 (2.4%)	2 (4%)	0 (0%)	.238
Treatment				
Oxygen therapy	13 (15.5%)	7 (14%)	6 (17.6%)	.650
Inotropic therapy	28 (33.3%)	21 (42%)	7 (20.6%)	**.041**
Endotracheal intubation	22 (26.2%)	11 (22%)	11 (32.4%)	.289
Dexamethasone	29 (34.5%)	17 (34%)	12 (35.3%)	.670
Third generation cephalosporins	80 (95.2%)	50 (100%)	30 (88.2%)	**.013**
Other antibiotics	4 (4.8%)	0	4 (11.8%)	**.013**
Laboratory features				
Leukocytes ($\times 10^9$/L)	12.5 (7.8–19)	11.6 (7.8–21.4)	13.7 (6.9–18.3)	.964
Neutrophils ($\times 10^9$/L)	10.6 (4.9–17.5)	9.68 (3.6–18.3)	13.1 (5.1–17.1)	.625
Platelets ($\times 10^9$/L)	191.5 (134.5–308.7)	220 (142–327)	173 (106.5–236.5)	.053
CPR (mg/dL)	10.7 (3.9–22.1)	10.7 (3.7–21.2)	11.1 (7.9–24)	.471
Procalcitonin (ng/mL)	12.3 (1.6–46.6)	9.4 (2.7–36.5)	25.5 (0.4–76.2)	.964
aPTT (seg.)	32.6 (29.1–41.4)	33.9 (29.9–36.5)	27.6 (25.9–32.7)	**.007**
INR	1.4 (1.2–1.7)	1.5 (1.3–1.8)	1.3 (1–1.4)	**.026**

aPTT, activated partial thromboplastin time; CPR, C-reactive protein.
Statistically significant differences are presented in boldface.
We have expressed categorical variables as absolute frequencies and percentages (%) and continuous variables as median and interquartile range.

already been described in the rest of Europe, where we are witnessing the lowest incidence of IMD due to MenB in the past 20 years.[10] However, this serogroup characteristically emerges in epidemic waves, which, added to the considerable morbidity and mortality associated with IMD, underscores the importance of vaccination, even in periods with a low incidence.

In recent years, the incidence of IMD caused by serogroups Y and W has increased worldwide,[11] accounting for up to 50% of cases of IMD in some European countries.[12] This trend has also been observed in Spain, with a surge of cases caused by serogroup W,[13] which increased 4-fold in the 2015–2016 season compared to the previous season.[14] In our study, we found no cases caused by serogroups W or Y. However, since some of the strains were not available for serotyping, we cannot rule out the presence of these serotypes in our case series. We find the high percentage of cases in which *N. meningitidis* was isolated in culture without subsequent identification of the serotype surprising (24/84; 28.6%). One possible explanation is that the isolates were typed in the reference laboratory of the Centro Nacional de Microbiología but the results were not entered in the patients' electronic health records.

The mortality of IMD ranges between 3.5% and 15% depending on the population and is higher in adults.[8,9,15,16] In our study, the overall mortality was 6%, with a higher proportion in adults compared to children (11.8% vs 2%). These data are similar to those reported by a recent study conducted in Canada (overall mortality of 8.4%; 4% in children and 12% in adults).[8] All deaths occurred within 24 h of admission, which

Table 3 Comparison of characteristics of confirmed versus probable cases.

	Total $n = 84$ (100%)	Confirmed $n = 72$ (85.7%)	Probable $n = 12$ (14.3%)	*P*
Demographic characteristics				
Age (years)	9.6 (1.4–36.1)	13.8 (1.4–39.3)	5.1 (1.3–23.3)	.399
Age group (children)	50 (59.5%)	41 (56.9%)	9 (75%)	.345
Sex (male)	47 (56%)	42 (58.3%)	5 (41.7%)	.282
Clinical manifestations				
Diagnosis				
Meningitis	24 (28.6%)	20 (27.8%)	4 (33.3%)	1.000
Bacteraemia	47 (56%)	41 (56.9%)	6 (50%)	
Meningitis and bacteraemia	13 (15.5%)	11 (15.3%)	2 (16.7%)	
Fever	81 (96.4%)	71 (98.6%)	10 (83.3%)	.052
Purpuric rash	40 (47.6%)	31 (43.1%)	9 (75%)	.040
Meningeal signs	25 (29.8%)	20 (27.8%)	5 (41.7%)	.329
Altered mental status	37 (44%)	30 (41.7%)	7 (58.3%)	.282
Low blood pressure	36 (42.9%)	29 (40.3%)	7 (58.3%)	.242
Hypoxaemia	23 (27.4%)	11 (22%)	12 (35.3%)	.230
Vomiting	33 (39.3%)	28 (38.9%)	5 (41.7%)	1.000
Headache	25 (29.8%)	22 (30.6%)	3 (25%)	1.000
Painful swallowing	8 (9.5%)	7 (9.7%)	1 (8.3%)	1.000
Cough	5 (6%)	5 (6.9%)	0 (0%)	1.000
Seizures	2 (2.4%)	2 (2.8%)	0 (0%)	1.000
Treatment				
Oxygen therapy	13 (15.5%)	11 (15.3%)	2 (16.7%)	1.000
Inotropic therapy	28 (33.3%)	23 (31.9%)	5 (41.7%)	.523
Endotracheal intubation	22 (26.2%)	17 (23.6%)	5 (41.7%)	.285
Admission to ICU	54 (64.3%)	44 (61.1%)	10 (83.3%)	.197
Dexamethasone	29 (34.5%)	25 (34.7%)	4 (33.3%)	1.000
Laboratory features				
Leukocytes ($\times 10^9$/L)	12.5 (7.8–19)	12.8 (6.8–20.6)	10.7 (8.6–14)	.450
Neutrophils ($\times 10^9$/L)	10.6 (4.9–17.5)	11.2 (4–18.1)	7.7 (5.7–12.3)	.407
Platelets ($\times 10^9$/L)	191 (134–309)	189 (131–325)	196 (140–217)	.459
CPR (mg/dL)	10.7 (3.9–22.1)	10.2 (3.8–24)	10.8 (5.3–14.6)	.644
Procalcitonin (ng/mL)	12.3 (1.6–46.6)	18.9 (1.3–49.1)	6.5 (2.5–70.8)	.964
aPTT (seg.)	32.6 (29.1–41.4)	31.9 (28.1–41.9)	33.3 (30.7–39.3)	.687
INR	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.4 (1.2–1.7)	.921
Outcome				
Sequelae	12 (14.3%)	11 (15.3%)	1 (8.3%)	1.000*
Death	5 (6%)	4 (5.6%)	1 (8.3%)	.547

aPTT, activated partial thromboplastin time; CPR, C-reactive protein.
Statistically significant differences are presented in boldface.
We have expressed categorical variables as absolute frequencies and percentages (%) and continuous variables as median and interquartile range.
* No differences in *P*-values after excluding cases ending in death.

demonstrates the fulminant course of lethal cases already described in other studies, in which the deaths occurred in the first 48 h.[8,17]

There is evidence that MenC is associated with more severe disease and a higher mortality,[8] although in our case series none of the deaths were associated with this serogroup. In our population, thrombocytopaenia and endotracheal intubation were risk factors for an adverse outcome (death or sequelae). Several previous studies have analysed the presence of risk factors for a poor outcome and have reported an association with low WBC count,[8,18–20] thrombocytopaenia,[8,21] shock,[8,18,20,22] coagulopathy,[19,22,23] petechiae,[18,20] ecchymotic rash[8] or coma.[17,22] The early identification of clinical or laboratory features associated with a poorer prognosis could be useful to identify patients requiring even closer monitoring.

Some studies have found better outcomes in patients managed in the ICU,[8,24,25] although we found no evidence of this association in our case series. In our study, the proportion of patients admitted to the ICU was greater in the paediatric age group. Numerous studies have described an increase in survival when the initial stabilisation is

Table 4 Univariate and multivariate analysis of factors associated with severity at diagnosis (need of mechanical ventilation and/or inotropic therapy).

Variable	Univariate analysis			Multivariate analysis[a]	
	Severe cases (%) $n = 34$ (40.5%)	OR (95% CI)	*P*	aOR (95% CI)	*P*
Sex (male)					
Female	14 (27.8%)				
Male	20 (42.6%)	1.22 (0.50–2.94)	.662		
Age group					
Child	21 (61.8%)				
Adult	13 (38.2%)	0.79 (0.32–1.92)	.599		
Type of case					
Probable	8 (66.7%)				
Confirmed	26 (36.1%)	0.28 (0.08–1)	.006		
Purpuric rash					
No	10 (22.7%)				
Yes	24 (60%)	5.10 (1.98–13.15)	.001	3.42 (1.02–11.51)	.047
Meningeal signs					
No	21 (35.6%)				
Yes	13 (52%)	1.96 (0.76–5.06)	.161		
Dexamethasone					
No	18 (34%)				
Yes	11 (42.3%)	1.43 (0.54–3.74)	.470		
Isolation from CSF[b]					
Negative	16 (43.2%)				
Positive	5 (20%)	0.33 (0.10–1.06)	.058		
Blood culture					
Negative	11 (39.3%)				
Positive	23 (41.8%)	1.11 (0.44–2.81)	.824		
Group B					
No MenB	21 (42%)				
MenB	13 (38.2%)	0.86 (0.35–2.08)	.730		
Group C					
No MenC	29 (40.8%)				
MenC	5 (38.5%)	0.90 (0.27–3.05)	.872		
Untyped/nontypeable					
Typeable	18 (38.3%)				
Not typed	16 (43.2%)	1.23 (0.51–2.95)	.647		
Leukopenia ($<5 \times 10^9$/L)					
No	21 (30%)				
Yes	13 (92.9%)	30.33 (3.72–247.02)	<.001	15.64 (1.68–145.8)	.016
Thrombocytopenia ($<150 \times 10^9$/L)					
No	19 (32.2%)				
Yes	15 (60%)	3.16 (1.20–8.32)	.018		
Prolonged aPTTP >34 s					
No	18 (29.5%)				
Yes	16 (69.6%)	5.46 (1.92–15.52)	.001		
Prolonged INR >1.2					
No	13 (31.7%)				
Yes	21 (48.8%)	2.06 (0.84–5.00)	.110		

aOR, adjusted odds ratio (multivariate analysis); aPTT, activated partial thromboplastin time; CI, confidence interval; CSF, cerebrospinal fluid; INR, international normalised ratio; OR, odds ratio.

We have expressed categorical variables as absolute frequencies and percentages (%) and continuous variables as median and interquartile range.

Variables included in the multivariate analysis are presented in boldface.

[a] Final multivariate model.

[b] Isolation of *N. meningitidis* by culture or identification by polymerase chain reaction (PCR).

Table 5 Univariate and multivariate analysis of the factors associated with an adverse outcome (death and/or sequelae).

Variable	Univariate analysis			Multivariate analysis[a]	
	Cases with adverse outcomes (%) $n = 17$ (20.2%)	OR (95% CI)	*P*	aOR (95% CI)	*P*
Sex					
Female	8 (21.6%)				
Male	9 (19.1%)	0.86 (0.29–2.50)	.779		
Age group					
Child	9 (18.4%)				
Adult	8 (22.9%)	1.32 (0.45–3.84)	.614		
Type of case					
Probable	2 (16.7%)				
Confirmed	15 (20.8%)	1.81 (0.37–8.90)	.739		
Purpuric rash					
No	**3 (6.8%)**				
Yes	**14 (35%)**	**7.36 (1.93–28.11)**	**.001**		
Meningeal signs					
No	12 (20.3%)				
Yes	5 (20%)	0.98 (0.30–3.15)	.972		
Dexamethasone					
No	9 (16.4%)				
Yes	8 (27.6%)	1.95 (0.66–5.75)	.224		
Isolation from CSF[b]					
Negative	8 (21.6%)				
Positive	2 (8%)	0.31 (0.06–1.63)	.153		
Blood culture					
Negative	**2 (7.1%)**				
Positive	**15 (27.3%)**	**4.87 (1.03–23.10)**	**.032**		
Group B					
No MenB	**7 (14%)**				
MenB	**10 (29.4%)**	**2.56 (0.86–7.59)**	**.084**		
Group C					
No MenC	13 (18.3%)				
MenC	4 (30.8%)	1.98 (0.53–7.44)	.304		
Nontypeable/untyped					
Typed	14 (29.8%)				
Not typed	3 (8.1%)	0.21 (0.05–0.79)	.014		
Admission to ICU					
No	**2 (6.7%)**				
Yes	**15 (27.8%)**	**5.38 (1.14–25.45)**	**.021**		
Leukopenia (<5 × 10^9/L)					
No	**8 (11.4%)**				
Yes	**9 (64.3%)**	**13.95 (3.73–52.12)**	**<.001**		
Thrombocytopenia (<150 × 10^9/L)					
No	**5 (8.5%)**				
Yes	**12 (48%)**	**9.97 (2.98–33.31)**	**<.001**	**24.66 (2.77–219.28)**	**.004**
Prolonged aPTT >34 s					
No	**8 (13.1%)**				
Yes	**9 (39.1%)**	**4.26 (1.39–13.05)**	**.008**		
Prolonged INR >1.2					
No	7 (17.1%)				
Yes	10 (23.3%)	1.47 (0.50–4.33)	.481		

Table 5 (*Continued*)

Variable	Univariate analysis			Multivariate analysis[a]	
	Cases with adverse outcomes (%) *n* = 17 (20.2%)	OR (95% CI)	*P*	aOR (95% CI)	*P*
Endotracheal intubation					
No	**3 (4.8%)**				
Yes	**14 (63.6%)**	**34.42 (8.08–146.6)**	**<.001**	**73.02 (8.08–659.8)**	**<.001**
Inotropic therapy					
No	**3 (5.4%)**				
Yes	**14 (50%)**	**17.67 (4.45–70.16)**	**<.001**		

aOR, adjusted odds ratio (multivariate model); aPTT, activated partial thromboplastin time; CI, confidence interval; CSF, cerebrospinal fluid; INR, international normalised ratio; OR, odds ratio.
We have expressed categorical variables as absolute frequencies and percentages (%) and continuous variables as median and interquartile range.
Variables included in the multivariate analysis are presented in boldface. We excluded the variable ''nontypeable/untyped serotype'', as it was associated with identification of group B and absence of isolation in culture (in the case of untyped strains), which were variables already included in the multivariate analysis.
[a] Final multivariate model.
[b] Isolation of *N. meningitidis* by culture or identification by polymerase chain reaction (PCR).

optimal and shock management adequate.[25,26] It is essential to ensure that the patient is closely monitored in the early stages of disease, and the patient should be admitted to the ICU if there is any indication of disease progression.[27]

One third of the patients received systemic corticosteroids at the beginning of treatment. Several guidelines recommend the use of steroid therapy in the management of bacterial meningitis.[28] Contrary to the cases caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*, in which the use of steroid therapy appears to improve outcomes,[29] the usefulness of this treatment in cases caused by *N. meningitidis* remains under debate. Some experts[30] recommend the use of corticosteroids in meningococcal meningitis due to the lower mortality found in several studies[29] and the absence of significant associated risks. Nevertheless, the data available to date are not conclusive in demonstrating the benefits of administering corticosteroids to patients with meningococcal meningitis.

The proportion of patients that developed sequelae in our study was 15.6%, and there were no differences between age groups, contrary to the findings of other studies where sequelae were more frequent in children.[8] In previous case series, the most frequent sequelae were neurologic (including hearing loss), skin scarring and amputation of extremities.[31,32] These findings are similar to those of our study, in which cosmetic sequelae were most frequent. However, only 1 patient in our sample had hearing loss.

There are limitations to our study. Its retrospective design impeded the rigorous collection of data for all analysed variables, including the vaccination status of most adults. Due to the small number of cases, the analysis did not have sufficient statistical power to establish the association between severity of IMD and potential risk factors or to perform analysis of specific sample subsets. Furthermore, the collection of data in a single centre provides a limited perspective on the global situation of IMD in Spain. The main strength of the study is that it included and analysed together the paediatric and adult populations, which allowed a comparison of the differential characteristics in both groups.

In conclusion, the incidence of IMD has decreased in our region in recent decades, and MenB is the most prevalent serogroup. Invasive meningococcal disease continues to be more frequent in children, especially infants younger than 1 year, in whom infection by MenB is most prevalent. In opposition, in the adult population, infection by MenC is more frequent, probably due to a lower vaccination coverage in this age group. Despite advances in its diagnosis and treatment, IMD can have a fulminant course and cause serious sequelae, which demands improvement in strategies for prevention and early detection. The detection of risk factors at onset, such as thrombocytopaenia, a low WBC count or a purpuric rash, can help identify patients at increased risk of adverse outcomes.

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Conflicts of interest

The authors have no conflicts of interest to declare

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