

Adult bacterial meningitis: aetiology, penicillin susceptibility, risk factors, prognostic factors and guidelines for empirical antibiotic treatment

C. N. Meyer^{1,2}, I. S. Samuelsson³, M. Galle³ and J. M. Bangsbo⁴

¹Department of Internal Medicine F and ²Department of Respiratory Medicine Y, Gentofte Hospital, Hellerup, ³Department of Epidemiology, Statens Serum Institut, Copenhagen and ⁴Department of Clinical Microbiology, Herlev Hospital, Herlev, Denmark

ABSTRACT

Episodes of adult bacterial meningitis (ABM) at a Danish hospital in 1991–2000 were identified from the databases of the Department of Clinical Microbiology, and compared with data from the Danish National Patient Register and the Danish National Notification System. Reduced penicillin susceptibility occurred in 21 (23%) of 92 cases of known aetiology, compared to an estimated 6% in nationally notified cases ($p < 0.001$). Ceftriaxone plus penicillin as empirical treatment was appropriate in 97% of ABM cases in the study population, and in 99.6% of nationally notified cases. The notification rate was 75% for penicillin-susceptible episodes, and 24% for penicillin-non-susceptible episodes ($p < 0.001$). Cases involving staphylococci, *Pseudomonas* spp. and Enterobacteriaceae were under-reported. Among 51 ABM cases with no identified risk factors, nine of 11 cases with penicillin-non-susceptible bacteria were community-acquired. Severe sequelae correlated independently with age, penicillin non-susceptibility, mechanical ventilation and non-transferral to a tertiary hospital ($p < 0.05$; logistic regression). Other factors that correlated with severe sequelae by univariate analysis only were inappropriate clinical handling, abnormal consciousness, convulsions and nosocomial infection. Overall, the data indicated that neither age alone, community-acquired infection nor absence of identified risk factors can predict susceptibility to penicillin accurately. Recommendations for empirical antibiotic treatment for ABM should not be based exclusively on clinical notification systems with possible unbalanced under-reporting.

Keywords Adult bacterial meningitis, antibiotic treatment, meningitis, penicillin susceptibility

Original Submission: 10 February 2003; **Revised Submission:** 13 November 2003; **Accepted:** 5 December 2003

Clin Microbiol Infect 2004; 10: 709–717

INTRODUCTION

Despite the availability of effective antibiotics, adult bacterial meningitis (ABM) still has severe sequelae and is fatal in 10–50% of patients, depending on the bacterial aetiology [1–4]. The optimal empirical antibiotic regimens are seldom tested in randomised studies, but are usually based on surveillance data. The incidence of penicillin-non-susceptible (PNS) isolates in several northern European countries is <5% for invasive pneumococci, <15% for *Haemophilus influenzae*,

and <1% for meningococci (<http://www.earss.rivm.nl>) [5, 6], while penicillin-susceptible bacteria account for c. 95% of ABM cases according to surveillance data [7, 8]. Discussion has therefore continued as to whether penicillin is an optimal empirical antibiotic regimen for adult meningitis in patients aged <50 or 60 years with no special risk factors [7–9]. In such cases, penicillin alone is recommended in The Netherlands [7, 9], while a third-generation cephalosporin is preferred in the UK [8]. The only existing official guideline in Denmark currently recommends penicillin for all adults, irrespective of age, supplemented with ceftriaxone according to clinical judgement [10]. No specific treatment advice with regard to risk factors, suspected primary focus of infection or nosocomial meningitis is given [10].

Corresponding author and reprint requests: C. N. Meyer, Department of Respiratory Medicine Y, KAS-Gentofte Hospital, Niels Andersens Vej 65, 2900 Hellerup, Denmark
E-mail: cnm@dadlnet.dk

A survey in 1990 demonstrated the absence of consensus in Denmark regarding empirical antibiotic regimens for community-acquired ABM, and indicated that either a penicillin alone, or a third-generation cephalosporin plus a penicillin, was recommended by departments of clinical microbiology and infectious diseases [11]. A follow-up survey in 2001 of 87 departments of internal medicine, infectious diseases and clinical microbiology in Denmark, with a 95% reply rate, demonstrated an equal division between the same two alternatives for empirical treatment [12]. As a substantial number of cases of ABM appear not to be reported to the compulsory National Notification System for Infectious Diseases, the true proportion of bacteria with susceptibility to penicillin, on which the recommendations are based, remains uncertain.

The aim of this study was to identify all cases of ABM admitted to a Danish county hospital during the period 1991–2000, focusing on the aetiology, susceptibility to penicillin, and relationship between risk factors, prognostic factors and outcome, and to assess the expected efficacy of the UK, Dutch and Danish recommendations regarding empirical antibiotic treatment. The following hypotheses were tested: (1) that the aetiological distribution and incidence of penicillin susceptibility in the study population did not differ from that of nationally notified cases of ABM; (2) that the two empirical antibiotic regimens recommended locally would both be effective in >95% of the cases in the study population; (3) that the prevalence of predisposing factors and prognostic factors might differ between patients infected with penicillin-susceptible bacteria and those infected with PNS bacteria.

MATERIALS AND METHODS

Study population

This comprised adult patients (aged >14 years) with bacterial meningitis admitted to Copenhagen County Hospital of Gentofte (a suburban university hospital admitting all patients from a Danish community with 124 470 adult inhabitants) during the period 1991–2000. Neurosurgery was not performed in the hospital, apart from surgery for acoustic schwannomas in the Department of Oto-Rhino-Laryngology (21–39 patients/year). The indication for referral to the department of infectious diseases at a tertiary hospital was not standardised during the study period. The age-group proportions in 1995 in Denmark overall ($n = 5\,215\,718$)

and in the Gentofte Hospital admittance area ($n = 146\,911$), respectively, were: 0–14 years, 17.3% and 15.3%; 15–30 years, 22.9% and 17.9%; 31–40 years, 14.6% and 14.0%; 41–50 years, 15.0% and 15.6%; 51–60 years, 11.3% and 11.6%; 61–70 years, 8.8% and 10.4%; >70 years, 10.2% and 15.3% (<http://www.dst.dk>). A difference in proportions of >0.3% was statistically significant.

Case definition of bacterial meningitis

In patients with a clinical picture of meningitis, *verified bacterial aetiology* was defined as:

1. positive Gram stain or culture-positive cerebrospinal fluid (CSF), or
2. negative Gram stain and culture-negative CSF, with positive blood culture and biochemical findings in CSF compatible with bacterial meningitis not induced by other diseases such as haemorrhage, infarct, or blood admixture (neutrophil pleocytosis $>10 \times 10^6/L$ and protein concentration $>0.6\text{ g/L}$, or a glucose ratio <0.4).

Non-repeated culture of apathogenic bacteria without compatible biochemical changes in CSF was not regarded as significant.

Probable but not verified bacterial meningitis (*unknown aetiology*) was defined as:

1. negative Gram stain and culture-negative CSF and blood, but biochemical findings in CSF compatible with bacterial meningitis not induced by other diseases (haemorrhage, infarct, blood admixture), or
2. when CSF was not available, if the clinical presentation and course of disease were judged as bacterial meningitis and the patient was treated as such.

The latter two groups were identified, but were not included in further analyses. Cases of tuberculous meningitis, mycotic meningitis and neuroborreliosis were excluded. Community-acquired (as opposed to nosocomial) meningitis was categorised according to Centers for Disease Control definitions [13], and was based on the timing of central nervous system symptoms in relation to admission and recent discharge, and on the absence of central nervous system shunts and catheters.

Data sources

1. Department of Clinical Microbiology of Copenhagen County, Herlev Hospital, Denmark, which receives all microbiological samples from Gentofte Hospital: cases with a positive Gram stain or culture-positive CSF in the ADBakt database (Autonik, Sköldinge, Sweden). In addition, all cases with negative microbiological results, but with polymorphonuclear leukocytosis in CSF, were reviewed for possible bacterial meningitis in the medical records.
2. Department of Internal Medicine F, Gentofte Hospital, Denmark: cases with a discharge diagnosis of bacterial meningitis.
3. The National Notification System for Infectious Diseases, Department of Epidemiology, Statens Serum Institut (SSI data), Copenhagen, Denmark: notified cases of bacterial meningitis with a clinical diagnosis of bacterial meningitis or identified bacteria in CSF. Notification is compulsory, independent of whether infection was nosocomial or community-acquired.

4. Departments of Medical Officers of Health for Copenhagen Municipality and County: cases with bacterial meningitis notified by telephone or in writing, and admitted to Gentofte Hospital, with no differentiation between community-acquired and nosocomial infection.
5. The National Patient Register: cases with a discharge diagnosis of bacterial meningitis admitted to Gentofte Hospital in 1991–2000.

Definitions

Empirical antibiotic treatment of adult bacterial meningitis

This was defined as the initial therapy prescribed by the Department of Internal Medicine at Gentofte Hospital before the aetiology was indicated or identified by Gram stain or culture. From 1991 to 1995, this comprised intravenous penicillin 15–20 million U/day or ampicillin 12 g/day, as recommended during the entire study period on a national basis. From 1996, intravenous penicillin or ampicillin was prescribed in the doses indicated above plus ceftriaxone 4 g/day, as recommended by the local department of internal medicine and the regional tertiary hospital departments of infectious diseases and clinical microbiology. The presence of nosocomial infection, identified risk factors or immunosuppression necessitated relevant broad-spectrum antibiotic therapy, but this was not specified in the local or national recommendations.

Antibiotic susceptibility testing

Criteria for determining reduced susceptibility to penicillin were those of the Swedish Reference Group for Antibiotics (SRGA; <http://www.ltkronoberg.se/ext/raf/artmic2.htm>). Antibiotic susceptibility testing was performed with AB Biodisks (Solna, Sweden) on PDM II sensitivity medium, with blood supplementation if relevant. The breakpoints used were generally according to the recommendations of the SRGA then in force. For penicillin G, these were: susceptible (S), MIC ≤ 2 mg/L; intermediately susceptible (I) or resistant (R) (= PNS), MIC > 2 mg/L. Species-specific breakpoints for *Streptococcus pneumoniae* were: S, MIC ≤ 0.094 mg/L; I, MIC 0.094 to < 2 mg/L; R, MIC ≥ 2 mg/L.

Data on antibiotic susceptibility were not available in the National Notification System of Infectious Diseases, but were expected to be similar to published data for bacteraemia [14]. Therefore, all enteric Gram-negative bacilli, all *Staphylococcus epidermidis*, 90% of *Staphylococcus aureus*, 15% of *H. influenzae* and 2% of *S. pneumoniae* causing ABM were assumed to have reduced susceptibility to penicillin in the SSI data.

Primary meningitis was defined as a case with no verified primary focus of infection following clinical, microbiological and radiological tests.

Data analysis

Clinical data for ABM patients identified in the medical records included: the pre-admittance course and antibiotic treatment; time-points of admittance, lumbar puncture and empirical antibiotic treatment; risk factors as defined below; symptoms; clinical observations; final antibiotic therapy and supplementary treatment; microbiological findings, penicillin susceptibility and advice given by the doctors from the Department of Clinical Microbiology; biochemical findings; and sequelae. Risk factors included alcohol misuse, liver

cirrhosis, diabetes mellitus, splenectomy, malignancy, severe rheumatological disease, primary or secondary immunosuppression, recent head trauma (within 2 months), hydrocephalus with CSF shunt, previous meningitis, or surgery for acoustic schwannoma. Severe sequelae included bilateral anacusis, comprehensive vestibular, neurological or cognitive deficits, amputation of extremities, and death. Mild sequelae included moderate hearing loss, mild tinnitus, slight vestibular, neurological or cognitive deficits, and peripheral joint amputation of fingers or toes.

Any delays in diagnosis or in administration of empirical antibiotic treatment were noted on the basis of times of admittance, CSF and blood sampling, and intravenous antibiotic administration, all of which were documented accurately. Time-points of the accompanying symptoms and clinical findings were documented less accurately. From the symptoms and clinical findings described in the medical records, the diagnosis of bacterial meningitis at the time of admittance to the hospital was assessed as obvious, possible, or not to be expected. Accordingly, the *clinical handling* of each patient admitted to hospital was defined as *appropriate* if the delay in diagnosis was ≤ 4 h, the delay in administration of empirical antibiotic treatment was ≤ 2 h, and a regimen of empirical antibiotics, as defined above, was given initially at $\geq 0.5 \times$ the recommended dosage for cases of suspected bacterial meningitis. *Inappropriate* handling was defined as a delay in diagnosis of > 4 h, or a delay in administration of empirical antibiotic treatment of > 2 h, or empirical antibiotic treatment that differed from the recommendations above, or an initial dosage $< 0.5 \times$ the recommended dosage for cases of suspected bacterial meningitis.

Clinical microbiological advice, as recorded in the patient chart and in the ADBakt data base, was defined as *appropriate* if any deviations from departmental guidelines and recommendations were considered of minor importance. *Inappropriate* advice was recorded when one of the following was advised: penicillin alone for nosocomial meningitis, for immunodeficient patients, or for patients who had recently visited (< 3 days) countries with a high prevalence of PNS pneumococci; ampicillin as monotherapy for Gram-negative bacteria before susceptibility results were known; single-antibiotic therapy (including ceftriaxone alone) for *Pseudomonas* spp.; an antibiotic dose of $< 0.5 \times$ the recommended dose; and if immediate microscopy was not advised despite a clinical suspicion of meningitis, as these major deviations from recommendations could contribute to an unfavourable outcome.

Statistics

Non-parametric analysis with chi-square test with likelihood ratio, Yates's correction or Fisher's exact test was used for categorical data and proportions. The Mann–Whitney *U*-test and the Kruskal–Wallis test were used for continuous data. Logistic regression modelling was performed for outcome data. The expected probable correlations were decided beforehand, and corrections for multiple testing were not performed on these grounds. Epi-Info software v. 6.04b (WHO, Geneva, Switzerland) and SPSS software v. 6.1.2. (SPSS Inc., Chicago, IL, USA) were used. The level of statistical significance was defined as $p < 0.05$.

The study was approved by the Danish Register Authorities (j. no. 2001-41-1017; Datatilsynet, Copenhagen, Denmark).

RESULTS

In total, 130 patients with verified or probable ABM were admitted, with 92 cases of verified bacterial aetiology (Table 1) and 38 (29%) cases of unknown aetiology. Mortality was 25% for all cases and 32% for verified cases. Further analyses were done on verified ABM cases only. Fifty-eight (63%) of the verified ABM cases were reported, but notification rates were lower for cases involving *Staph. aureus* or enteric Gram-negative bacteria (Table 1). The notification rate was 72% (58/81) for community-acquired meningitis cases vs. 0/11 for nosocomial cases. The overall notification rates did not change between age groups or with time, apart from a difference in notification rates seen for *S. pneumoniae* between the first and second 5-year periods (35% and 92%, respectively), coinciding with the implementation of active surveillance for this species. Active surveillance for *Neisseria meningitidis* was on-going during the entire study period.

A comparison between the study population and all cases of ABM notified nationally (SSI data) demonstrated a significant difference in the microbiological distribution ($p < 0.001$), with relatively fewer cases of *N. meningitidis* (16% vs. 54%) and more cases of *Staph. aureus* (12% vs. 3%) and *Escherichia coli* (5% vs. 0.8%) in the study population (Table 1). The median age was higher in the study population (69 vs. 50 years; $p < 0.001$; Fig. 1A), and the male:female ratio was lower (0.50 vs. 0.99; $p < 0.05$), compared to the SSI data. According to the criteria in the case definition, the diagnostic contributions to ABM in the study population are presented in Table 2.

One patient had a CSF sample with 1456 leukocytes that contained Gram-negative diplococci with no positive cultures, but with cutaneous petechiae. This patient was included as an *N. meningitidis* case with predictable susceptibility to penicillin.

Twenty-one of the 92 cases in the study population had reduced susceptibility to penicillin (23%; 95% CI 15–33), comprising ten *Staph. aureus* (10/11 *Staph. aureus*), eight Enterobacteriaceae (8/8), one *H. influenzae* (1/3), one *Staph. epidermidis* (1/1), and one *S. pneumoniae* (1/40) (Table 3). Ten of these 21 patients received adequate initial antibiotic treatment according to post-hoc evaluation. A primary focus was identified in 14 of these 21 cases, although with a considerable time lapse between the diagnosis of meningitis and identification of the primary focus (range 0–72 h). The proportion of bacterial isolates with reduced penicillin susceptibility among the cases of ABM notified nationally (SSI data), as estimated from regional bacteraemia data, was 6% (86/1437) of cases (Table 3), compared with 23% (21/92) in the study population ($p < 0.001$). The PNS bacteria were not found among patients in the study population aged <30 years ($n = 34$), but the proportion of these bacteria was higher in all other age groups compared to the SSI data population. This was also found with the community-acquired cases only (Fig. 1B). These differences were statistically significant by subgroup analysis in the three groups aged >50 years ($p < 0.05$).

Reduced susceptibility to penicillin occurred in 13 (16%) of the 81 community-acquired cases in the study population, compared to eight (73%) of the 11 episodes among the nosocomial cases

	Gentofte Hospital					SSI data ^a	
	Fatal cases	Notified cases	Community-acquired	Nosocomial	All cases (%)	All (notified) cases (%)	p
<i>Streptococcus pneumoniae</i>	12	29	40	–	40 (43)	597 (42)	0.72
<i>Neisseria meningitidis</i>	–	15	15	–	15 (16)	643 (54)	< 0.001
<i>Listeria monocytogenes</i>	2	5	7	–	7 (8)	53 (4)	0.09
<i>Staphylococcus aureus</i>	6	3	8	3	11 (12)	44 (3)	< 0.001
Haemolytic streptococci	3	3	4	2	6 (7)	38 (3)	0.04
<i>Haemophilus influenzae</i>	2	2	3	–	3 (3)	34 (2)	0.48
<i>Escherichia coli</i>	2	–	3	2	5 (5)	12 (0.8)	0.002
<i>Pseudomonas</i> spp.	2	–	–	2	2 (2)	3 (0.2)	
<i>Staphylococcus epidermidis</i>	–	–	–	1	1 (1.1)	0	
<i>Capnocytophaga canimorsus</i>	–	1	1	–	1 (1.1)	4 (0.3)	
<i>Enterobacter cloacae</i>	–	–	–	1	1 (1.1)	1 (0.1)	
Others, known	–	–	–	–	–	8 (0.6)	1.0
Total no.	29 (32%)	58 (63%)	81	11	92 (100)	1437 (100)	

^aNational Notification System for Infectious Diseases.

Table 1. Distribution of pathogens in patients with verified adult bacterial meningitis 1991–2000

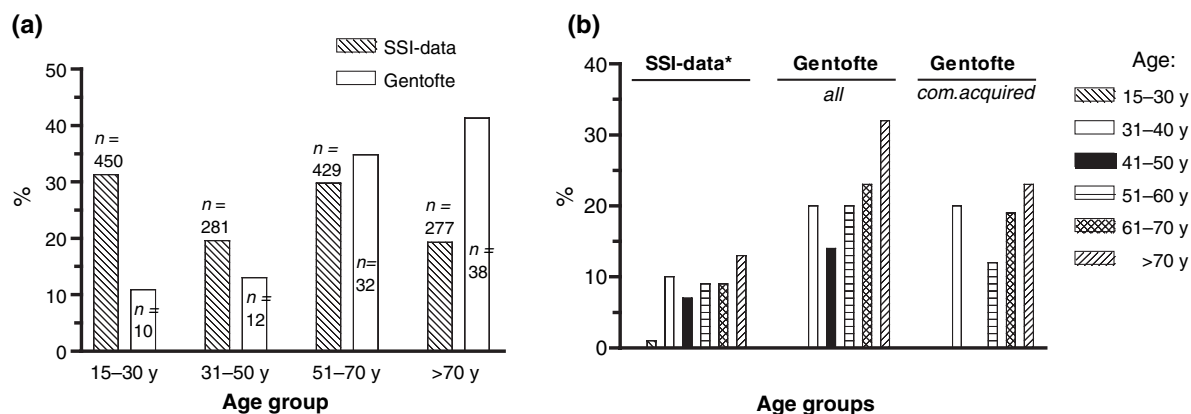


Fig. 1. (a) Age distribution for cases of verified adult bacterial meningitis (ABM) at Gentofte Hospital ($n = 92$) compared to nationally notified cases (SSI data, $n = 1437$), 1991–2000. (b) Percentage of penicillin non-susceptibility in ABM patients according to age group in SSI data, and at Gentofte Hospital for all cases and for community-acquired cases only, 1991–2000.

Table 2. Diagnostic indications for 92 cases of verified adult meningitis at Gentofte Hospital during 1991–2000

	CSF positive by Gram stain	Culture- positive CSF	Culture- positive blood	Biochemistry- positive CSF
Total	55 (60%)	75 (82%)	73 (79%)	78 (85%)
Single diagnostic result	1 (1%)	9 (10%)	10 (11%)	0
Missing data	1 (1%)	1 (1%)	1 (1%)	6 (6%)

($p < 0.001$). The 13 community-acquired cases included eight *Staph. aureus*, three *E. coli*, one *H. influenzae* and one *S. pneumoniae*, and nine of these 13 patients had no risk factors. Among the 51 cases of ABM without risk factors, 11 patients (age range 33–93 years) were infected with PNS

bacteria. Most (9/11) of these cases were community-acquired infections, with one patient aged < 50 years.

Staph. aureus accounted for almost half of the PNS cases and deserves special attention. The mortality rate among cases of *Staph. aureus* meningitis was 55%, and no sequelae resulted among the survivors. Eight of the 11 *Staph. aureus* cases were community-acquired infections, and five of these eight patients had no risk factors (age range, 60–84 years). Three patients had no identified primary focus if bacteraemia was excluded. Nosocomial meningitis was secondary to neurosurgery (one case), post-operative subcutaneous wound infection (one case), and the presence of a central nervous system shunt (one case). Other

Table 3. Distribution of pathogens according to penicillin susceptibility among patients with verified adult bacterial meningitis during 1991–2000

	Gentofte Hospital		SSI data ^a	
	Penicillin non-susceptible $n = 21$	Penicillin susceptible $n = 71$	Penicillin non-susceptible $n = 86$	Penicillin susceptible $n = 1351$
<i>Streptococcus pneumoniae</i>	1 ^b	39	15	582
<i>Neisseria meningitidis</i>	0	15	0	643
<i>Listeria monocytogenes</i>	0	7	0	53
<i>Staphylococcus aureus</i>	10	1	42	2
Haemolytic streptococci	0	6	0	38
<i>Haemophilus influenzae</i>	1	2	5	29
<i>Escherichia coli</i>	5	0	12	0
<i>Pseudomonas</i> spp.	2	0	3	0
<i>Staphylococcus epidermidis</i>	1	0		
<i>Klebsiella</i> spp.			3	0
<i>Capnocytophaga canimorsus</i>	0	1	0	4
<i>Salmonella</i> spp.			1	0
<i>Enterobacter cloacae</i>	1	0	1	0
<i>Proteus vulgaris</i>			1	0
Enterococci			1	0
Anaerobes, unspecified			2	0
Notified	5	53	86	1351

^aEstimated from regional bacteraemia data.

^bIntermediate susceptibility (MIC 0.125–1 mg/L).

primary infectious foci were identified later during the illness in one patient with endocarditis, two patients with septic arthritis, one patient with osteomyelitis, and one patient with a subcutaneous abscess. Although all cases except the post-neurosurgical patient had positive blood cultures, the tentative diagnosis of septicaemia or meningitis was not made initially. Instead, the tentative diagnoses on hospital admittance included back pain, myocardial infarction, pneumonia, influenza, intoxication, hydrocephalus and liquorrhea.

The Danish national recommendation of initial empirical treatment of ABM with penicillin monotherapy was assessed as adequate according to the susceptibility results in 77% (71/92) of the cases in the study population, and in 94% (1351/1437) of the cases in the SSI data (Table 3). Excluding the patients with risk factors, nosocomial infection or aged >60 years (by analogy with the Dutch recommendations [7]), 88% (15/17) would be treated adequately with penicillin monotherapy. If the UK recommendation of ceftriaxone or cefotaxime was used [8], possibly implying that listeriosis occurs seldom in patients aged 18–50 years without risk factors, the patients in the study population were all (20/20) treated appropriately.

An alternative antibiotic regimen used widely in Denmark for ABM [12], consisting of a penicillin plus ceftriaxone, was adequate for 97% of the episodes (89/92) in the study population, and in 100% of community-acquired cases ($n = 81$). Two cases caused by *Pseudomonas* spp. and one caused by a methicillin-resistant *Staph. aureus* strain among the nosocomial cases would not be covered initially by this latter antibiotic regimen, which would be expected to be adequate in 99.6% (1430/1437) of cases notified nationally (SSI data; Table 3).

In the study population, the patient group with ABM caused by bacteria with reduced penicillin susceptibility had a higher rate of severe sequelae, including death (62% vs. 30%; Table 4), and had a lower rate of notification (24% vs. 75%; Table 3), compared to patients with ABM caused by penicillin-susceptible bacteria. With regard to the prognostic factors (Table 4), a higher proportion of patients with PNS bacteria had nosocomial infection (38% vs. 4%), experienced deteriorating consciousness during their hospital stay (57% vs. 31%), were handled in a clinically inappropriate manner (52% vs. 25%), and were associated with

Table 4. Outcome, prognostic factors and predisposing factors among cases of verified adult bacterial meningitis at Gentofte Hospital during 1991–2000

	Known aetiology		p value ^a	Total $n = 92$
	Penicillin non-susceptible $n = 21$	Penicillin susceptible $n = 71$		
Outcome				
Death	10	19	0.12	29
Sequelae, severe	13	21	0.01	34
Sequelae, total	14	37	0.35	51
Prognostic factors				
Inappropriate handling	12	18	0.01	30
CMA, inappropriate	5	2	0.006	7
DIC	0	8	0.19	8
Septic shock syndrome	9	27	0.88	36
Mechanical ventilation	7	42	0.06	49
Reduced consciousness	16	61	0.32	77
Deteriorated consciousness	12	22	0.05	34
Convulsions < 24 h	1	16	0.11	17
Tertiary transferral ^b	7	37	0.20	44
Age, median (years)	72	68	0.09	–
Nosocomial meningitis	8	3	< 0.001	11
Predisposing factors				
Risk factors, any	10	31	0.94	41

CMA, clinical microbiological advice; DIC, disseminated intravascular coagulation.

^aUnivariate estimates (chi-squared test).

^bTransferral to the Department of Infectious Diseases at a tertiary-level university hospital.

inappropriate advice from the Department of Clinical Microbiology (24% vs. 3%). No statistically significant differences were demonstrated between the two groups in terms of age, mortality rate, prevalence of septic shock syndrome or disseminated intravascular coagulation, or prevalence of any risk factors.

The possible association of prognostic factors and relevant biochemical parameters with outcome was analysed for all 92 episodes of ABM. The outcome measure of severe sequelae (which included death) was associated by univariate analysis ($p < 0.05$) with older age, reduced penicillin susceptibility, nosocomial infection, inappropriate clinical handling, delay in administration of adequate antibiotic treatment, abnormal mental state at admission, deteriorating consciousness, convulsions, a higher proportion of positive blood cultures, a higher level of leukocytosis in CSF, a lower level of leukocytosis in peripheral blood, a low haemoglobin concentration, and failure to transfer the patient to a tertiary hospital department of infectious disease. In a logistic regression model, severe sequelae were associated independently with age (OR = 1.10; 95% CI 1.05–1.17; $p < 0.001$), mechanical ventilation (OR = 7.9; 95% CI 1.8–33.9; $p < 0.01$), reduced penicillin susceptibility (OR = 6.5; 95% CI 1.4–30.9; $p < 0.05$), and transfer

to a department of infectious diseases (OR = 0.21; 95% CI 0.06–0.80; $p < 0.05$).

DISCUSSION

Notification of bacterial meningitis in other countries has been described as incomplete [15, 16], and at Gentofte Hospital, a notification rate of only 63% for verified cases was demonstrated by thorough case finding using all available data sources. Registration bias concerning primary diagnoses and notification was demonstrated in the study population, as notification occurred in only 24% of cases with reduced susceptibility to penicillin and in none of the nosocomial cases. Episodes with these aetiologies may also be under-represented markedly among the notified cases on a national level, and the extent of this under-notification needs to be clarified further. Jensen *et al.* [17] retrospectively described 104 Danish cases of *Staph. aureus* meningitis from 1986 to 1989, but only 14 cases were notified nationally in the same period, confirming the very low notification rates of certain bacteriological aetiologies if an active surveillance system is not established. As neither the age-group-specific rates of notification nor the median age of ABM patients from other Danish hospitals were available, it is uncertain whether the noted deviation towards older meningitis patients in the study population is representative. Cases of purulent meningitis where a bacterial aetiology could not be demonstrated were excluded from further analyses, as the clinical picture and biochemical changes might have been caused by other events, including viral infection or vascular-related episodes.

The aetiological distribution of ABM in a recent Dutch national survey [7] implicated PNS bacteria (staphylococci, enterococci, *P. aeruginosa*, *E. coli*) in c. 10% of cases. The median age of the patients was not stated, but an age-based classification was used [7]. In the present study population, the age distribution of the cases with reduced susceptibility to penicillin was not statistically different from that of the cases caused by penicillin-susceptible bacteria. Compared to cases notified nationally, the higher median age in the study population may contribute to a different microbiological spectrum because of an association with a higher prevalence of risk factors, immuno-incompetence and vulnerability to disease.

Despite age-group stratification, the proportion of penicillin-susceptible bacteria differed between the two populations. An unbalanced national under-reporting of nosocomial cases could contribute to this result. As no national data were available regarding the prevalence of risk factors in all notified ABM patients, the possible influence on the distribution of bacterial pathogens and the related outcome could not be evaluated. The male:female ratio decreased with advanced age in both ABM populations, similar to the official demographic data (<http://www.dst.dk>), and the higher mean age of the study population may thus explain the difference in gender ratio between the two populations.

A substantial proportion of the identified bacteria in the study population were PNS, compared with the estimated proportion from the SSI data. A penicillin susceptibility rate of <93% was also found among the subgroups of community-acquired cases aged 30–60 years with no risk factors (as categorised in the Dutch recommendations). In practice, the presence of risk factors or a primary focus in ABM may often be concealed at the time of initial antibiotic treatment, but previous reports have not supplied data on the frequency of this problem. With this background, empirical penicillin monotherapy cannot be recommended initially for the group aged 30–60 years (the Dutch and the Danish recommendations), regardless of the absence of risk factors. As the frequency of highly penicillin-resistant pneumococci (MIC ≥ 2 mg/L) is extremely low in Denmark (none were found in the present study), vancomycin still has no role in the initial treatment of pneumococcal meningitis before susceptibility results are available.

Bacterial meningitis results in a large proportion of serious sequelae, and several authors have considered the extent to which the prognosis is changed by a moderate delay in diagnosis or by a delay in administration of adequate treatment [1, 18–20]. No exact consensus is evident, as bacterial meningitis is heterogeneous with regard to bacterial aetiology and virulence, rate of disease progression, risk factors (such as impaired host immunocompetence) and disease severity, but treatment delay in relation to symptom progression is not expected to benefit patient outcome.

In the present study, with a relatively modest number of ABM cases, age, reduced susceptibility to penicillin, mechanical ventilation and

failure to transfer the patient to a tertiary hospital each correlated independently with severe sequelae by multivariate model analysis. Correlation with severe sequelae by univariate analysis was demonstrated for several other parameters (delay in initiation of antibiotic treatment, inappropriate clinical handling in general, inappropriate microbiological advice, a low peripheral leukocyte count, and a high CSF leukocyte count at the time of lumbar puncture), all of which may be associated closely with the age parameter. This is in accordance with the more non-specific symptoms and clinical signs of ABM noted with greater age [21, 22], and underscores the importance of a low threshold of suspicion regarding bacterial meningitis, especially among elderly patients. Other factors related closely to the outcome measure were not included in the logistic regression model, but in accordance with earlier reports [1, 23], decreased mental status at admission, deteriorating consciousness and the occurrence of convulsions were also associated with a poor outcome by univariate analysis. The factor of transferral to a tertiary hospital department of infectious diseases was associated with a better outcome, but the importance of this is uncertain because triage of the patients did not follow standardised guidelines during the period, and may therefore conceal confounding factors. The incidence of cases with inappropriate clinical handling (33% overall) and inappropriate microbiological advice (8% overall) should not be neglected, and may indicate a need for further case analyses and quality control of clinical practice.

Possible factors that may influence the outcome of ABM include early diagnosis based on a high level of clinical attentiveness, compliance with updated and evidence-based guidelines, and swift and adequate antibiotic treatment based on the expected susceptibility and appropriate clinical microbiological advice. These factors may be improved by on-going systematic quality control and feedback. In many northern European countries, the prevalence of PNS *S. pneumoniae* isolates is <5%, while the prevalence of methicillin-resistant *Staph. aureus* is <1% in The Netherlands and in Scandinavian countries (<http://www.earss.rivm.nl>). Despite similar susceptibility patterns, evident differences appear in the national guidelines for ABM. Future therapeutic guidelines should not be based exclusively on the bacterial distributions reported in compulsory

notification systems of infectious diseases, delivered overwhelmingly by clinicians, as unbalanced under-reporting of certain bacteria seems to be present. In contrast to (e.g.) the present Dutch guidelines, penicillin monotherapy may not be adequate as initial empirical antibiotic therapy for patients aged 30–60 years, even when no risk factors or co-morbidities are identified. As several of the current national recommendations for ABM may be based on partially incomplete data, there is a further need to minimise unbalanced under-reporting, possibly by supplementary active surveillance with data from electronic laboratory reporting.

REFERENCES

1. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998; **129**: 862–869.
2. Sigurdardottir B, Bjornsson OM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S. Acute bacterial meningitis in adults. A 20-year overview. *Arch Intern Med* 1997; **157**: 425–430.
3. Schmutzhard E, Williams KJ, Vukmirovits G, Chmelik V, Pfäusler B, Featherstone A. A randomised comparison of meropenem with cefotaxime or ceftriaxone for the treatment of bacterial meningitis in adults. Meropenem Meningitis Study Group. *J Antimicrob Chemother* 1995; **36**(suppl A): 85–97.
4. Hussein AS, Shafran SD. Acute bacterial meningitis in adults. A 12-year review. *Medicine (Baltimore)* 2000; **79**: 360–368.
5. Kyaw MH, Bramley JC, Clark S, Christie P, Jones IG, Campbell H. Prevalence of moderate penicillin resistant invasive *Neisseria meningitidis* infection in Scotland, 1994–9. *Epidemiol Infect* 2002; **128**: 149–156.
6. Hasbun R, Aronin SI, Quagliarello VJ. Treatment of bacterial meningitis. *Comp Ther* 1999; **25**: 73–81.
7. van De Beek D, de Gans J, Spanjaard L, Vermeulen M, Dankert J. Antibiotic guidelines and antibiotic use in adult bacterial meningitis in The Netherlands. *J Antimicrob Chemother* 2002; **49**: 661–666.
8. Begg N, Cartwright KA, Cohen J *et al.* Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. British Infection Society Working Party. *J Infect* 1999; **39**: 1–15.
9. Roord JJ, Kaandorp CJ. CBO-guideline 'Bacterial meningitis'. *Ned Tijdschr Geneesk* 2001; **145**: 211–214.
10. Justesen T, Korsager B, Kolmos HJ, Gerstoft J. Recommendations in the use of antibiotics. In: Aldershvile J, Hansen MS, Kampmann JP, Vej-Hansen B, eds. *The drug index 2001/2002*. Copenhagen: The Danish Medical Association, 2002; 831–855.
11. Eriksen NH, Scheibel J, Vejlsgaard R. Purulent meningitis in Denmark. *Nord Med* 1990; **105**: 252–254.

12. Meyer CN. Empirical antibiotic therapy for purulent meningitis in Danish adults. *Ugeskr Laeger* 2003; **165**: 34–37.
13. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16**: 128–140.
14. Pedersen G, Schonheyder HC, Steffensen FH, Sorensen HT. Risk of resistance related to antibiotic use before admission in patients with community-acquired bacteraemia. *J Antimicrob Chemother* 1999; **43**: 119–126.
15. Goldacre MJ, Miller DL. Completeness of statutory notification for acute bacterial meningitis. *BMJ* 1976; **2**: 501–503.
16. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. *J Infect Dis* 1990; **162**: 1316–1323.
17. Jensen AG, Espersen F, Skinhoj P, Rosdahl VT, Frimodt-Moller N. *Staphylococcus aureus* meningitis. A review of 104 nationwide, consecutive cases. *Arch Intern Med* 1993; **153**: 1902–1908.
18. Radetsky M. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. *Pediatr Infect Dis J* 1992; **11**: 694–698.
19. Johnson JR. Delayed treatment of bacterial meningitis. *Ann Intern Med* 1999; **131**: 715.
20. Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. *J Emerg Med* 2001; **21**: 387–392.
21. Miller LG, Choi C. Meningitis in older patients: how to diagnose and treat a deadly infection. *Geriatrics* 1997; **52**: 43–55.
22. Rasmussen HH, Sorensen HT, Moller-Petersen J, Mortensen FV, Nielsen B. Bacterial meningitis in elderly patients: clinical picture and course. *Age Ageing* 1992; **21**: 216–220.
23. Moller K, Frederiksen EH, Wandall JH, Skinhoj P. Meningitis caused by streptococci other than *Streptococcus pneumoniae*: a retrospective clinical study. *Scand J Infect Dis* 1999; **31**: 375–381.