Bacterial meningitis in adults

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Chapter 4

Antibiotic Guidelines and Antibiotic Use in Adult Bacterial Meningitis in The Netherlands

Diederik van de Beek, Jan de Gans, Lodewijk Spanjaard, Marinus Vermeulen, Jacob Dankert

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ABSTRACT

In The Netherlands, national consensus-based guidelines for the treatment of adult patients with bacterial meningitis were introduced in October 1997. In 1998 we began a prospective, nationwide study to evaluate the compliance with these consensus-based guidelines. In addition, we evaluated whether the recommended initial treatment provides adequate microbiological coverage. From October 1998 to January 2000, 365 adults with bacterial meningitis were identified using information from The Netherlands Reference Laboratory for Bacterial Meningitis; 263 patients were classified into four categories depending on patient's age and underlying health status. In the first category, patients 16 to 60 years without risk factors, Neisseria meningitidis was the most common pathogen (53 percent); 62 of 127 patients (49 percent) received treatment in compliance with the guidelines. In the second and third categories, patients >60 years without risk factors and those with risk factors independently of age, Streptococcus pneumoniae caused 61 percent and 58 percent of cases, respectively. Compliance in these categories was about 17 percent. Overall, 33 percent of patients received treatment in compliance with the guidelines. The microbiological coverage of patients treated in compliance and not in compliance with the guidelines was 98 percent and 93 percent, respectively. In conclusion, one year after national consensus-based guidelines for the initial treatment of adult patients with bacterial meningitis were introduced in The Netherlands, only one-third of Dutch physicians were adhering to the guidelines. The microbiological coverage for the patients who were treated in compliance with the guidelines was almost complete (98 percent).

INTRODUCTION

Since chemotherapeutics and antibiotics became clinically available, bacterial meningitis has become a curable disease. Nevertheless, lethality of this disease and frequency of sequelae among those surviving remain substantial. Early administration of an optimal antibiotic therapy for bacterial meningitis has shown to be essential to minimize lethality and morbidity. For many years, penicillin was the drug of choice in the treatment of bacterial meningitis. The increasing prevalence of resistant bacteria and reduction in incidence rates of Haemophilus influenzae type b (Hib) meningitis due to Hib vaccination have changed the behavior of most physicians in prescribing antibiotics for patients with meningitis in the last 10 year. Recommendations in various countries for the initial antibiotic therapy in children and adults with bacterial meningitis have been provided. In The Netherlands in 1996, a working-group was asked to provide national guidelines for the initial treatment of patients with bacterial meningitis. This working-group consisted of 17 Dutch experts in the field of bacterial meningitis and included pediatricians, neurologists, medical microbiologists, internists, neurosurgeons and public health care workers. They prepared draft guidelines, which were discussed and adjusted in a national consensus meeting in 1997. All medical doctors involved in the treatment of patients with bacterial meningitis were invited to participate in the consensus meeting, and all received a booklet containing the guidelines. After the meeting, this booklet was widely disseminated in 1997. In 1998, 1 year after the guidelines were published, we began a prospective, nationwide
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study to evaluate the compliance with these consensus-based guidelines. In addition, we evaluated whether the recommended initial treatment provided adequate microbiological coverage.

Table 1. National recommendations for the initial treatment of adults with bacterial meningitis in The Netherlands (1997).10

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 16-60 years</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>Amoxicillin and third-generation cephalosporin</td>
</tr>
<tr>
<td>With risk factor present* and age &gt;16 years</td>
<td>Amoxicillin and third-generation cephalosporin</td>
</tr>
<tr>
<td>Recent neurosurgery and age &gt;16 years</td>
<td>Vancomycin and third-generation cephalosporin</td>
</tr>
</tbody>
</table>

*Alcohol abuse, altered immune status, recent head injury, cerebrospinal fluid leak.

METHODS

Patients of at least 16 years of age with meningitis in the period from October 1998 to January 2000 were identified using the database of The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM). This laboratory is a collaboration of the Academic Medical Center (AMC, Amsterdam, The Netherlands) and the National Institute of Public Health and the Environment (RIVM, Bilthoven, The Netherlands). Since 1975, the NRLBM has received cerebrospinal fluid and blood isolates from approximately 85 percent of all patients with bacterial meningitis in The Netherlands (population, 15.8 million).11,12

Daily, the NRLBM provided the investigators with the names of the physicians and hospitals where adult patients with bacterial meningitis had been admitted 2 to 6 days earlier. Physicians were contacted by telephone, and were informed about the study. All patients received written information concerning the study and were asked to give informed consent for participation. Subsequently, data on patient's history, microbiologic features and treatment were collected by questionnaire [case record form, (CRF)]. According to the national guidelines patients were classified into four categories depending on patient's age and underlying health status (Table 1). The antibiotic therapy started on admission in the hospital was assumed to be the initial therapy. This observational study with anonymous patient data was carried out in accordance with the Dutch privacy legislation. Written informed consent to use data made anonymous was obtained from the patient (if possible) or from the patient's legal representative.

Penicillin susceptibility of meningococci was determined by inoculating strains on chocolate agar containing 0.1 mg/L penicillin. Penicillin-resistance in pneumococci was determined using a one µg oxacillin disc. Whenever a strain showed antibiotic resistance the Etest (AB Biodisk, Solna, Sweden) was used for determining the MIC of the antibiotic. Inoculation procedure and susceptibility testing were performed according to the guidelines described by the National Committee for Clinical Laboratory Standards.13 The MIC criteria used for the Etest were those used for micro-organisms tested by dilution susceptibility test methods.13

Initial antimicrobial treatment was defined as compliant if antibiotics were used as recommended in the national guidelines. The microbiological coverage for Neisseria meningitidis, Streptococcus pneumoniae and H. influenzae was based on the results of in vitro antibiotic susceptibility testing. Intermediate resistance for penicillin was categorized as inadequate
coverage if penicillin monotherapy was given. For the other isolates coverage was based on the antimicrobial spectrum of the antibiotic agents, as mentioned previously.14

RESULTS

From October 1998 to January 2000, isolates from 365 adult patients with meningitis (>16 years old) were received by the NRLBM. Distribution of species was as follows. *S. pneumoniae* in 164 patients, *N. meningitidis* in 119 patients, *H. influenzae* in 10 and various bacterial species in 72 patients. In total 324 (89 percent) questionnaires were sent to the patient's physician. Of the 41 patients not included, 33 patients were untraceable and 8 physicians refused to participate. The response rate in returning the CRF was 263/324 (81 percent).

The distribution according to species of the 263 meningitis patients for each category formulated in the guidelines (Table 1) is shown in Table 2. *N. meningitidis*, the most common causative micro-organism of community-acquired meningitis in the category adult patients ≤60 years of age without risk factors, accounted for 54 percent of all species in this category. *S. pneumoniae* occurred particularly in the elderly and in patients with risk factors, and accounted for 61 percent and 58 percent of all species in these two categories, respectively. Gram-negative enteric bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) were isolated from three patients >60 years old without risk factors (3 percent) and from one patient with a history of recent neurosurgery (6 percent). *Listeria monocytogenes* was isolated from the cerebrospinal fluid in six patients with risk factors (19 percent). From meningitis patients with a history of recent neurosurgery, *Staphylococcus aureus* was isolated from six patients (33 percent); *Staphylococcus epidermidis, Enterococcus faecalis* and *Enterococcus faecium* were each isolated from one patient, accounting for 6 percent in this category. Results of Gram staining were available for 227 cerebrospinal fluid specimens of 264 patients (86 percent). From 189 of 227 (83 percent) cases, microscopic examination of the Gram-stained cerebrospinal fluid specimens revealed the presence of the microorganism cultured later on.

Susceptibility testing showed that 1.6 percent of the 122 *S. pneumoniae* isolates had a decreased susceptibility to penicillin (with MICs ranging from 0.25 to 0.75 mg/L). One of the 84 (1.2 percent) *N. meningitidis* isolates had a decreased susceptibility to penicillin (MIC 0.75 mg/L).

### Table 2. Distribution of species causing bacterial meningitis over treatment categories among 263 Dutch adult patients.

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of patients</th>
<th>16-60 years (%)</th>
<th>&gt;60 years (%)</th>
<th>Risk factor present ≥16 years (%)</th>
<th>Recent neurosurgery ≥16 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>122</td>
<td>N=127 (37)</td>
<td>N=88 (61)</td>
<td>N=31 (58)</td>
<td>N=17 (18)</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td>84</td>
<td>68 (54)</td>
<td>13 (15)</td>
<td>3 (10)</td>
<td>-</td>
</tr>
<tr>
<td><em>L. monocytogenes</em></td>
<td>13</td>
<td>1 (1)</td>
<td>6 (7)</td>
<td>6 (19)</td>
<td>-</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>12</td>
<td>1 (1)</td>
<td>4 (5)</td>
<td>1 (3)</td>
<td>6 (35)</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>5</td>
<td>4 (3)</td>
<td>-</td>
<td>-</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Other species</td>
<td>27</td>
<td>6* (5)</td>
<td>11† (13)</td>
<td>3‡ (10)</td>
<td>7§ (41)</td>
</tr>
</tbody>
</table>

*S. pyogenes* (N=2), *S. agalactiae* (N=1), negative culture (N=1).
*S. salivarius* (N=3), *E. coli* (N=2), group G streptococci (N=2), *S. constellatus* (N=1), *S. agalactiae* (N=1), *K. pneumoniae* (N=1), negative culture (N=1).
*E. faecalis* (N=1), group C streptococci (N=1), *S. amnii* (N=1).
*P. aeruginosa* (N=2), *E. faecalis* (N=1), *E. faecium* (N=1), *E. coli* (N=1), *S. epidermidis* (N=1), negative culture (N=1).

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On the first day of hospitalization the most frequently prescribed antibiotics were amoxicillin and penicillin (44 percent), a third-generation cephalosporin (18 percent) and a combination of penicillin or amoxicillin with a third-generation cephalosporin (14 percent; Table 3). Of the patients without risk factors and ≤60 years old and of those aged >60 years, 39 and 30 percent, respectively, were initially treated with a third generation cephalosporin with or without amoxicillin or penicillin. Of the patients with risk factors, 38 percent received a third-generation cephalosporin.

In total, only 87 patients (33 percent) received treatment compliant with the guidelines.

Table 3. Initial antibiotic therapy in 263 adult bacterial meningitis patients in The Netherlands.

<table>
<thead>
<tr>
<th>Antibiotic(s) used</th>
<th>16-60 years</th>
<th>&gt;60 years</th>
<th>Risk factor present</th>
<th>Recent neurosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/penicillin</td>
<td>N=127</td>
<td>N=88</td>
<td>N=31</td>
<td>N=17</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Amoxicillin/penicillin</td>
<td>62 (49)</td>
<td>39 (44)</td>
<td>14 (45)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Third-generation cephalosporin</td>
<td>21 (16)</td>
<td>11 (13)</td>
<td>7 (21)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Amoxicillin/penicillin</td>
<td>29 (23)</td>
<td>17 (19)</td>
<td>5 (16)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>+ third-generation cephalosporin</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Amoxicillin/penicillin</td>
<td>1 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+ chloramphenicol</td>
<td>66 (7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vancomycin-based regimen</td>
<td>11 (9)</td>
<td>12 (14)</td>
<td>4 (12)</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In guidelines the initial treatment should be based on the most common bacterial species causing the disease in the different age groups or clinical settings, and on antibiotic susceptibility patterns of the predominant microorganisms. In The Netherlands, a guideline with recommendations for the initial treatment of four patient categories with meningitis was provided in 1997. Our
Table 4. The proportion of treatments microbiologically appropriate for patients treated compliant or non-compliant with national guidelines by patient category.

<table>
<thead>
<tr>
<th>Species</th>
<th>16-60 years non-compliant</th>
<th>16-60 years compliant</th>
<th>&gt;60 years non-compliant</th>
<th>&gt;60 years compliant</th>
<th>Risk factor present ≥16 years non-compliant</th>
<th>Risk factor present ≥16 years compliant</th>
<th>Recent neurosurgery ≥16 years non-compliant</th>
<th>Recent neurosurgery ≥16 years compliant</th>
<th>All patients non-compliant</th>
<th>All patients compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. meningitidis</td>
<td>35/35</td>
<td>33/33</td>
<td>5/5</td>
<td>8/8</td>
<td>1/1</td>
<td>2/2*</td>
<td>-</td>
<td>-</td>
<td>41/41</td>
<td>43/43</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>-</td>
<td>1/1</td>
<td>2/2</td>
<td>2/4</td>
<td>-</td>
<td>2/6</td>
<td>-</td>
<td>-</td>
<td>2/2</td>
<td>5/11</td>
</tr>
<tr>
<td>S. aureus</td>
<td>-</td>
<td>1/1</td>
<td>-</td>
<td>4/4</td>
<td>1/1</td>
<td>-</td>
<td>2/2</td>
<td>2/4</td>
<td>3/3</td>
<td>7/9</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>0/2</td>
<td>2/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1/1*</td>
<td>2/2</td>
<td>3/3</td>
<td>7/9</td>
</tr>
<tr>
<td>Other species</td>
<td>3/3</td>
<td>3/3</td>
<td>1/1</td>
<td>10/10</td>
<td>-</td>
<td>3/3</td>
<td>1/1</td>
<td>2/6</td>
<td>5/5</td>
<td>18/22</td>
</tr>
</tbody>
</table>

Microbiological coverage (%) 60/62 (97) 65/65 (100) 17/17 (100) 69/71 (97) 5/5 (100) 22/26 (85) 3/3 (100) 8/14 (57) 85/87 (98) 164/17 (93)

*Including 1 strain with decreased susceptibility to penicillin.
†β-lactamase producing H. influenzae.
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analysis of compliance and microbiological coverage one year after the guidelines became available shows that the distribution of species for each patient category is consistent with reports in literature.\(^\text{2,15,16}\) Although prospective, nationwide data are lacking in most countries, in The Netherlands the distribution of species is reported annually.\(^\text{16}\) These data also showed that among adult patients with bacterial meningitis the distribution of the species causing meningitis has been stable during the last decade.\(^\text{16}\) Antibiotic resistance among isolates was low. Of the meningococci and pneumococci only 1.2 percent and 1.6 percent, respectively, showed intermediate penicillin-resistance. Similar rates were found in a nationwide study in The Netherlands on antimicrobial susceptibility of cerebrospinal fluid isolates from patients with meningitis during 1993 and 1994.\(^\text{17}\)

With such low resistance rates, penicillin remained the drug of choice for the initial treatment of patients 16-60 years old with meningitis predominantly caused by \(S.\ pneumoniae\) and \(N.\ meningitidis\). For the initial treatment of patients >60 years old, and of patients with risk factors, a combination of penicillin or amoxicillin with a third generation cephalosporin was recommended (Table 1). The use of third-generation cephalosporins is necessary, since a substantial portion of patients in these two categories had meningitis due to \(S.\ aureus\) or Gram negative coliform bacteria (\(E.\ coli\) and \(K.\ pneumoniae\)) and the activity of penicillin or amoxicillin on such bacteria is poor. Cephalosporins are combined with penicillin or amoxicillin because \(L.\ monocytogenes\), rather a common cause of meningitis in these categories, is resistant to cephalosporins. Our study showed that 12 (10 percent) patients in these two categories had meningitis due to \(L.\ monocytogenes\). Finally, for meningitis patients with a history of recent neurosurgery, vancomycin plus a third-generation cephalosporin (a broad-spectrum combination effective against both Gram-positive and -negative organisms) was recommended in the national guidelines. Vancomycin is not found in the cerebrospinal fluid of persons without meningitis, but bactericidal levels have been found in the cerebrospinal fluid of most patients with bacterial meningitis.\(^\text{14}\) Although a rare cause of post-neurosurgical meningitis, enterococci show a bacteriostatic response to vancomycin and are cephalosporin resistant, and are therefore not covered by this combination of antibiotics.

The highest compliance was found in the first patient category (patients ≤60 years old without risk factors): 49 percent of them were treated according to the recommendations. Penicillin, recommended as the initial treatment in this patient category, covered isolates from all except five of the 127 patients. \(H.\ influenzae\) was cultured from four of these patients, and \(S.\ aureus\) from one. In the UK and USA, a combination of amoxicillin and cephalosporins has been recommended for the treatment of patients 16-60 years old.\(^\text{5,7-9}\) A major reason for the usage of third-generation cephalosporins is the emerging problem of microbial resistance, found particularly among \(S.\ pneumoniae\).\(^\text{5,7}\) In the USA, Spain, Hungary and other countries, antibiotic-resistant \(S.\ pneumoniae\) strains have become prevalent and have emerged as a major problem in the treatment of patients with bacterial meningitis.\(^\text{18}\) In a recent surveillance study in the USA on antimicrobial resistance of invasive \(S.\ pneumoniae\) strains, 24 percent were resistant to penicillin.\(^\text{18}\) In the UK, a trend analysis revealed the prevalence of penicillin-resistance among pneumococci causing bacteraemia ranging from 1 percent in 1990 to 3.6 percent in 1998.\(^\text{19}\) In The Netherlands, the recommendation to treat this patient group with penicillin is still valid for
patients with meningitis due to *N. meningitidis* and *S. pneumoniae*. For the small minority of patients in this category with meningitis due to other bacteria, this recommendation will not be optimal for all cases, and a third-generation cephalosporin would usually have been more appropriate. For the other categories the compliance was rather low, ranging from 17 to 18 percent.

Only one-third of the physicians adhered to the recommendations contained within the guidelines. The microbiological coverage for the 87 patients who were treated in compliance with the guidelines was almost complete (98 percent). Although guidelines can be varied by a clinician according to the circumstances, the question arises why was the compliance so poor? First, national guidelines are often of limited efficacy because medical practices are most often locally driven. In The Netherlands, >70 percent of hospitals have antibiotic formularies recommending antibiotic treatment. Local hospital committees preparing guidelines for antibiotic treatment should have been aware of the existence of the national consensus, since after the consensus meeting in 1997 a booklet containing the guidelines was widely disseminated. However, the current antibiotic policies of the eight Dutch academic hospitals still recommend a considerable diversity of antibiotics for the initial treatment of bacterial meningitis. Secondly, the meningitis guidelines have probably not been disseminated effectively. Dissemination must be supported by various interventions. Simply publishing guidelines has been associated with low rates of compliance before. In 1997, all medical specialists in The Netherlands involved in the treatment of patients with bacterial meningitis were invited to participate in the consensus meeting, and received a booklet with the guidelines. At this meeting the recommendations were approved by experts in the field of bacterial meningitis. However, other interventions have not been made, and the guidelines were not published in a national medical journal until 2001. Thirdly, despite the availability of the guidelines, the individual doctor has to decide which antibiotic to prescribe. Leibovici *et al.* clearly describe the dilemma of the individual doctor in making the decision about which antibiotic should be used. Doctors fear that the recommended initial treatment will not match the antibiotic susceptibility of the bacteria and feel uneasy in prescribing a drug that affords less than the maximum coverage. Following antibiotic guidelines may well slow down the development of resistance, and give future patients a better chance of an uneventful recovery, but the main duty of a doctor is to treat the present patient. This dilemma may also explain why so few physicians adhere to the national guidelines. Although Dutch doctors receive annual information about antibiotic susceptibility of isolates causing meningitis, the great majority do not use the guidelines.

Treatment of adult meningitis patients was not according to the guidelines in 167 of 273 (61 percent) cases. The microbiological coverage in these 167 patients was 93 percent. Twelve (7 percent) of them were treated inappropriately according to our criteria. Six of these patients (50 percent) had meningitis due to *L. monocytogenes* and received inappropriate therapy, since treatment consisted of a third-generation cephalosporin only. The other patients had meningitis due to *S. aureus*, *Pseudomonas aeruginosa*, *E. faecalis*, *E. coli* and *S. epidermidis*.

In this study only the compliance of the initial antibiotic treatment, recommended in the
Dutch guidelines for treatment of adult meningitis patients, was analyzed. Therapy can be modified when results of cerebrospinal fluid Gram staining and cerebrospinal fluid culture and antibiotic susceptibility testing become available. Analysis of the step-down therapy, narrowing the initial treatment, and the outcome of this approach has been carried out. The results will be presented separately.

In conclusion, 1 year after national consensus-based guidelines for the initial treatment of adult patients with bacterial meningitis in The Netherlands were provided, only one-third of the Dutch physicians were adhering to the guidelines. The microbiological coverage for the patients who were treated in compliance with the guidelines was almost complete (98 percent), whereas of the patients who were not treated in compliance with the guidelines, 7 percent received inappropriate antibiotic therapy.


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