Open Forum Infectious Diseases

MAJOR ARTICLE

Invasive Meningococcal Disease: What We Should Know, Before It Comes Back

Carmen Cabellos, Ivan Pelegrín, Eva Benavent, Francesc Gudiol, Fe Tubau, Dolores Garcia-Somoza, Ricard Verdaguer, Javier Ariza, and Pedro Fernandez Viladrich

Infectious Diseases Service and Microbiology Service, Institut d'Investigació Biomédica de Bellvitge–Hospital Universitari de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat, Spain

Background. Invasive meningococcal disease (IMD), sepsis and/or meningitis continues to be a public health problem, with mortality rates ranging from 5% to 16%. The aim of our study was to further knowledge about IMD with a large series of cases occurring over a long period of time, in a cohort with a high percentage of adult patients.

Methods. Observational cohort study of patients with IMD between 1977 hand 2013 at our hospital, comparing patients with only sepsis and those with meningitis and several degrees of sepsis. The impact of dexamethasone and prophylactic phenytoin was determined, and an analysis of cutaneous and neurological sequelae was performed.

Results. A total of 527 episodes of IMD were recorded, comprising 57 cases of sepsis (11%) and 470 of meningitis with or without sepsis (89%). The number of episodes of IMD decreased from 352 of 527 (67%) in the first to 20 of 527 (4%) in the last quarter ($P < .001$). Thirty-three patients died (6%): 8 with sepsis (14%) and 25 with meningitis (5%) ($P = .02$). Cutaneous and neurological sequelae were present in 3% and 5% of survivors of sepsis and meningitis, respectively. The use of dexamethasone was safe and resulted in less arthritis, and patients given prophylactic phenytoin avoided seizures.

Conclusions. The frequency of IMD has decreased sharply since 1977. Patients with sepsis only have the highest mortality and complication rates, dexamethasone use is safe and can prevent some arthritis episodes, and prophylactic phenytoin might be useful in a selected population. A rapid response and antibiotic therapy may help improve the prognosis.

Keywords. Invasive meningococcal disease; sepsis; sequelae

Invasive meningococcal disease (IMD), involving sepsis and/or meningitis, continues to be a public health problem, with an overall mortality rate ranging from 5% to 16%. Meningococcal disease was first described as an outbreak in Geneva, Switzerland, in 1805 [1]. The etiological agent was later identified as *Neisseria meningitidis,* and in the first half of the 20th century there were major advances in therapy and, therefore in prognosis, with the discovery and implementation of sulfonamides and penicillin therapy [2].

Effective vaccines for some of the serogroups were also introduced in the second half of the 20th century [3–5]. Recently, much attention has been focused on serogroup B prevention after the licensure of novel, protein-based, multicomponent vaccines in Europe [6]. However, IMD remains prevalent throughout the world and is a serious health problem. Characteristics of the disease, such as the rapidity with which it may cause death in previously healthy persons, the potentially large size of outbreaks due to person-to-person spread through the air, and hyperendemic situations, make it a dreaded disease and often the cause of tremendous public concern. Several problems and questions remain unresolved: the existence of the "meningitis belt" in sub-Saharan Africa, the treatment of fulminant meningococemia, the widespread availability of effective vaccines, and the best antibiotic therapy and its duration in cases with resistance to penicillin or changes in prevalent serogroups as vaccines are administered.

The epidemiology of IMD is dynamic, and there are continuous changes in its incidence rate and predominant serogroups. In the United States, the annual incidence rate varies in multiyear cyclical waves, from 0.5 to 2.0 cases per 100 000 persons. In sub-Saharan Africa the rate ranged from 10–25/100 000 before the successful use of MenAfriVac and can exceed 500/100 000 during epidemics [7–12].

Endemic disease may be due to one of several serogroups, but 85%–90% of cases are due to serogroups A, B, or C. Serogroups B and C are more common in Europe and the Americas, and serogroups A and C predominate in Africa and Asia [8, 9, 13, 14]. There has been a remarkable increase in invasive capsular group W disease causing severe disease in England and Wales in recent years [15], as also observed in other European countries

Received 4 December 2018; editorial decision 30 January 2019; accepted 5 February 2019.

Correspondence: Carmen Cabellos, Infectious Disease Department, Hospital Universitari de Bellvitge, 08907 L'Hospitalet de Llobregat, Barcelona, Spain (ccabellos@bellvitgehospital.cat).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofz059

and in Chile, Argentina, and South Africa [16]. Serogroup Y was most common in Japan [16]. Recently, a higher incidence and several clusters of meningococcal disease have been described among men who have sex with men [17]. In Spain, endemic cases are mostly due to serogroup B. The last epidemic outbreak was in 1996–1997 and was due to serogroup C; as a consequence, meningococcal C conjugate vaccine was introduced to the childhood vaccination schedule in 2000 [18]. In Catalonia, the rate in 2016 was 0.8/100 000 but had been as high as 18.6/100 000 in 1979 [19].

Besides vaccination, the key means of prevention, early recognition and aggressive treatment are the only effective measures against this invasive disease. The immediate administration of antibiotic therapy and the recognition and treatment of patients who may have complications of IMD, such as shock, raised intracranial pressure, or both, are required in order to prevent death. As meningococcal disease incidence fluctuates, knowledge about the disease and the responsiveness necessary to act effectively in a new case may be scarce in new generations of health personnel. The objective of the present study was to increase knowledge about IMD with a large series of cases occurring over a long period of time, in a cohort with a high percentage of adult patients.

METHODS

Patients

This was an observational cohort study of patients admitted to our hospital from 1977 to 2013 with IMD. The Hospital Universitari de Bellvitge is a large university hospital in Barcelona. Since 1977, all cases of bacterial meningitis or IMD have been routinely recorded in a 120-variable protocol. For the purpose of the present study, we selected all episodes of IMD, with or without meningitis. An episode was considered to have occurred when there were clinical findings of sepsis and/or meningitis and *N. meningitidis* was isolated in blood, cerebrospinal fluid (CSF), pharyngeal swab, or joint fluid samples, or, in the absence of positive cultures, when gram-negative diplococci were detected from the CSF Gram stain or when patients presented with findings of acute bacterial meningitis or sepsis with characteristic skin lesions; both confirmed and possible cases are included. Patients with IMD were classified as those with sepsis (meningococcal disease without meningitis) and those with meningitis. Meningitis was diagnosed based on inflammatory CSF parameters, white blood cell (WBC) count ≥5/μL, or positive CSF culture. Patients with meningitis manifested varying symptoms and signs of the sepsis criteria, ranging from none to septic shock.

From 1977 to 1994 our hospital admitted patients as young as 7 years. Since 1994, however, only patients aged ≥14 years have been admitted. From 1987, all patients with either suspected pneumococcal meningitis or another type of bacterial meningitis with CSF pressure ≥30 cm H_2O were systematically treated with dexamethasone (4 mg/6 h for 48 hours, initiated before or combined with the first antibiotic dose), and from 2002 onward dexamethasone was widely used to treat bacterial meningitis, so several of our patients received this drug in the first 48 hours, always at the same dose (4 mg/6 h). Prophylaxis of seizures with phenytoin has also been carried out in patients with suspected pneumococcal meningitis or CSF pressure ≥30 cm H_2O since 1987, so several patients who had meningococcal meningitis received this prophylaxis.

All patients were evaluated daily and underwent complete hematological counts and biochemical tests within 48 hours of admission, during hospitalization, and once more at the outpatient clinic. All patients surviving IMD were monitored at the outpatient clinic and were followed up until resolution of all symptoms or their consideration as permanent sequelae 1 year after the initial infection.

Deaths during hospitalization were recorded. The mechanism of death was classified as early (first 48 hours) sepsis or neurological or late neurological or nonneurological (due to complications other than neurological problems). Lesions requiring plastic surgery repair or amputation were considered cutaneous sequelae. Neurological sequelae were considered at 1 year. The duration of therapy was 7 days from 1977 to 1983 and 4 days from 1984 to 2013 [20, 21].

The isolates were identified using conventional microbiological methods [22]. Antibiotic susceptibility was systematically determined from 1993 (1 strain per patient). Minimum inhibitory concentrations (MICs) for penicillin, cefotaxime, chloramphenicol, rifampicin, and cotrimoxazole were determined by a microdilution method using commercial panels from the Sensititre system (TREK Diagnostic Systems), according to Clinical Laboratory Standards Institute recommendations. Clinical Laboratory Standards Institute criteria were used to define susceptibility or resistance [23].

Statistical Analysis

Simple linear regressions were conducted to assess changes in the frequency of IMD. Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR). For descriptive analysis, categorical data were compared using χ^2 or Fisher exact tests, and continuous data with *t* or Mann-Whitney tests.

RESULTS

Between 1977 and 2013, a total of 527 episodes of IMD were recorded at our hospital: 57 cases of sepsis (11%) and 470 of meningitis with or without sepsis (89%). The number of episodes of IMD decreased sharply during the study period, from 352 of 527 (67%) recorded in the first quarter to 20 of 527 (4%) in the last quarter (r = −1.208; 95% confidence interval [CI],

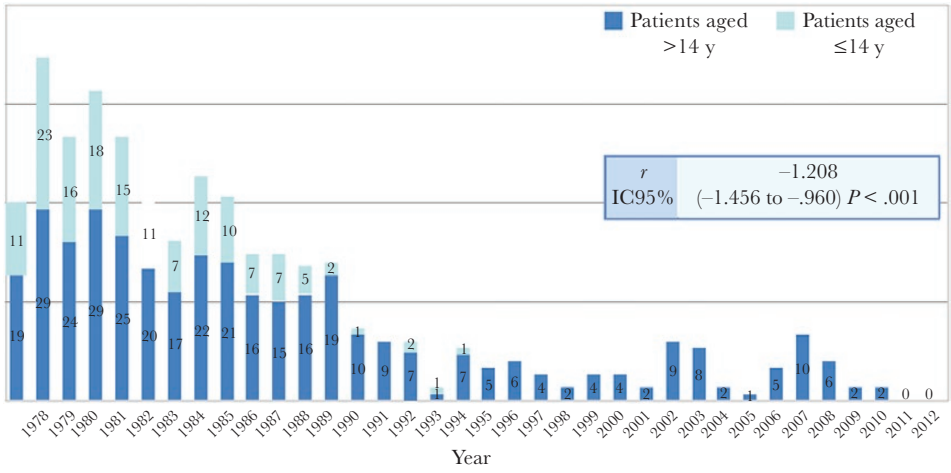

Figure 1. Number of cases of invasive meningococcal disease (IMD) per year. Abbreviation: CI, confidence interval.

−1.456 to −.960; $P < .001$), with 466 episodes (88%) occurring in the first half of the study period (Figure 1). For meningitis, the relative presence of each cause over time is presented in Table 1. In the first 2 periods, meningococci represented the primary cause and in the third and fourth periods they were the second most prevalent. In the final period, *Listeria monocytogenes* was as prevalent as meningococci.

Clinical Characteristics

Demographic and clinical characteristics and details about the treatment and outcome of in patients with sepsis, patients with meningitis, and all patients combined are presented in Tables 2–4. Sixty-one percent of patients were women. A significant underlying disease was present in 103 patients (20%); among these, diabetes mellitus was present in 49 (9%), 3 were receiving corticosteroids, and 1 was receiving chemotherapy. A total of 330 episodes (63%) occurred in the autumn-winter period. There were differences in the time of consultation between sepsis-only and meningitis episodes, with patients with sepsis presenting earlier (<12 hours) or later (>48 hours) (Table 2).

Some ear, nose, and throat symptoms were common, with 201 patients (38%) referring to a previous cold and 210 (41%) presenting with odynophagia. Fever was reported by 491 patients (93%) though present in the emergency room in only 330 (67%); 301 patients (69%) presented with chills, and shock was present in 68 (13%), 14 patients with sepsis only (25%) and 54 with meningitis (12%) ($P = .008$). Skin lesions were present in 443 patients (84%), and petechiae or ecchymosis in 416 (79%).

On admission, 217 patients (41%) were alert, 229 (44%) obtunded, 76 (14%) in a coma, and 2 (0.3%) in an arreactive coma; as expected, there were differences between patients with sepsis and those with meningitis: 2 patients with sepsis (4%) versus 76 (16%) with meningitis were in a coma or arreactive coma ($P = .004$), and 16 (28%) versus 291 (62%), respectively, were obtunded or in a coma ($P < .001$). Cranial nerve palsies were present in 37 patients, and only in patients with meningitis (8%). Hemiparesis and seizures were present before or after

Table 1. Causes of Community-Acquired Bacterial Meningitis in Hospital Universitari de Bellvitge, 1977–2013

	Cases, No. (%)			
Bacterial Cause	1977–1986 (n = 529)	1987–1996 (n = 223)	1997–2006 (n = 178)	2007–2013 (n = 128)
Neisseria meningitidis	321 (62)	95 (43)	34 (19)	20 (17)
Streptococcus pneumoniae	104 (20)	64 (29)	74 (42)	65 (51)
Listeria monocytogenes	10 (2)	12 (5)	22 (12)	22 (17)
Other streptococci	11 (2)	11 (5)	15 (8)	7 (5)
Haemophilus influenzae	5 (1)	5 (2)	9 (5)	7 (5)
Staphylococcus aureus	5 (1)	5 (2)	3 (2)	0
Escherichia coli	10 (2)	2 (1)	2 (1)	0
Other[a]	8 (1.5)	1 (0.4)	1 (1)	1 (0.7)
Unknown	55 (10)	28 (13)	18 (10)	6 (5)

[a]"Other" included *Klebsiella pneumoniae* (n = 5), *Salmonella enteritidis* (n = 2), other gram-negative bacteria (n = 3), and *Enterococcus faecalis* (n = 1).

Table 2. Clinical Characteristics of Patients With Sepsis and or Meningitis

Characteristic	Patients, No. (%)[a]		*P* Value	Total, No. (%) (N = 527)
	Sepsis (n = 57 [11%])	Meningitis (n = 470 [89%])		
Age, median (IQR), y	20 (15–58)	19 (14–49)	.46	19 (14–50)
Female sex	38 (67)	287 (61)	.25	325 (61)
Serogroup				
A	0 (0)	9 (4)		9 (3)
B	18 (62)	193 (78)		211 (76)
C	9 (31)	29 (12)	.007	38 (14)
Other	0 (0)	8 (3)		8 (3)
Underlying disease				
Any disease	18 (32)	85 (18)		103 (20)
Diabetes mellitus	5 (9)	44 (10)	.56	49 (9)
Alcoholism	3 (5)	14 (3)	.28	17 (3)
Chronic hepatic disease	2 (4)	7 (1)	.25	9 (2)
Solid neoplasm or hematological cancer	1 (2)	2 (0.64)	.29	4 (0.7)
Immunodeficiency[b]	7 (14)	13 (3)	<.001	20 (4)
Epidemiological contact	14 (25)	54 (11)	.008	68 (13)
Previous antibiotic treatment[c]	5 (9)	138 (29)	<.001	143 (28)
Duration of disease				
<12 h	18 (32)	84 (18)	.01	102 (19)
>48 h	16 (28)	61 (13)	.002	77 (15)
Clinical characteristics				
Odynophagia	23 (40)	187 (41)	.51	210 (41)
Fever	54 (95)	437 (93)	.59	491 (93)
Fever in emergency room	43 (78)	287 (65)	.04	330 (67)
Shock	14 (25)	54 (12)	.008	68 (13)
Headache	36 (63)	432 (93)	<.001	468 (91)
Nuchal stiffness	15 (27)	424 (90)	<.001	439 (83)
Nausea or vomiting	30 (55)	400 (88)	<.001	430 (84)
Skin lesions	52 (91)	391 (83)	.12	443 (84)
Maculopapular rash	7 (12)	18 (4)		25 (5)
Petechiae	33 (58)	305 (65)		338 (64)
Ecchymosis	11 (19)	67 (14)	.32	78 (15)
Vesicular rash	1 (2)	1 (0.2)		2 (0.4)
Consciousness				
Alert	41 (72)	176 (38)		217 (41)
Obtunded	14 (25)	215 (46)		229 (44)
Coma or arreactive coma	2 (4)	76 (16)	.004	78 (15)
Cranial nerve palsy				
Any	0	37 (8)	.01	37 (7)
VI	0	18 (4)		18 (3)
VIII	0	10 (2)		10 (2)
Other III/VII	0	6 (1.4)		6 (1.4)
Several nerves	0	3 (0.6)		3 (0.6)
Hemiparesis	0	13 (3)	.22	13 (2)
Before therapy	0	7 (2)		7 (1)
After starting therapy	0	6 (1.2)		6 (1.2)
Seizures	3 (5)	26 (6)	.62	29 (6)
Before therapy	2 (4)	14 (3)		16 (3)
After starting therapy	1 (2)	12 (3)	.59	13 ()

Abbreviations: IQR, interquartile range.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Immunodeficiency also includes splenectomy, systemic lupus erythematosus, chemotherapy, and corticosteroid therapy.

[c]Any effective antibiotic by any route and at any dosage and duration administered once symptoms had started and before arrival at the hospital.

Table 3. Laboratory Test Results in Patients With Sepsis and/or Meningitis

Laboratory Result	Patients, No. (%)[a]		
	Sepsis (n = 57)	Meningitis (n = 470)	Total (n = 527)
Positive blood culture	37 (65)	172 (37)[b]	209 (40)
Positive pharyngeal swab sample	13/22 (59)	47/181 (46)[b]	60/203 (30)
Other positive cultures	8	11	19 (4)
Blood findings			
Hemoglobin, median (IQR)	12.5 (12–13)	13 (12–14)	13 (12–14)
WBC count >10 000/μL	36 (67)	409 (87)[b]	445 (86)
WBC count <5000/μL	7 (13)	16 (3)[b]	23 (4)
Thrombocytopenia	15 (28)	78 (17)[b]	93 (18)
Prothrombin time >1.3	21 (41)	208 (44)	229 (43)
Hyponatremia	8 (15)	106 (23)	114 (22)
Hypokaliemia	15 (28)	166 (37)	181 (36)
Hypernatremia	0	6 (1)	6 (1)

Abbreviations: IQR, interquartile range; WBC, white blood cell.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Significant at $P < .05$.

therapy (between 24 hours and 1 week) (Table 2). Seizures were also present in patients with sepsis (5%) as febrile seizures.

Laboratory Data

Blood cultures were positive in 209 patients (40%), more frequently in patients with sepsis only (37 patients [65%]) than in those with meningitis (172 [37%]) ($P < .001$); other cultures (skin and joint fluid) were positive in 19 patients (4%). Among patients with meningitis, the median (IQR) CSF pressure was 30 (21–37) cm H_2O; CSF was clear in 68 patients (16%), opalescent in 21 (5%), cloudy in 260 (59%), purulent in 85 (19%) and hemorrhagic in 4 (1%). The median CSF WBC count was 1970/μL (IQR, 407–6200/μL), hypoglycorrhachia was present in 286 patients (61%), proteinorrhachia >1 g/L in 116 patients (27%), and >5 g/L. Gram stain was positive in 276 patients (61%), and CSF culture in 312 (69%).

The serogroup was identified in 266 patients. The most frequent serogroup was B, responsible for 211 episodes (76%), without significant variations during the study period. Serogroup C was the second more frequent, responsible for 38 episodes (14%), 9 of 57 episodes of sepsis (31%) and 29 of 470 episodes of meningitis (12%) ($P = .007$).

Data on susceptibility were available for 89 strains. For penicillin, MICs were ≤0.06 mg/L (susceptible) in 59 of 89 strains (66%), 0.12–0.25 mg/L (intermediate) in 25 (28%), and ≥0.5 mg/L (resistant) in 5 (6%). The highest MIC was 1 mg/L; for cotrimoxazole, MICs were ≤0.12/2.4 mg/L (susceptible) in 38 of 89 strains (43%) and ≥0.5 mg/L (resistant) in 51 (57%). For cefotaxime, rifampicin, and chloramphenicol, all 89 strains (100%) were susceptible, with MICs ≤0.06, ≤0.5, and ≤2 mg/L respectively.

Thrombocytopenia was more frequent (28%) in patients with sepsis than in those with meningitis (17%) ($P = .04$). The cause was established in 147 patients by positive blood and CSF culture, in 62 by blood culture only, in 165 only by CSF culture only, in 13 by positive pharyngeal swab samples, in 2 by other positive cultures, and in 12 by the presence in CSF of gram-negative diplococci with negative culture. In 126 patients, the cause was assumed based on the presence of petechiae or ecchymosis with other compatible clinical findings.

A computed tomographic scan was obtained at admission in 54 patients and was abnormal in 15, demonstrating brain edema in 4, hydrocephalus in 3, cerebritis in 1, brain infarction in 1, and previous disease in 6. In 20 patients, computed tomography was performed during the hospital stay; 10 scans were considered normal, and the other 10 demonstrated hydrocephalus in 4 patients (not present at admission in 3), infarction in 3, cerebritis in 1, and previous disease in 2.

Therapy

Antibiotic Therapy

Antibiotic use is shown in Table 4. Penicillin and ceftriaxone were the most commonly used. There were no differences in therapy used between patients with sepsis and those with meningitis. Short-duration therapy (4 days) was used in 263 patients (50%), considering patients with sepsis and those with meningitis together.

Corticosteroid Therapy

After 1987, early dexamethasone (either before or combined with the first antibiotic dose) was used in 72 patients with meningitis (14%). A comparison between patients with meningitis admitted since 1987 who did or who did not receive early dexamethasone showed that patients receiving early dexamethasone were older (median [IQR] age, 38 [21–63] vs 21 [16–45] years; $P < .001$), more frequently had neck stiffness (98% vs 83%; $P = .002$), were more likely to be comatose at admission (28% vs 6%; $P = .001$), and more frequently had a CSF protein concentration >1 g (94%

Table 4. Therapy and Outcome in Patients with Sepsis and/or Meningitis

Therapy and Outcome	Patients, No. (%)[a]		
	Sepsis (n = 57 [11%])	Meningitis (n = 470 [89%])	Total (N = 527)
Therapy			
Short therapy (4 d)	33 (58)	230 (49)	263 (50)
Penicillin	32 (56)	305 (65)	337 (64)
Ampicillin	2 (4)[b]	5 (1)[c]	7 (1)
Cefotaxime	2 (4)	10 (2)	12 (2)
Ceftriaxone	19 (33)	136 (29)	155 (29)
Chloramphenicol	1 (2)	9 (2)	10 (2)
Other	1	3	4
No therapy	0	2 (0.4)	2 (0.4)
Antiseizure prophylaxis	0	25 (5)	25 (5)
Heparin	6/53 (11)	33/465 (7)	39/518 (7.5)
Mechanical ventilation	8 (14)	47 (10)	55 (10)
Outcome			
Time to improvement in consciousness, median (IQR), d	1 (1–1)	1 (1–2)	1 (1–2)
Time to fever <38°C, median (IQR), d	1 (1–2)	1 (1–3)	1 (1–3)
Relapse of fever	6 (11)	74 (16)	80 (16)
Arthritis	11 (19)	29 (6)[d]	40 (8)
Pericarditis	1 (2)	9 (2)	10 (2)
Heart failure	11 (19)	36 (7)[d]	47 (9)
Renal failure	8 (14)	39 (8)	47 (9)
Impaired liver function	2 (4)	35 (8)	37 (7)
DIC	12 (21)	60 (13)	72 (14)
Herpes	4 (7)	120 (26)[d]	124 (24)
Catheter phlebitis	10 (18)	128 (27)	138 (27)
Gastrointestinal symptoms[e]	5 (9)	30 (6)	35 (7)
Total hospital stay, median (IQR), d	8 (6–10)	9 (7–11)	9 (7–11)
Relapse	0	0	0
Sequelae	1 (2)	37 (8)	38 (7)
Cutaneous necrosis	1 (2)	16 (4)	17 (3)
Epilepsy	0	1 (0.2)	1 (0.2)
Cranial nerve palsy	0	2 (0.5)	2 (0.4)
Hearing impairment	0	11 (2.5)	11 (2.4)
Hemiparesis	0	4 (1)	4 (1)
Hydrocephalus-shunt	0	1 (0.2)	1 (0.2)
Other	0	2 (0.5)	2 (0.4)
Deaths (by mechanism)			
Total	8 (14)	25 (5)[d]	33 (6)
Early neurological	1 (2)	5 (1)	6 (1)
Late neurological	0	2 (0.4)	2 (0.4)
Early sepsis	6 (11)	12 (2.5)	18 (3)
Late nonneurological	1 (2)	6 (1)	7 (1)

Abbreviations: DIC, disseminated intravascular coagulation; IQR, interquartile range.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Two of them + aminoglycosides.

[c]One of them + aminoglycosides.

[d]Significant at $P < .05$.

[e]Gastrointestinal symptoms included gastrointestinal bleeding, abdominal pain, and diarrhea.

vs 65%; $P < .001$) or >5 g (45% vs 19%; $P = .001$). They also presented with a lower frequency of fever (89% vs 99%; $P = .01$), fever in the emergency room (50% vs 70%; $P = .01$), shock (3% vs 16%; $P = .009$), and skin lesions (76% vs 89%; $P = .04$). Despite these differences, there were no differences in outcome, in either mortality or complication rates, except for fewer cases of catheter phlebitis (10% vs 25%; $P = .02$) and arthritis (3% vs 10%; $P = .04$) in patients receiving dexamethasone.

Antiseizure Propylaxis and Therapy

Antiseizure therapy was administered in 28 patients (5%) and antiseizure prophylaxis with phenytoin in 25 (5%), all of them

patients with meningitis. Patients receiving the prophylaxis were significantly older (median [IQR] age, 55 [29–66] vs 23 [16–50] years; $P < .001$), more likely to show abuse of alcohol (13% vs 0%; $P < .001$), and more likely to have chronic hepatic disease (4% vs 0%; $P = .02$) or any predisposing disease (39% vs 13%, $P = .02$) than those not receiving prophylaxis. No seizures were seen in patients with antiseizure prophylaxis. No differences in mortality or complication rates were seen among these patients.

Outcome

The median (IQR) duration to improved consciousness was 1 (1–2) days, and the median duration to fever below 38°C was 1 (1–3) days, both significantly longer ($P = .008$ and .03, respectively) among patients with meningitis. Relapse of fever occurred in 80 patients (16%). The most frequent complications (Table 4) were catheter phlebitis, herpes simplex labialis, disseminated intravascular coagulation (DIC), heart failure, renal failure and arthritis, with arthritis and heart and renal failure more frequent and herpes less frequent among patients with sepsis. There were no relapses.

Deaths

Thirty-three patients died (6%), 8 with sepsis (14%) and 25 with meningitis (5%) ($P = .02$). The mechanism of death was mainly early sepsis (Table 4). Mortality rates decreased slightly over time, but no significantly. A comparison between dead and alive patients can be found in the Supplementary Data.

Cutaneous Sequelae

Among the survivors, cutaneous sequelae mainly due to necrosis were present in 17 patients (3%). In the univariate analysis of the survivors, statistically significant differences were found between patients with and those without cutaneous sequelae, including the presence of shock (53% vs 12%; $P < .001$), presence of ecchymosis (94% vs 12%; $P < .001$) or petechiae/ecchymosis 100% vs 78%; $P = .02$), positive blood cultures (82% vs 38%; $P < .001$), lower CSF WBC count (median [IQR], 44/μL [9–750/μL] vs 1700/μL [266–6000/μL]; $P = .002$), less proteinorrhachia >1 g/L (43% vs 69%; $P = .045$), presence of thrombocytopenia (65% vs 17%; $P < .001$), prothrombin time >1.3 (94% vs 45%; $P < .001$), and presence of hypokalemia (69% vs 35%; $P = .006$).

All these parameters pointed to more severe sepsis in patients with cutaneous sequelae. There were also differences in outcome, with patients with cutaneous sequelae requiring more mechanical ventilation (41% vs 10%; $P = .001$) and use of heparin (41% vs 6%; $P < .001$), and having a higher frequency of heart failure (47% vs 8%; $P < .001$), DIC (65% vs 12%; $P < .001$), or gastrointestinal complications (29% vs 6%, $P = .003$). Hospital stays were longer, with a median (IQR) of 12 (9–20) versus 9 (7–11) days ($P = .004$). Previous antibiotic use was significantly more likely in patients without cutaneous sequelae (29% vs 0% in those with sequelae; $P = .004$), and patients with sequelae had a lower frequency of meningeal signs such as nuchal stiffness (65% vs 86%; $P = .03$) or nausea/vomiting (65% vs 85%; $P = .04$).

Multivariate analysis showed ecchymosis as the only independent risk factor related to cutaneous sequelae (odds ratio [OR], 54; 95% CI, 6.126–480.795). If we exclude ecchymosis, because it could be considered the same process as the dependent variable, the presence of DIC (OR, 4.8; 95% CI, 1.291–18.379) was the only independent risk factor, whereas young age (0.9; .940–.999) was protective.

Neurological Sequelae

Neurological sequelae were present only in 21 (5%) of the patients surviving meningitis (Table 4). In the univariate analysis of the survivors, variables related to neurological sequelae were age (median [IQR], 45 [12–60] vs 18 [14–44] years; $P = .03$), late consultation (>48 hours) (28% vs 12%; $P = .02$), presence of nausea/vomiting (100% vs 88%; $P = .02$), cranial nerve palsy (28% vs 6%; $P < .001$), hemiparesis (19% vs 2%; $P < .001$), seizures at any time (16% vs 4%; $P = .01$), and seizures after antibiotic therapy (13% vs 1%; $P = .001$). The duration to improved consciousness was longer in patients with neurological sequelae (median [IQR], 2 [1–3] vs 1 [1–2] days; $P = .03$), and hospital stays were also longer (median, 11 [10–19] vs 9 [7–10] days; $P < .001$).

In the multivariate analysis age (OR, 1.023; 95% CI, 1.004–1.042) hemiparesis (2.9; 1.3–6.5) and cranial nerve affectation (1.6; 1.1–2.3) were independent risk factors. Because cranial nerve palsy and hemiparesis could be considered as cause and effect, an analysis excluding these 2 factors was performed, showing age (OR, 1.019; 95% CI, 1.002–1.036), presence of seizures either at any time (3.8; 1.2–12.3) or after therapy (11.8; 2.5–56.8), and late consultation (2.5; 1.0–6.2) as independent risk factors.

DISCUSSION

According to our results, cases of IMD decreased dramatically in our hospital throughout the study period. IMD has been notifiable on clinical suspicion in Spain since 1981. The average annual incidence rate of meningococcal disease in Barcelona during the period 1987–1992 was 6.41/100 000 [24], and during the period 1982–2010 the incidence of meningococcal meningitis decreased by 66% ($P < .001$) [25]. Other global data for Spain [8] show an incidence of 3.52/100 000 in 1999 and 0.88/100 000 in 2010, after the vaccine for group C was introduced in 2001.

Studies in European countries confirm a clear decrease [26, 27]. In the Netherlands, annual incidence rates increased from 0.5/100 000 in 1960 to 4.5 in 2001, and subsequently decreased to 0.6/100 000 in 2012 [28]. The change in incidence in our

area and in Spain is in part due to vaccination against group C meningococci, with a decrease in group C meningococcal disease of 93% from 1987 to 2015 and 75% from 2001 to 2015 in Catalonia, and in part due to herd immunization, as has been suggested in other European countries [29–31]. However, because group B was the most frequent etiological agent, the large decrease in overall IMD also seems to be due to stochastic changes in epidemiology of unknown causes, including possibly changes in population behaviors. In fact the incidence of the different serogroups is constantly changing in the different countries, and these changes are not always is due to vaccine implementation or antibiotic use.

Our patients presented with meningitis in a high percentage of cases, with several degrees of accompanying sepsis. A high percentage of patients with meningitis presented with the classic signs and symptoms of meningitis, and the only features that suggested meningococcal meningitis were symptoms such as odynophagia, which were present in 40% of cases and are very rare in other etiologies, and, of course, skin lesions.

Treatment of IMD has not been a problem in terms of antibiotic susceptibility in our patients, because the widespread use of third-generation cephalosporin, the antibiotic in use since the 1980s, is very safe. Another consideration in the treatment of meningitis is the use of dexamethasone. Before 1987, dexamethasone was sometimes used as rescue therapy in patients whose condition worsened after the start of antibiotic therapy, but it seemed to be ineffective. After 1987, dexamethasone used as early adjunctive therapy before the antibiotic was a good treatment option for our patients. Patients who received dexamethasone, whose condition had been more severe, showed no differences in outcome compared with those who did not receive dexamethasone. We could not demonstrate a better evolution, and this was not a randomized trial, but some complications, such as arthritis, were less common among patients receiving early dexamethasone, maybe owing to the immunoallergic mechanisms of most arthritis-related episodes [32]. The same finding was reported in a Dutch study [33] comparing 2 cohorts of patients with meningococcal meningitis, the first from the era before use of dexamethasone and the second after implementation of dexamethasone therapy. The authors of that study found no differences in outcome and no adverse effects but a significantly lower number of cases of arthritis in patients receiving dexamethasone.

Seizures are an important complication that could perhaps be avoided in selected cases by means of phenytoin prophylaxis. In our patients, phenytoin was used in certain particularly severe cases, and no patient receiving phenytoin experienced seizures. In a Brazilian series [34] the presence of seizures was independently related to mortality rate. Although ours was not a clinical trial, our data support the notion that selected patients (including elderly patients and those with previous brain infarction or lesions) may benefit from seizure prophylaxis in cases of meningococcal meningitis.

In conclusion, in this large series of IMD cases covering an extensive period of time, the frequency of IMD has decreased sharply. Sepsis-only cases had the highest mortality and complication rates, dexamethasone was demonstrated to be safe and to prevent some arthritis episodes, and the use of prophylactic phenytoin seemed useful in a selected population. A very rapid response and antibiotic therapy may help improve the prognosis.

Acknowledgments

C. C., F. G., and J. A. are members of the Spanish Network for Research in Infectious Diseases, and C. C. and I. P. are members of European Society of Clinical MIcrobiology and Infectious Diseases Study Group for Infectious Diseases of the brain (ESGIB).

Financial support. This work was supported by the Institut d'Investigació Biomédica de Bellvitge (personal grant to I. P.)

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Vieusseux G. Memoire sur la maladie qui a regné a Genève au printemps de 1805. *J Med Chir Pharmacol* **1805**; 11:163–82.
2. Schwentker FF, Gelman S, Long PH. The treatment of meningococcic meningitis with sulfanilamide: preliminary report. *JAMA* **1937**; 108:1407–8.
3. Poland GA. Prevention of meningococcal disease: current use of polysaccharide and conjugate vaccines. Clin Infect Dis **2010**; 50(suppl 2):S45–53.
4. Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against *Neisseria meningitidis*. N Engl J Med **2010**; 362:1511–20.
5. Holsta J, Nøklebya H, Bettingerb JA. Considerations for controlling invasive meningococcal disease in high income countries. Vaccine **2012**; 30S:B57–62.
6. Isaacs D, McVernon J. Introducing a new group B meningococcus vaccine. BMJ **2014**; 348:g2415.
7. Diaz PS. The epidemiology and control of invasive meningococcal disease. Pediatr Infect Dis J **1999**; 18:633–4.
8. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr **2013**; 11:17.
9. World Health Organization. Meningococcal meningitis. **2016**; Available at: http://www.who.int /mediacentre/factsheets/fs141/ en/index.html.
10. Greenwood BM, Bradley AK, Wall RA. Meningococcal disease and season in sub-Saharan Africa. Lancet **1985**; 2:829–30.
11. Brighama KS, Sandorab TJ. *Neisseria meningitidis*: epidemiology, treatment and prevention in adolescents. Curr Opin Pediatr **2009**; 21:437–43.
12. Memisha ZA, Goubeaudb A, Brökerb M, et al. Invasive meningococcal disease and travel. J Infect Public Health **2010**; 3:143–51.
13. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. Lancet **2007**; 369:2196–210.
14. Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease. N Engl J Med **2001**; 344:1378–88.
15. Ladhani SN, Beebeejaun K, Lucidarme J, et al. Increase in endemic *Neisseria meningitidis* capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis **2015**; 60:578–85.
16. Borrow R, Alarcón P, Carlos J, et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines **2017**; 16:313–28.
17. Folaranmi TA, Kretz CB, Kamiya H, et al. Increased risk for meningococcal disease among men who have sex with men in the United States, 2012–2015. Clin Infect Dis **2017**; 65:756–63.
18. Carmona G, Vives N. Resum de les malalties de declaració obligatòria a Catalunya durant l'any 2016. Butlletí Epidemiològic de Catalunya **2018**; 39:25–42.
19. Soult Rubio JA, Muñoz Sáez M. Invasive meningococcal disease. An Pediatr (Barc) **2005**; 62:297–303.
20. Viladrich PF, Pallares R, Ariza J, et al. Four days of penicillin therapy for meningococcal meningitis. Arch Intern Med **1986**; 146:2380–2.

21. Cabellos C, Pelegrín I, Benavent E, et al. Invasive meningococcal disease: Impact of short course therapy. A DOOR/RADAR study. J Infect **2017**; 75:420–5.
22. Janda WM, Gaydos CH. Neisseria. In: Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, eds. Manual of Clinical Microbiology. 9th ed. Vol 1. Washington, DC: ASM Press; **2007**:601–20.
23. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 27th ed. CLSI supplement document M100, Wayne, PA: Clinical and Laboratory Standards Institute; **2017**.
24. Barquet N, Domingo P, Cayla JA, et al. Meningococcal disease in a large urban population (Barcelona, 1987–1992): predictors of dismal prognosis. Arch Intern Med **1999**; 159:2329–40.
25. Domingo P, Pomar V, Benito N, Coll P. The changing pattern of bacterial meningitis in adult patients at a large tertiary university hospital in Barcelona, Spain (1982-2010). J Infect **2013**; 66:147–54.
26. Gil-Prieto R, García-García L, Álvaro-Meca A, et al. The burden of hospitalizations for meningococcal infection in Spain (1997–2008). Vaccine **2011**; 29:5765–70.
27. Mação P, Januário G, Ferreira S, et al. Meningococcal disease admissions in a paediatric intensive care unit. Acta Medica Portuguesa **2014**; 27:291–4.
28. Bijlsma MW, Bekker V, Brouwer MC, et al. Epidemiology of invasive meningococcal disease in the Netherlands, 1960–2012: an analysis of national surveillance data. Lancet Infect Dis **2014**; 14:805–12.
29. Bijlsma MW, Brouwer MC, Spanjaard L, et al. A decade of herd protection after introduction of meningococcal serogroup C conjugate vaccination. Clin Infect Dis **2014**; 59:1216–21.
30. Martínez AI, Domínguez A, Oviedo M, et al; Grupo de Trabajo sobre Enfermedad Meningocócica de Catalunya. Epidemiology of the meningococcal disease in Catalonia before and after vaccination against serogroup C. Rev Esp Salud Publica **2009**; 83:725–35.
31. Cano R, Larrauri A, Mateo S, et al. Impact of the meningococcal C conjugate vaccine in Spain: an epidemiological and microbiological decision. Euro Surveill **2004**; 9:11–5.
32. Cabellos C, Nolla JM, Verdaguer R, et al. Arthritis related to systemic meningococcal disease: 34 years' experience. Eur J Clin Microbiol Infect Dis **2012**; 31:2661–6.
33. Heckenberg SG, Brouwer MC, van der Ende A, van de Beek D. Adjunctive dexamethasone in adults with meningococcal meningitis. Neurology **2012**; 79: 1563–9.
34. Strelow V, Kolbe K, Peixoto de Miranda E, Vidal JE. Meningitis Meningocócica (MM) en el Instituto de Infectologia Emílio Ribas (IIER), San Pablo-Brasil, 2006–2011: Características Clínico-Laboratoriales, Letalidad y Factores Asociados a Mortalidad Intrahospitalaria. XVI Congreso Panamericano de Infectologia. Santiago, Chile: Libro de Resúmenes; **2013**:78.