Meningococcal Disease in a Large Urban Population (Barcelona, 1987-1992)

Predictors of Dismal Prognosis

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Context: Studies on meningococcal disease in large urban communities have rarely been performed and are usually based on passive epidemiologic surveillance. Active surveillance may provide new insights.

Objectives: To determine epidemiologic, clinical, and bacteriological characteristics and predictors of dismal prognosis (death and sequelae) in meningococcal disease.

Design: Prospective, population-based study.

Setting: All the acute care hospitals (n = 24) in Barcelona, Spain.

Patient: The 643 patients whose conditions were diagnosed from 1987 through 1992 were detected by 2 active surveillance methods.

Outcome Measures: Incidence and notification to Public Health Service. Clinical and bacteriological features were determined. Dismal prognosis predictors were determined by logistic regression.

Results: Average annual incidence was 6.41 per 100 000 inhabitants, with no clear trend of change ($P = .08$). Sensitivity of the Public Health Service surveillance system was 69.1%. Children younger than 10 years from the inner city were at higher risk than those from the highest income district (relative risk, 3.00; 95% confidence interval [CI], 1.84-5.06). Increasing annual incidence of serogroup C (0.82-1.29/100 000; $P = .008$) and decreasing incidence of serogroup B (5.11-2.82/100 000; $P = .004$) was noted. Average annual mortality was 0.40 per 100 000 inhabitants, while the annual average potential years of life lost was 18 per 100 000 inhabitants. Overall case-fatality rate was 6.4%. Independent predictors of death were hemorrhagic diathesis (odds ratio [OR], 63; 95% CI, 21-194), focal neurologic signs (OR, 10; 95% CI, 3-30), and age 60 years or older (OR, 6; 95% CI, 2-17), whereas preadmission antibiotic therapy was associated with favorable outcome (OR, 0.07; 95% CI, 0.02-0.3). Four percent of survivors presented with sequelae. Independent predictors of sequelae were hemorrhagic diathesis (OR, 21; 95% CI, 3-131), focal neurologic signs (OR, 16; 95% CI, 5-53), age 60 years or older (OR, 7; 95% CI, 2-26), and age between 15 and 59 years (OR, 5; 95% CI, 2-14), whereas preadmission antibiotic therapy had a protective effect (OR, 0.2; 95% CI, 0.04-0.5).

Conclusions: Active epidemiologic surveillance significantly improved detection of cases and allowed us to observe that meningococcal disease still causes much morbidity and mortality, especially among children living in the inner city. Hemorrhagic diathesis, focal neurologic signs, and age were independent predictors of dismal prognosis, whereas preadmission antibiotic therapy had a protective effect.

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MENINGOCOCCAL disease has been known clinically since Vieusseux[1] reported the epidemic outbreak in Geneva, Switzerland, in 1805. In its 2-century history, the discovery of the etiologic agent, ie, *Neisseria meningitidis*, by Weichselbaum[2] in 1887, the introduction of sulfonamides[3] and penicillin[4] in its treatment, in 1937 and 1944, respectively, and finally the development of meningococcal vaccines[5-8] greatly improved the ominous prognosis of meningococcal disease and contributed to the control of epidemics. However, meningococcal disease still represents a major public health problem in many areas of the world.[9] Issues that remain unresolved are the still high case-fatality rate (CFR) of fulminant meningococcemia, the temporal changes in serogroup and/or serotype predominance, the increasing emergence of resistance to penicillin, and the lack of an effective vaccine against serogroup B.

Information on the epidemiologic trends of meningococcal disease is usually based on passive surveillance studies, but

METHODS

STUDY SETTING

We performed a prospective, population-based study in the city of Barcelona from January 1, 1987, through December 31, 1992. The municipal area is divided into 10 districts. The population declined from 1 703 744 in 1987 to 1 630 635 inhabitants in 1992, with an average density of 16 895 persons per square kilometer. The age distribution was as follows: younger than 15 years, 16.2%; 15 to 64 years, 67.7%; and 65 years and older, 16.1%. The municipal district with the lowest family income, highest rate of illiteracy, highest unemployment, and poorest home conditions is Ciutat Vella (district 1), and the best standards are those found in Sarrià-Sant Gervasi (district 5). Population densities were 21 024 and 7 048 inhabitants per square kilometer, respectively.

CASE IDENTIFICATION AND INCIDENCE

A *case* was defined as any resident of the city of Barcelona who was diagnosed as having meningococcal disease. The diagnosis was made when *N meningitidis* was isolated from blood culture, cerebrospinal fluid (CSF) culture, or both, or for an illness with fever and petechiae, diagnosed as meningococcal disease by the local physician, in a person with no blood or CSF isolate of *N meningitidis*.[16] Two active epidemiologic surveillance systems for detecting the patients were used. The main system consisted of a member of the Barcelona Meningococcal Disease Surveillance Group that reviewed, on a daily basis, the diagnostic orientations written in the blood culture or CSF culture requests that had been sent to the microbiology laboratories serving all the acute care hospitals (n = 24) in the area of the city of Barcelona, together with the pertinent sample, to search for a presumptive diagnosis consistent with meningococcal disease. The main system also included the monitoring of the cultures and the rapid notification when a strain of *N meningitidis* was isolated and identified. The complementary system involved reviewing, on a daily basis, the diagnoses on admission and discharge of all the patients attended on at the 24 acute care hospitals existing in the area of the city of Barcelona. When a diagnosis consistent with meningococcal disease was detected, for example meningitis of unknown cause, the patient was evaluated by a member of the Barcelona Meningococcal Disease Surveillance Group.

DEFINITIONS

Coprimary and secondary cases were defined as previously described.[16] Secondary attack rate was calculated by dividing the number of secondary cases by the number of persons exposed to a primary or coprimary single case in a day care center, school, or house (ie, children and caregivers in day care centers, excluding primary and coprimary cases).

Preadmission receipt of adequate antibiotic therapy was only considered when the patient had received at least 1 adequate dose of antibiotics active against *N meningitidis* at intervals considered adequate from a therapeutic point of view.

The interval in hours from onset of symptoms and signs until therapy (interval of symptoms to therapy [IST]) was the time elapsed between the appearance of the first symptom or sign attributable to meningococcal disease and the initiation of antibiotic therapy in the hospital. When the precise beginning of symptoms could not be determined, the onset of illness was assumed to be the mean interval between the last time the patient was asymptomatic as observed by a household member and the first time the patient was seen ill.

Shock was defined as persistent hypoperfusion and an initial systolic blood pressure of less than 70 mm Hg in children younger than 12 years, or an initial systolic blood pressure less than 85 mm Hg or a decrease of 60 mm Hg from the previous measured blood pressure in patients 12 years or older who required fluid therapy, vasoactive drugs, or both for at least 24 hours or until death.[17]

Coma was defined by a Glasgow Coma Scale score of 6 or less in the absence of sedative treatment.[18] For children, a modified Pediatric Coma scale was used,[19] and coma was defined by a score less than 8. If sedative therapy had been administered, the data for coma were considered as missing.

Hemorrhagic diathesis was defined as spontaneous clinically apparent bleeding, including bleeding from wounds, hematoma, hematuria, spontaneous gingival bleeding, epistaxis, or gastrointestinal or gynecologic bleeding, together with ecchymosis or hemorrhage in the places of puncture (venous or arterial access, intramuscular injection, lumbar puncture, or others). The diagnosis of hemorrhagic diathesis was made irrespective of the presence of petechiae and once prior coagulation disorders or anticoagulant therapy had been ruled out by assessing patient's medical history.

Focal neurologic signs were defined as motor, sensory, or cranial nerve disturbances of central origin that were not present before the episode of meningococcal disease.

Deaths were attributed to meningococcal disease if the patient died within 7 days of receiving in-hospital antimicrobial therapy and had a clinical course that suggested persistent infection, or if death occurred during the phase of acute infection.

Sequelae were defined as any disability, disorder, or injury demonstrated during the hospital stay or on discharge from hospital that were not present before the episode of meningococcal disease and persisted for 5 years after discharge from hospital. *Moderate neuropsychological sequelae* were defined as those that did not prevent the patient from doing autonomous daily life activities. *Severe neuropsychological sequelae* were those that prevented the patient from doing autonomous daily life activities.

BACTERIOLOGICAL METHODS

Strains of *N meningitidis* were identified at microbiology laboratories serving the acute care hospitals in the area of the city of Barcelona by using standard bacteriological methods, including Gram stain, oxidase, catalase and aminopeptidase activity, and carbohydrate degradation test.[20] All strains (302 isolated from blood and 315 from CSF samples) were sent to the Spanish Meningococcal Reference Laboratory at Majadahonda, Madrid, Spain, for confirmatory identification, serogrouping, serotyping, subtyping, and antimicrobial susceptibility testing. Serogroups were determined by slide agglutination test with polyclonal serum

samples produced in the laboratory in rabbits by using the inoculation protocol of Vedros.[21] The strains used to produce antiserum samples to serogroups A, B, C, X, Y, Z, and W135 were obtained from N. E. Vedros, MD (*Neisseria* Repository, Berkeley, Calif), and the strain used to produce antiserum samples to serogroup 29E (Z′) was obtained from the International Meningococci Reference Center, Marseille, France. Serotypes and subtypes were determined by a whole-cell enzyme-linked immunoabsorbent assay. Antigens were prepared as described by Abdillahi and Poolman.[22] Monoclonal antibodies with serotype specificities 1, 2a, 2b, 4, 14, and 15 and subtype specificities P1.1, P1.2, P1.3, P1.4, P1.6, P1.7, P1.9, P1.10, P1.12, P1.14, P1.15, and P1.16 were supplied by J. T. Poolman, MD (Rijksinstituut voor Volksgezondheid en Milieuhygiëne, Bilthoven, the Netherlands).[20,22,23]

All meningococcal strains were stored frozen at – 80°C in skim milk until their minimum inhibitory concentration (MIC) was determined. The MIC was defined as the lowest concentration of antibiotic that prevented growth visible without the microscope after an overnight incubation. Susceptibility to penicillin, cefotaxime sodium, and chloramphenicol was tested using the agar dilution method as described by the National Committee for Clinical Laboratory Standards, Wayne, Pa.[24] The medium used for growth and determination of susceptibility studies was cation-adjusted Mueller-Hinton agar (Difco Laboratories, Detroit, Mich) supplemented with 5% lysed sheep blood. Plate cultures with an inoculum of 10^5 colony-forming units per milliliter were incubated in 5% carbon dioxide atmosphere at 35°C for 24 hours. The concentrations of penicillin tested were 0.015, 0.03, 0.06, 0.12, 0.25, 0.5, and 1 mg/L. Two strains of *N meningitidis* were used as controls for susceptibility to penicillin: M6280 (MIC, 0.015 mg/L) and M6293 (MIC, 0.25 mg/L). The MIC ranges used to classify the susceptibility of the strains to penicillin were as follows: MIC, 0.06 mg/L or less, susceptible (Pen^S); MIC between 0.125 and 1 mg/L, moderately resistant (Pen^{MR}); MIC more than 1 mg/L, resistant (Pen^R). β-Lactamase production was tested by using liquid chromogenic cephalosporin nitrocefin (Glaxo Research, Greenford, Middlesex, England) as the indicator for the presence of β-lactamase.[25]

CLASSIFICATION OF MENINGOCOCCAL DISEASE

On the basis of the IST and the presence of shock at the time of admission to the hospital, meningococcal disease was classified in 3 clinical forms: "fulminant" (IST <7 hours with shock), "acute" (IST <7 hours without shock, IST >24 hours with shock, or IST between 7 and 24 hours [with or without shock]), and "subacute" (IST >24 hours without shock).

Based on microbiological studies, meningococcemia was diagnosed when *N meningitidis* was isolated from blood cultures but not from CSF samples. Meningococcal meningitis was diagnosed when *N meningitidis* was isolated from CSF samples but not from blood culture. Meningococcemia with meningitis was diagnosed when *N meningitidis* was isolated from blood and CSF cultures, or when there was a positive blood culture result together with CSF findings consistent with purulent meningitis, a CSF gram-stained smear showing gram-negative diplococci, or detection of *N meningitidis* antigen in CSF despite a negative culture result. When CSF and blood cultures were negative, the patient was said to have microbiologically unproved meningococcal disease.

DATA COLLECTION

The following data were collected at the time of admission to hospital for use in the prognostic analysis: age, sex, comorbid conditions, upper respiratory tract infection on admission or during the 5 days prior to admission, preadmission antibiotic therapy, shock, clinical form of meningococcal disease, meningeal signs, hemorrhagic diathesis, coma, and focal neurologic signs. All data were collected daily by a member of the Barcelona Meningococcal Disease Surveillance Group and were entered into a computerized database. Each patient, the person(s) living with him or her, and the hospital physician were contacted personally to obtain and confirm clinical data, including information on outcome.

Data on mortality were obtained by monitoring the patients during hospitalization and reviewing the clinical records of the outpatient clinic and records of deaths. Data on sequelae were obtained by monitoring the patients during hospitalization and at outpatient clinics for 5 years after discharge: physical, audiometric, neurologic, and psychometric examination, including intelligence tests, neuropsychological skills, academic achievement, and judgments by parents and teachers of each child's behavior, school performance, and adaptive abilities. Patient examinations for detecting and evaluating late sequelae were performed on all survivors 1, 3, and 6 months after discharge, with further examinations being carried out at 12 months and then yearly up to 5 years after discharge for those patients with sequelae.

DATA ANALYSIS

Statistical analyses were performed with the SPSS-PC+ statistical package.[26] The χ^2 test, with Yates correction when indicated, and the Fisher exact test were used to compare categorical qualitative variables. All results for continuous variables are expressed as means (SD). The Student *t* test was used for comparison of continuous qualitative and quantitative variables. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were also used for comparison of qualitative variables. The χ^2 for trend test was used to analyze the evolution of the incidence, both overall and by serogroup, and the evolution of the susceptibility to penicillin in *N meningitidis* strains. Logistic regression analysis was performed with the EGRET[27] statistical package, using the backwards elimination procedure. The goodness of fit of the logistic regression model was tested with the Hosmer-Lemeshow test[28] and with appropriate indications when some columns had no observed values.[29,30]

All dichotomous variables, including converted ones, associated with outcome with a *P* value <.15 at univariate level and without problems of collinearity were entered in a logistic regression model to identify independent predictors of death and sequelae among survivors. The risk was quantified using OR with 95% CI. Reference categories were those with the patients having the lowest case-fatality or sequelae rate. For upper respiratory tract infection and preadmission adequate antibiotic therapy, the reference categories were the ones with the highest case-fatality or sequelae rate to determine any beneficial effect.

Table 1. Meningococcal Disease in Large Urban Populations (1987-1992): Incidence

City (References)	No. (Rate/100 000) of Cases per Year					
	1987	1988	1989	1990	1991	1992
Greater London, England (31, 32)	129 (1.90)*	157 (2.33)*	198 (2.93)	169 (2.48)	159 (2.33)	136 (2.00)
New York City, NY (33-38)	57 (0.77)	103 (1.40)	87 (1.18)	79 (1.07)	30 (0.41)	28 (0.38)
Washington, DC (33-38)	12 (1.92)	11 (1.78)	19 (3.14)	25 (4.11)	18 (2.96)	3 (0.49)
Barcelona Public Health Services	87 (5.11)	62 (3.62)	86 (5.02)	67 (3.92)	64 (3.89)	78 (4.78)
Barcelona, present study	142 (8.33)	98 (5.72)	105 (6.13)	78 (4.57)	127 (7.73)	93 (5.70)

**Only meningococcal meningitis was notifiable in London.*

these studies neglect a number of details concerning meningococcal disease, and many cases are lost. Although some excellent studies based on active surveillance exist,[10-15] none of them included the active search systems used in the present study. The objective of this study was to determine epidemiologic, clinical, and bacteriological characteristics of meningococcal disease, placing particular emphasis on dismal prognostic factors (death and sequelae), in a large urban environment by means of 2 active epidemiologic surveillance systems covering the population of Barcelona, Spain, and involving all laboratories in the area for 6 years.

RESULTS

INCIDENCE

A total of 643 patients living in the city of Barcelona were diagnosed as having meningococcal disease from 1987 through 1992. The average annual incidence rate of meningococcal disease was 6.41 per 100 000 inhabitants, ranging from 8.33 in 1987 to 4.57 per 100 000 in 1990 but with no clear trend of change ($P = .08$; **Table 1**).

Seventeen patients (2.6%) were coprimary cases and 31 patients (4.8%) were secondary cases. The secondary attack rate was 529 per 100 000 among household members (7 of 1323), 169 per 100 000 among day care center contacts (18 of 10 651), and 28 per 100 000 among schoolchildren (6 of 21 428). The relative risk (RR) of household members was 3 times greater than day care contacts (RR, 3.12; 95% CI, 1.31-7.46; $P = .01$) and the latter in turn had an RR 6 times greater than schoolchildren contacts (RR, 6.03; 95% CI, 2.39-15.18; $P<.001$). The annual incidence in those 4 to 14 years of age was 14.71 per 100 000 population, which implies that the RR of disease among schoolchildren contacts in Barcelona is 1.87 (95% CI, 1.00-3.49; $P = .05$).

NOTIFYING THE PUBLIC HEALTH SERVICE

In all, 199 patients (30.9%) had not been reported to the Public Health Service. The overall sensitivity of this surveillance system was 69.1%.

AGE AND SEX

The mean age (SD) was 14.1 (20.3) years (median, 5.0 years; range, 28 days to 89 years). Most patients (70.5%) were younger than 15 years, and patients older than 60 years accounted for 7.3% of the series. The maximum annual incidence was found among infants (**Figure 1**). There were 344 females (53.5%) and 299 males (46.5%).

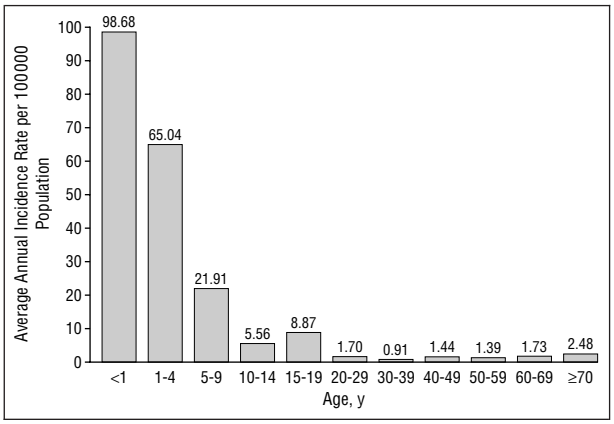

Figure 1. *Meningococcal disease in Barcelona, Spain (1987-1992): average annual incidence rate by age group.*

DISTRICT OF RESIDENCE

The average annual incidence rate in district 1, inner city (9.90/100 000), was twice that of district 5, the highest income district (5.00/100 000). The differences were even more striking when the population of those younger than 10 years was compared; the RR in district 1 was 3 times greater (RR, 3.00; 95% CI, 1.84-5.06; $P<.001$).

PREADMISSION ANTIBIOTIC THERAPY

A total of 281 patients (43.7%) were receiving antibiotics before admission, mainly because of upper respiratory tract infection. The mean interval between first dose of antibiotic and hospital admission was 25 (SD, 4.1) hours (median, 37.9 hours; range, 1.5-76 hours). Preadmission adequate antimicrobial agents included β-lactams (mostly amoxicillin alone or combined with clavulanic acid), oral second-generation and third-generation cephalosporins (211 patients), macrolides (56 patients), trimethoprim-sulfamethoxazole (7 patients), quinolones (5 patients), and others (2 patients). One patient died because of anaphylaxis to penicillin and was not included in the analysis. The CFR of patients who had received antibiotics was 0.7% vs 10.5% of those who had not (OR, 0.06; 95% CI, 0.01-0.24; $P<.001$); also there were significant differences in fulminant (0% vs 55.0%; $P = .04$), acute (1.3% vs 7.8%; $P = .004$), and subacute forms (0% vs 9.4%; $P = .008$).

Table 2. Meningococcal Disease in Barcelona, Spain (1987-1992): Clinical Manifestations by Bacteriological Form

Clinical Feature	Meningococcal Disease, No. (%) of Patients				
	Meningococcemia (n = 152)	Meningitis (n = 165)	Meningococcemia With Meningitis (n = 150)	Meningococcal Disease Not Microbiologically Proved (n = 176)	All Cases (n = 643)
Fever	148 (97.4)	165 (100)	148 (98.7)	176 (100)	**637** (99.1)
Petechiae	112 (73.7)	94 (57.0)	121 (80.7)	176 (100)	**503** (78.2)
Headache*	25 (16.4)	123 (74.5)	105 (70.0)	101 (57.4)	**354** (55.1)
Nausea/vomiting	51 (33.6)	92 (55.8)	73 (48.7)	85 (48.3)	**301** (46.8)
Meningeal signs	12 (7.9)	129 (78.2)	83 (55.3)	59 (33.5)	**283** (44.0)
Pharyngeal erythema	46 (30.3)	70 (42.4)	58 (38.7)	65 (36.9)	**239** (37.2)
Chills*	67 (44.1)	36 (21.8)	33 (22.0)	29 (16.5)	**165** (25.7)
Abnormal level of consciousness (excluding coma)	11 (7.2)	55 (33.3)	49 (32.7)	40 (22.7)	**155** (24.1)
Maculopapular rash	32 (21.1)	20 (12.1)	26 (17.3)	23 (13.1)	**101** (15.7)
Ecchymosis	20 (13.2)	12 (7.3)	17 (11.3)	24 (13.6)	**73** (11.4)
Myalgia*	22 (14.5)	9 (5.5)	15 (10.0)	21 (11.9)	**67** (10.4)
Abdominal pain*	12 (7.9)	3 (1.8)	9 (6.0)	12 (6.8)	**36** (5.6)
Coma	3 (2.0)	17 (10.3)	5 (3.3)	6 (3.4)	**31** (4.8)
Arthralgia*	6 (3.9)	9 (5.5)	6 (4.0)	6 (3.4)	**27** (4.2)
Hemorrhagic diathesis	9 (5.9)	3 (1.8)	8 (5.3)	5 (2.8)	**25** (3.9)
Seizures	2 (1.3)	6 (3.6)	6 (4.0)	8 (4.5)	**22** (3.4)
Cranial nerve palsies	1 (0.7)	10 (6.1)	3 (2.0)	1 (0.6)	**15** (2.3)
Other focal neurologic signs	0 (0)	5 (3.0)	3 (2.0)	3 (1.7)	**11** (1.7)

**Only patients 6 years or older were considered.*

DIAGNOSTIC DELAY

Seventy-nine patients (12.3%) had been seen by a hospital physician but sent home because they were believed to have an upper respiratory tract infection, meningococcal disease being diagnosed during a subsequent visit. The mean interval between the first visit and the diagnosis was 5.1 (SD, 4.7) hours (median, 8.0 hours; range, 1-27 hours). Three (3.8%) of these 79 patients, compared with 501 (88.8%) of the remaining 564 patients whose conditions were diagnosed while attending the emergency service for the first time, had petechiae ($P<.001$). There were statistically significant differences between patients seen twice and those whose conditions were diagnosed during their first visit, with respect to preadmission antibiotic therapy (59.5% vs 41.5%; OR, 2.07; 95% CI, 1.25-3.46; $P = .003$). The CFR among patients seen twice is statistically lower than that of patients whose conditions were diagnosed in their first hospital visit (0% vs 7.6%; $P = .01$).

COMORBID CONDITIONS

Twenty-four patients (3.7%) had comorbid conditions: liver cirrhosis (11 patients), cancer (5 patients), autoimmune diseases (3 patients), complement deficit (2 patients), acquired immunodeficiency syndrome (1 patient), neutropenia (1 patient), and previous splenectomy (1 patient) performed. The mean age of those patients was 39.8 (SD, 23.7) years (median, 45.0 years; range, 3-89 years). Strikingly, 12 patients (1.9%) had purulent conjunctivitis within 10 days, although the meningococcal cause was ascertained only twice. Serum levels of complement and immunoglobulins were measured, during convalescence, in 487 patients (75.7%). Five patients (1.0%) had a complement deficit, which was C7 in 3 cases and C8 in 2 others. All were children younger than 7 years. Two of them had experienced a previous episode of meningococcal disease.

OTHER EPIDEMIOLOGIC FEATURES

Sixty-three patients (9.8%) had close family members with a past history of proved meningococcal disease. The mean interval between close family member disease and the current episode was 5.2 (SD, 4.8) years (median, 6.9 years; range, 1-27 years). Twenty-four patients (3.7%) had a close relationship to the medical profession, through their own or a household member's job exposure to patients. Sixty-five percent of the cases were diagnosed between November and April, with the maximum in January (96 cases), followed by March (87 cases) and February (78 cases).

CLINICAL FEATURES

In all, 293 patients (45.6%) had an upper respiratory tract infection on admission or during the 5 days prior to admission. The most frequent clinical features were fever and petechiae (**Table 2**). Only 28.2% of patients younger than 2 years and 36.0% of those older than 65 years with meningitis had meningeal signs compared with 78.8% of patients between 2 and 65 years of age ($P<.001$).

CLASSIFICATION

Twenty-five patients (3.9%) had fulminant, 463 (72.0%) acute, and 155 (24.1%) subacute clinical form. The beginning of symptoms could not be determined in only 4

(0.6%) patients and the IST was estimated as previously described. One hundred fifty-two (23.6%) patients had meningococcemia, of whom 13 had occult meningococcemia, 150 (23.3%) meningococcemia with meningitis, 165 (25.7%) meningococcal meningitis, and 176 (27.4%) meningococcal disease not microbiologically proved.

BACTERIOLOGICAL FEATURES

Meningococcal disease was proved microbiologically in 467 patients (72.6%). *N meningitidis* was isolated from 47.0% of blood cultures and from 68.3% of CSF cultures. The diagnostic sensitivity of blood culture decreased by 41.7% (23.5% vs 65.2%, $P<.001$), that of CSF culture decreased by 35.5% (43.6% vs 79.1%, $P<.001$), and that of the gram-stained smear of the CSF by 32.2% (32.9% vs 65.1%, $P<.001$) in patients who had taken preadmission antibiotics. Serogroup B was identified in 360 patients (77.1%), followed by serogroups C (18.8%), Y (0.4%), Z (0.4%), and A (0.2%). Meningococci were nongroupable in 14 patients (3.0%). However, from 1987 to 1992, the incidence of serogroup C increased from 0.82 to 1.29 per 100 000 ($P = .008$), whereas the incidence of serogroup B decreased from 5.11 to 2.82 per 100 000 ($P = .004$). There were no statistically significant differences in the age-specific incidence of serogroup B compared with serogroup C.

Among serogroup B strains, serotype 4 was identified in 189 patients (52.6%), followed by serotypes 15 (23.1%), 2 (3.3%), 1 (2.8%), and 14 (0.28%). Serogroup B meningococci were nontypable in 65 patients (18.1%). The most prevalent subtypes among serogroup B strains were P1.15 (62.8%), followed by subtypes P1.16 (13.6%), P1.7 (13.1%), P1.14 (5.8%), and P1.4 (4.7%). Strains of the P1.15 subtype were most frequently serotype 4 and those of the P1.7 and P1.16 subtype were usually serotype 15.

In regard to serogroup C strains, serotype 2b was identified in 72 patients (81.8%), followed by serotypes 1 (4.5%), 2a (4.5%), and 15 (1.1%). Serogroup C meningococci were nontypable in 7 patients (8.0%). It was not possible to subtype most serogroup C strains (75 patients; 85.2%), the most frequent subtypes being P1.2 (10.2%) and P1.1 (4.5%). Non–subtypable strains were most frequently serotype 2b.

SUSCEPTIBILITY TO ANTIBIOTICS

Only 7 (1.5%) of 467 strains tested were susceptible to sulfonamides, but 296 strains (63.4%) were susceptible to penicillin. However, moderate resistance to penicillin strains increased from 26.5% in 1987 to 43.8% in 1992 ($P<.001$). The MICs of Pen^{MR} strains were 0.1 mg/L in 84 patients (49.1%), 0.2 mg/L in 73 (42.7%), and 0.4 mg/L in 14 (8.2%). No strains were β-lactamase producers. Fifty-nine percent of serogroup C and 27.5% of serogroup B strains were Pen^{MR} (OR, 3.81; 95% CI, 2.28-6.37; $P<.001$). Among serogroup B strains, serotype 15 were more frequently Pen^{MR} than serotype 4 (72.3% vs 21.2%; OR, 9.72; 95% CI, 5.16-18.45; $P<.001$) or nontypable strains (72.3% vs 24.6%; OR, 7.99; 95% CI, 3.59-18.01; $P<.001$). However, in this serogroup, no statistically significant differences with respect to susceptibility to penicillin were found among serotype 4 and nontypable strains (21.2% vs 24.6%; $P = .56$). All the strains were susceptible to chloramphenicol and cefotaxime. However, the range of MICs to cefotaxime of Pen^{MR} strains significantly increased along with the MICs to penicillin. No association was found between mortality or sequelae and susceptibility to penicillin, not even among those who had meningococcal disease caused by Pen^{MR} strains and who were treated with penicillin.

CLINICAL COURSE

The most severe complications were shock in 12.1% of patients, consumption coagulopathy in 7.6%, acute respiratory failure in 6.4%, acute renal failure in 6.4%, seizures in 5.1%, coma in 5.0%, myocarditis in 4.4%, rhabdomyolysis in 2.2%, focal neurologic signs in 0.9%, and hypothermia in 0.2%. Less severe complications included arthritis in 2.3% of patients, cutaneous necrosis in 2.2%, and pleuropericarditis in 0.8%. The mean inpatient stay for survivors was 11.6 (SD, 8.2) days (median, 9.6 days; range, 2-207 days).

MORTALITY

Forty-one patients (6.4%) died, including the one who died of anaphylaxis to penicillin. The CFR was 6.2%. The average annual mortality rate was 0.40 per 100 000 and among children younger than 10 years was 2.23 per 100 000. The potential years of life lost were 1842 (average annual, 18 per 100 000 inhabitants). The fulminant form had a CFR of 44.0%, acute 5.6%, and subacute 1.9% ($P<.001$). Meningococcemia had a CFR of 11.2%, meningococcemia with meningitis 4.7%, and meningococcal meningitis 4.2%. The CFR strongly increased with age (**Figure 2**).

The patient who died because of anaphylaxis to penicillin was excluded from the analysis. There were 19 females (47.5%) and 21 males (52.5%). The mean (SD) age was 41.0 (23.1) years (median, 32.0 years; range, 0.08-79 years). The causes of death were multiorganic failure (26 patients), cerebral edema (10 patients), and myocarditis (4 patients). Meningococcemia was associated with multiorganic failure and myocarditis, whereas all patients with cerebral edema had meningococcal meningitis. Results of univariate analysis for the clinical factors on admission influencing mortality are shown in **Table 3**. The presence of comorbid conditions, shock, fulminant form of meningococcal disease, coma, focal neurologic signs, hemorrhagic diathesis, and age 60 years or older were associated with a poor outcome at the univariate level, whereas the presence of upper respiratory tract infection and adequate preadmission antibiotic therapy were associated with a favorable outcome.

Multivariate analysis identified the following independent predictors of poor prognosis in descending order: hemorrhagic diathesis, focal neurologic signs, and age 60 years or older. Preadmission adequate antibiotic therapy was associated with a favorable prognosis (**Table 4**). Comorbid conditions, upper respiratory tract infection, shock, fulminant form of meningococcal dis-

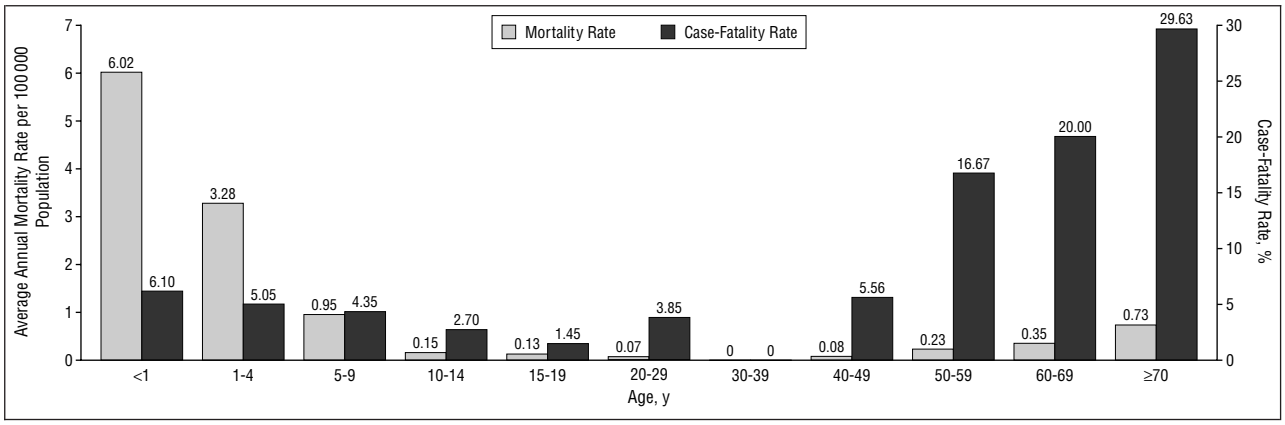

Figure 2. *Meningococcal disease in Barcelona, Spain (1987-1992): average annual mortality rate and case-fatality rate by age group.*

Table 3. Factors on Admission Influencing Mortality in 642 Patients With Meningococcal Disease (Barcelona, Spain, 1987-1992): Univariate Analysis*

Variable	Deaths, No. (n = 40)/ Patients, No. (n = 642)	Case-Fatality Rate, %	OR (95% CI)	*P* Value†
Age, y				
<15‡	22/452	4.9	. . .	. . .
15-59	6/143	4.2	0.85 (0.28-2.23)	.74
≥60	12/47	25.5	6.69 (2.76-15.44)	<.001
Comorbid conditions				
Absent‡	29/618	4.7	. . .	. . .
Present	11/24	45.8	17.19 (6.31-45.25)	<.001
Upper respiratory tract infection				
Absent‡	33/349	9.5	. . .	. . .
Present	7/293	2.4	0.23 (0.09-0.55)	<.001
Preadmission antibiotic				
Not taken‡	38/361	10.5	. . .	. . .
Taken	2/281	0.7	0.06 (0.01-0.24)	<.001
Shock				
Absent‡	17/564	3.0	. . .	. . .
Present	23/78	29.5	13.46 (6.40-28.40)	<.001
Clinical form of meningococcal disease				
Subacute‡	3/154	1.9	. . .	. . .
Acute	26/463	5.6	2.99 (0.90-15.66)	.06
Fulminant	11/25	44.0	39.55 (8.70-235.44)	<.001
Coma				
Absent‡	27/611	4.4	. . .	. . .
Present	13/31	41.9	15.62 (6.28-37.51)	<.001
Focal neurologic signs				
Absent‡	31/616	5.0	. . .	. . .
Present	9/26	34.6	9.99 (3.59-25.85)	<.001
Hemorrhagic diathesis				
Absent‡	25/617	4.1	. . .	. . .
Present	15/25	60.0	35.52 (13.20-96.48)	<.001

**OR indicates odds ratio; CI, confidence interval. Ellipses indicate data not applicable.*
†P *values from* χ^2 *test with continuity correction.*
‡*Reference category.*

ease, and coma were excluded from the multivariate model because of collinearity. We grouped the observed and expected values in 6 categories and found these values to be similar ($P = .38$).

SEQUELAE

Twenty-four patients (3.7%) survived with permanent and disabling sequelae. All of these sequelae were apparent on discharge from hospital. The rate of sequelae was 4.0% (24/602). There were 15 females (62.5%) and 9 males (37.5%). The mean (SD) age was 20.1 (22.9) years (median, 20.0 years; range, 0.08-79 years). Sequelae were sensorineural hearing loss (8 cases), residual focal neurologic signs (5 cases), limb or finger-toe amputation (4 cases), moderate neuropsychological sequelae (4 cases), seizure disorder requiring anticonvulsant therapy (2 cases), and mental retardation (1 case). Residual focal neurologic signs included hemiparesis, ataxia, and blindness. Moderate neuropsychological sequelae included lan-

guage disorder or delay, learning disabilities, concentration and/or memory disorders. The patient with mental retardation also had spastic left hemiparesis, sensorineural hearing loss, and recurrent seizures. Two patients with residual focal neurologic signs also had seizures. A patient 23 years of age required amputations at different levels of all 4 extremities, spending 106 days in the intensive care unit and a total of 207 days in the hospital.

The rate of sequelae was 8.2% for meningococcal meningitis, 3.5% for meningococcemia with meningitis, 1.5% for meningococcemia, and 2.4% for microbiologically unproved meningococcal disease. Meningococcemia was only associated with the appearance of extraneurologic sequelae (limb or finger-toe amputation), whereas all patients with neurologic sequelae had meningococcal meningitis.

Results of univariate analysis for the clinical factors on admission influencing sequelae are shown in **Table 5**. The presence of comorbid conditions, shock, fulminant form of meningococcal disease, coma, focal neurologic signs, hemorrhagic diathesis, and age 15 years and older were associated with the appearance of disabling sequelae at the univariate level, whereas the presence of upper respiratory tract infection and adequate preadmission antibiotic therapy were associated with a favorable outcome without sequelae.

In multivariate analysis, independent predictors of sequelae were hemorrhagic diathesis, focal neurologic signs, and age older than 15 years, whereas receipt of adequate preadmission antibiotic therapy was associated with a favorable outcome without sequelae (**Table 6**). As with mortality, on carrying out the multivariate analysis of predictors of sequelae, comorbid conditions, upper respiratory tract infection, shock, fulminant form of meningococcal disease, and coma were excluded from the model because of collinearity. After grouping the ob-

Table 4. Factors on Admission Influencing Mortality in 642 Patients With Meningococcal Disease (Barcelona, Spain 1987-1992): Multivariate Analysis*

Variable	Coefficient	SE	OR (95% CI)	*P* Value
Preadmission antibiotic	–2.62	0.78	0.07 (0.02-0.34)	<.001
Age, y				
15-59	–0.26	0.60	0.77 (0.24-2.48)	.67
≥60	1.84	0.51	6.32 (2.35-16.99)	<.001
Focal neurologic signs	2.29	0.57	9.86 (3.26-29.83)	<.001
Hemorrhagic diathesis	4.15	0.57	63.38 (20.70-194.10)	<.001

**OR indicates odds ratio; CI, confidence interval.*

Table 5. Factors on Admission Influencing Sequelae in 602 Surviving Patients With Meningococcal Disease (Barcelona, Spain, 1987-1992): Univariate Analysis*

Variable	Patients With Sequelae, No. (n = 24)/ Surviving Patients, No. (n = 602)	Rate of Sequelae, %	OR (95% CI)	*P* Value†
Age, y				
<15‡	7/430	1.6	. . .	. . .
15-59	12/137	8.8	5.80 (2.05-17.71)	<.001
≥60	5/35	14.3	10.07 (2.35-39.02)	<.001
Comorbid conditions				
Absent‡	18/589	3.1	. . .	. . .
Present	6/13	46.2	27.19 (6.69-103.63)	<.001
Upper respiratory tract infection				
Absent‡	20/316	6.3	. . .	. . .
Present	4/286	1.4	0.21 (0.05-0.64)	. . .
Preadmission antibiotic				
Not taken‡	21/323	6.5	. . .	. . .
Taken	3/279	1.1	0.16 (0.03-0.53)	<.001
Shock				
Absent‡	11/547	2.0	. . .	. . .
Present	13/55	23.6	15.08 (5.78-39.32)	<.001
Clinical form of meningococcal disease				
Subacute‡	2/151	1.3	. . .	. . .
Acute	18/437	4.1	3.20 (0.75-28.73)	.17
Fulminant	4/14	28.6	29.80 (3.57-346.70)	<.001
Coma				
Absent‡	18/584	3.1	. . .	. . .
Present	6/18	33.3	15.72 (4.28-51.18)	<.001
Focal neurologic signs				
Absent‡	16/585	2.7	. . .	. . .
Present	8/17	47.1	31.61 (9.13-104.44)	<.001
Hemorrhagic diathesis				
Absent‡	21/592	3.5	. . .	. . .
Present	3/10	30.0	11.65 (1.80-55.06)	.005

**OR indicates odds ratio; CI, confidence interval. Ellipses indicate data not applicable.*
†P *values from* χ^2 *test with continuity correction.*
‡*Reference category.*

served and expected values in 6 categories, we found these values to be similar ($P = .51$).

COMMENT

Nonepidemic meningococcal disease, as is common in developed countries, is characterized by low incidence rates and some hyperendemic periods, the last of which in Spain occurred in the late 1970s, reaching a peak of 17.62 per 100 000 in 1979. Since then, the annual incidence has declined; a relative fall of 34.5% was observed during the study period. When compared with cities, such as London, England; New York, NY; and Washington, DC (Table 1),[31-38] the incidence in Barcelona was higher, probably due to its geographic location within an endemic area and to different notification rates.

The incidence of meningococcal disease is often underestimated by passive surveillance; undernotification ranges from 32% to 51%[39-44] and accounted for 30.9% of cases in the present study. Undernotification is of paramount importance since antimeningococcal chemoprophylaxis and vaccination, when indicated, are initiated when a case of meningococcal disease is reported to the Public Health Service. Thus, every third individual at risk of developing meningococcal disease did not receive adequate protection.

Ever since the first description by Vieusseux,[1] a higher incidence of meningococcal disease has been reported among people with low standards of living.[10,11] We observed the highest incidence in socioeconomically depressed districts, as occurs with other transmissible diseases, such as tuberculosis and acquired immunodeficiency syndrome. However, living in the inner city may have been a greater risk factor by itself, because people in these areas share many other risk factors, such as overcrowded homes, poor nutrition and hygiene, low levels of education, low family income, and higher rates of unemployment.

The issue of initiating antibiotic therapy for meningococcal disease prior to hospital admission has long been a controversial one. Recent articles involving early parenteral administration of penicillin have produced conflicting results,[45-47] but this has not stopped some experts from recommending immediate antibiotic therapy before transfer to hospital when meningococcal disease is suspected clinically.[48-50] The present study confirms that preadmission antibiotic therapy is an independent predictive factor of good prognosis in meningococcal disease not only in regard to mortality but also to the appearance of sequelae. This represents a substantial advance in relation to previous studies[45,46,51] as the beneficial effect in relation to mortality is confirmed and for the first time the capacity of preadmission antibiotic therapy to reduce sequelae in these patients is demonstrated.

Furthermore, the role played by preadmission antibiotic therapy in modifying the clinical form of the disease should also be taken into account.[52] In our cases antimicrobials were, however, given to treat what was thought to be an upper respiratory tract infection. Although evaluating preadmission antibiotic therapy for meningococcal disease was not an objective of the present study, our results suggest that patients with meningococcal disease clearly benefit from it.

Table 6. Factors on Admission Influencing Sequelae in 602 Surviving Patients With Meningococcal Disease (Barcelona, Spain, 1987-1992): Multivariate Analysis*

Variable	Coefficient	SE	OR (95% CI)	*P* Value
Preadmission antibiotic	−1.85	0.66	0.16 (0.04-0.58)	.005
Age, y				
15-59	1.57	0.54	4.79 (1.65-13.89)	.004
≥60	1.90	0.70	6.71 (1.71-26.30)	.006
Focal neurologic signs	2.74	0.63	15.52 (4.51-53.37)	<.001
Hemorrhagic diathesis	3.02	0.94	20.57 (3.24-130.80)	.001

**OR indicates odds ratio; CI, confidence interval.*

Some studies have examined the role of preadmission antibiotic therapy in patients with bacterial meningitis,[53-56] and all agree that the diagnostic sensitivity of microbiological tests is significantly reduced, while its beneficial effect on the mortality and neurologic sequelae rate is debatable.[53,56] However, we should bear in mind that most of these studies include patients with meningitis of different causes and not only meningococcal meningitis, and it would therefore seem logical to suppose that the administration of antibiotics prior to hospital admission may not be effective in these cases.

Meningococcal disease is clinically protean; the conditions of 12.3% of our patients were not diagnosed on the first hospital admission. This occurred more frequently in patients with upper respiratory tract infection, who did not present with petechiae, and whose final diagnosis was occult meningococcemia. Presence of petechiae is almost diagnostic in our circumstances because other diseases, such as rickettsioses and streptococcal or *Haemophilus influenzae* bacteremias, only rarely present such cutaneous signs.[57,58] Sending the patient home after a first visit to the hospital because of undiagnosed early meningococcal disease has 2 important implications. First, the case is generally not severe so the patient can be sent home and, second, they are usually discharged from the hospital with an antibiotic therapy regimen. These facts explain why these patients have a lower CFR than those seen only once, and thus why being seen by a hospital physician is a protective factor for a patient with meningococcal disease.

Serogroup B meningococci are recognized to be the major cause of sporadic meningococcal disease in western Europe.[9,59,60] However, in Spain, since 1988 incidence of meningococcal disease caused by serogroup B meningococci has declined, and incidence due to serogroup C meningococci has increased. These trends have also been observed in other countries.[10,61] This change of pattern has led to the carrying out of a mass vaccination campaign against serogroup C in Spain.

In 1985, the first clinical isolate of *N meningitidis* with decreased susceptibility to penicillin was identified in Spain.[62] The relatively resistant strains have steadily increased in frequency, reaching 43.2% in 1990. The data from our study are consistent with those reported nationwide. There was a great predominance in the resis-

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tance of serogroup C and nongroupable meningococci that were 3.44 times more common among Pen^{MR} strains than in general (81% of serogroup B). The reduction in the sensitivity to penicillin among meningococci did not represent an additional risk for our patients, as with the current levels of resistance, we did not observe statistically significant differences of mortality and sequelae between the cases caused by strains moderately resistant and those sensitive to penicillin.

Meningococcal disease in Barcelona exhibits a mortality rate similar to that reported in other European countries[31,63-65] and in Israel among the Arab population,[40] but higher than that reported in the United States[33-38] and in Israel for Jews.[40] Mortality rate of meningococcal disease in Barcelona is similar to that reported for other infectious diseases such as non-A hepatitis when considering the whole population. However, for children younger than 10 years, meningococcal disease represents the first cause of death of infectious origin, and in every other child younger than 10 years who dies of an infectious disease in Barcelona, the cause of death is meningococcal disease.

As demonstrated recently, hemorrhagic diathesis, focal neurologic signs, and age 60 years or older are independent predictors of death in meningococcal disease microbiologically proved, whereas receipt of adequate antibiotic therapy prior to admission to hospital is associated with reduced likelihood of death.[51] These findings are categorically confirmed in the present study, which includes patients with meningococcal disease not microbiologically proved, and stress the importance of preadmission antibiotic therapy.

The present study shows that only 4% of the survivors who had an episode of meningococcal disease presented with sequelae. Although this percentage is low, it is still very relevant as the sequelae tend to be important from a functional point of view, as occurs with the disabling neurologic sequelae or amputations of extremities. As with the factors predicting death, focal neurologic signs and hemorrhagic diathesis constitute the most reliable indicators of the appearance of sequelae. Moreover, the prior state of health of the individual and preadmission antibiotic therapy are also important, as suggested by the fact that the younger the patients, the less risk they have of presenting sequelae after having an episode of meningococcal disease, and the reduced risk associated with treatment with antibiotics prior to admission.

Meningococcal disease, despite its temporal decreasing incidence, causes substantial morbidity and mortality in Barcelona, especially in children living in the inner city. Active epidemiologic surveillance considerably improved the detection of cases of meningococcal disease. Hemorrhagic diathesis, focal neurologic signs, and age are independent predictors of dismal prognosis. Fortunately, preadmission antibiotic therapy can protect patients with meningococcal disease, as the results of the present study clearly demonstrate that early introduction of antibiotic therapy significantly improves the prognosis of this fearsome disease.

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