Diagnostic and prognostic research in paediatrics:
Children with meningeal signs

Diagnostisch en prognostisch onderzoek in de kindergeneeskunde:
Kinderen met meningeale prikkeling

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr.ir. J. H. van Bemmel
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
woensdag 13 juni 2001 om 15.45 uur

door
Rianne Oostenbrink
geboren te Culemborg

Promotiecommissie

Promotores:	Prof.dr. D. E. Grobbee
	Prof.dr. H. A. Büller
Overige leden:	Prof.dr. R. de Groot
	Prof.dr. W. F. M. Arts
	Prof.dr. F. F. H. Rutten
Copromotor:	Dr. H. A. Moll

The studies described in this thesis were supported by a grant from the Health Care Insurance Council of the Netherlands. The printing of this thesis was financially supported by the Julius Centre for Patient Oriented Research, Utrecht and Glaxo Wellcome B.V.

Cover: Chopin's Waterloo, 1962 Arman Archives, APA 8203.62.001 reprinted with kind permission from the artist.

ISBN 90-73235-34-0

Voor Arjan

Contents

1 Introduction

Clinical presentation and diagnostic dilemmas in children with meningeal signs

1.1

Clinical presentation

Meningeal signs are indicative of bacterial meningitis and therefore necessitate a full diagnostic work-up, although these signs are not pathognomonic. Meningeal signs are present in 50 - 70% of children older than one with bacterial meningitis, as well as in 25% of the children without meningitis in whom a lumbar puncture is performed. [1-3] In about 60% of children who have meningeal signs, another diagnosis may be assessed. [2,4] This diagnostic dilemma in children with meningeal signs is illustrated by the two case descriptions in Figure 1.

Meningeal irritation arises from inflammation of nerve roots and meninges in the cervical region. Flexion of the neck leads to stretching of these inflamed nerve roots and meninges, causing pain and muscular resistance manifesting itself as neck stiffness. [5] Typical tests evoking this nuchal spasm are the Brudszinsky 1 sign (flexion of the head causes flexion of the legs), the Brudszinsky 2 sign (flexion of one leg causes flexion of the contralateral leg) or the Kernig sign (extension of the knees while hips are 90° flexed evokes pain or resistance). Other characteristics are the tripod phenomenon and nuchal rigidity. [1,6] In children younger than one, meningeal signs are difficult to assess and often absent. [1,7] Additional signs such as irritability during manipulation or a bulging fontanel may cause suspicion of meningeal irritation in these infants. [7] Meningeal signs can also be present when there is no meningitis. This is known as 'meningism'. Children with pneumonia, in particular of the right upper lobe, often present with meningism due to pleural irritation in the apical region. Meningism may be caused by cervical lymphadenitis in children with upper respiratory tract infections or by non-infectious causes like torticollis or myalgia. [2,4] In chapter 2.1 we evaluate the differential diagnosis in children visiting the emergency department with meningeal signs (aim 1, as specified in chapter 1.2).

In children younger than one, non-specific signs, such as *fever, respiratory distress, feeding refusal, lethargy, bulging fontanelle* or *irritability* usually raise suspicion of bacterial meningitis. [1,7] In those older than one other clinical symptoms of meningitis include *nausea, vomiting, headache, fever, mental confusion* or *decreased consciousness.* [1,8] *Seizures* may also occur in patients with meningitis, usually presenting with additional features such as a focal seizure, long duration of seizure (> 15 min), paresis or paralysis and decreased consciousness. [9,10] Although fever is present in almost all children with meningitis (about 94%), absence of fever does not rule out meningitis. [1] In children with viral meningitis a sudden onset of the disease, a non-toxic appearance, or signs of photophobia or exanthema are also observed. [11,12]

In a survey we evaluated the main symptoms of 160 children with bacterial meningitis, admitted to the emergency department of the Sophia Children's Hospital from 1988 to 1998 (Table 1). Presence of meningeal signs was the main symptom (95/160; 59%); others were septicaemia (18/160; 11%), seizures (16/160; 10%) and fever without localising signs (28/160; 18%). The clinical presentation was dependent on the causative pathogens.

Table 1 Pathogen according to clinical presentation of meningitis*

	Meningeal signs	Septicaemia	Fever without source	Seizures	Other†	Total
N. Meningitidis	47 (49%)	12 (67%)	12 (43%)	7 (44%)	2 (67 %)	80
S. Pneumoniae	10 (11%)	2 (11%)	0	8 (50%)	0	20
H. Influenzae	26 (27%)	1 (6%)	9 (32%)	0	0	36
Other	12 (13%)	3 (17%)	7 (25%)	1 (6%)	1 (33%)	24
Total	95	18	28	16	3	160

* based on data from hospital information system and problem oriented patient classification system, Sophia Children's Hospital between 1988-1998
† other presentations as documented in the problem-oriented patient classification system

This thesis discusses diagnostic and prognostic aspects of children with meningeal signs. These are the most frequent signs at the onset of bacterial meningitis, but they may also be present in children with other bacterial infections or self-limiting diseases.

Diagnostic aspects

Bacterial meningitis is defined as an increased leukocyte cell count in cerebrospinal fluid (CSF) with a bacterial isolate from CSF or blood. [8] After the neonatal period, the most prominent pathogen in childhood bacterial meningitis is *Neisseria meningitis*, followed by *Streptococcus pneumoniae*. *Haemophilus influenzae* type B (HIB) has almost been eradicated since the introduction of the routine vaccination against HIB in the Netherlands in 1993. [13,14] If it is not possible to perform a lumbar puncture (e.g. increased intracranial pressure, instable patient, coagulation disorders), a blood culture will reveal the causative pathogen

in 80% of the cases. [8] In neonates and young infants, a urine culture may also be useful to reveal the etiologic agent for bacterial meningitis. [8] Bacterial meningitis in older children frequently results from bacterial invasion through the nasopharyngeal mucosa, and subsequent spread by the bloodstream and passage through the blood-brain barrier. [15] Cultures of nose and throat specimens, however, are not informative, because they prove to be positive as a result of non-invasive carriers. [8] Although precise identification of the pathogen may require more time, most positive CSF cultures are detected within 48 hours. [16,17] The Gram stained smear of CSF may confirm presence of bacteria in CSF early. However, it appears negative in about 25% of the cases with bacterial meningitis, in particular when low number of organisms are present, and false positives may occur in cases of aseptic meningitis. [8,18,19] Therefore the Gram stain is not reliable for ruling out bacterial meningitis in an early phase. If CSF culture is negative for bacterial microorganism, viral cultures may reveal the pathogen. The most frequent viral cause of meningitis is enterovirus (80-90%), with a peak incidence in summer and autumn. If no virus can be isolated from CSF, a stool culture with enterovirus and CSF pleocytosis confirms viral meningitis as well. [12] Due to poor growth of some enteroviral serotypes, viral cultures may require up to 14 days to identify the viral pathogen and have low sensitivity. [12,20,21] DNA amplification techniques such as the polymerase chain reaction techniques will identify the viral pathogen earlier with better sensitivity. These techniques, however, are not yet routinely available.

At the end of the 19th century the diagnostic value of the biochemical analysis of the cerebrospinal fluid (CSF) was reported for the first time. [22] CSF indices, indicative of bacterial meningitis while awaiting the culture results, are a high CSF leukocyte count (with a predominance of polymorphonuclear cells), a low CSF glucose concentration, and a high CSF protein concentration. [8,23] Antibiotic treatment in a child with meningeal signs preceding the performance of a lumbar puncture may result in a negative CSF gram stain smear and a sterile culture. Other CSF characteristics for bacterial infections like pleocytosis, high protein and low glucose levels do not change substantially after pre-treatment with antibiotics. [23] In viral meningitis, less pleocytosis is usually seen, comprising mainly lymphocytes, with normal CSF glucose levels and CSF protein levels. [12] For the CSF indices, however, there is no threshold value which discriminates completely between bacterial and viral or aseptic meningitis, since values found in bacterial meningitis overlap the range of values found in patients with viral or aseptic meningitis. [24-26] In addition to the CSF variables such as polymorphonuclear cell count, glucose ratio and protein level, a blood leukocyte count and serum CRP are useful in the differential diagnosis of bacterial meningitis. [19,26-29] More advanced tests, such as determination of lactate, cytokines, tumour necrosis factor or interleukine-6 in CSF, still do not completely differentiate between the presence and the absence of meningitis. [30,31]

In practice, most physicians will perform a lumbar puncture in every child with meningeal irritation at physical examination. When the cytology and biochemical

analysis of the cerebrospinal fluid cause suspicion of bacterial meningitis, empirical antibiotic treatment is started, since delayed treatment of bacterial meningitis worsens its prognosis. [32] This empirical treatment can be discontinued when cultures remain sterile after 2 - 3 days with improving clinical course. [16,17] Although a safe strategy, it results in a large proportion of patients with a less serious disease, for whom the lumbar puncture or empirical treatment may be considered unnecessary in retrospect.

Most studies on predictors for the presence or absence of bacterial meningitis selected their patients on the diagnosis or on whether they had undergone a lumbar puncture. [1,7,11,19,25,26,28,29] However, this method of patient selection leads to the inclusion of the most severe or most evident cases and subsequent overestimation of the value of diagnostic tests. [33] In clinical practice, the physician is faced with a patient showing a particular symptom, before any tests have been performed or a diagnosis has been assessed. Based on the findings of clinical evaluation, the physician will perform additional laboratory tests to assess or rule out meningitis. Laboratory tests may appear unnecessary after the clinical evaluation, since they provide the same but not additional information on the possible diagnosis. [34,35] Following this sequential diagnostic process in clinical practice, the reason of visiting the emergency department determined our selection of patients in this study. The patients were traced using the problem-oriented patient classification system, as applied in the Sophia Children's Hospital since 1988. [36,37] In brief, every medical problem at referral is characterised in a matrix by an internal organ system or disease entity, and by either a complaint or symptom, abnormal laboratory results or (presumed) diagnosis. The problem list contains 18 main categories of internal organ systems or diseases entities (e.g. infection, gastro-intestinal complaints, endocrinology, etc.) with a total of 144 items. For each patient, at initial referral to the emergency or outpatients department, the main problem is prospectively coded and eventually linked to a final diagnosis according to the international classification of diseases (ICD-9).

In patients with meningeal signs, two questions are at issue: 1) when should a lumbar puncture be performed to diagnose or to rule out bacterial meningitis? (aim 2) and, after a lumbar puncture has been performed, 2) when should empirical antibiotic treatment be started while awaiting the final culture results? (aim 3) At issue is whether and which clinical characteristics and diagnostic tests, as routinely performed in children visiting the emergency department with meningeal signs, independently contribute to the diagnosis of bacterial meningitis. Combining these independent predictors in a diagnostic rule may provide the physician with a rationale for performing a lumbar puncture, and to help ascertain the diagnosis of bacterial meningitis using the added valued of CSF indices. Therefore it may improve clinical efficiency. Once a diagnostic rule has been developed, the prospective performance of the rule in a similar patient group needs to be estimated. [34,35,38] Therefore, prospective evaluation of the rule in clinical practice is essential (aim 4).

Prognosis of bacterial meningitis

Despite adequate treatment, bacterial meningitis still has a mortality risk of 5%. In addition, a proportion of 15% of the survivors suffers from late serious sequelae, involving auditive and visual function, mental and motor development and neurological functioning (Table 2). [39,4]

The most important neurological sequela after bacterial meningitis is *hearing impairment*, present in about 10% of patients. [39,41,42] Bacterial meningitis is the leading cause of acquired deafness in children (90%), which means 6 - 10% of all deafness in childhood. [43] Deafness results from cochlear damage after direct bacterial invasion during the acute phase or from bacterial endotoxin release. [8,44,45] There are some rare case reports of retrocochlear deafness, occurring within a few months after recovering from the acute phase of meningitis, although controversial ideas exist on its mechanism. [42,46] Hearing loss is present more frequently during the acute phase of meningitis with subsequent spontaneous recovery by reduction of the inflammation process. [45,47] Hearing loss based on sensoneurinal damage, however, should be differentiated from conductive loss caused by otitis media with effusion. Sensoneurinal damage can reliably be detected by hearing function assessment within 4-6 weeks after the acute phase of meningitis. [42]

Table 2 Outcomes of bacterial meningitis by etiologic agent*

Pathogen	Mortality (%)	Outcome (%)			
		Mental retardation	Spasticity / paresis	Seizures	Hearing impairment
H. influenzae	3.8	6.1	53.1	6.1	10.2
N. meningitidis	7.5	2.1	2.1	1.4	6.4
S. pneumoniae	15.3	17.0	11.5	14.3	27.7
Total	4.8	4.2	3.5	4.2	10.5

* based on a meta-analysis of 4400 children, Baraff et al. [39]

Motor abnormalities are seen in 3.5% of the survivors of childhood bacterial meningitis and include hemiplegia, diplegia or quadriplegia, spastic disorders or ataxic disorders. *Cognitive disorders* occur in 4.5%; *cortical blindness* in 2 - 4% on long-term follow-up, varying from hemi-anopsia to total cortical blindness. *Late seizures* develop in 2 - 8% of the cases with meningitis and usually appear within two years after the acute illness. [8,39,40,48] With exception of hearing impairment, which usually occurs as an isolated deficit, the other persistent neurological deficits often occur in combination. [40] Minor neurological sequelae such as behavioural disorders and mild learning or attention disorders are reported in 18% of the cases, based on patients including HIB cases. [49,50] Information on the frequency of these minor sequelae since the HIB-vaccination, however, is scarce.

Persistent neurological sequelae are due to cerebral ischemia during acute bacterial meningitis or to neural damage caused by the host inflammatory response in the meningitis patient itself. The latter has led to the application of steroids in the early treatment phase, in order to modify inflammation processes

and diminish the neural damage. The beneficial effect of steroids to the prognosis has been proven most clearly in patients with HIB-meningitis, in particular for hearing function sequelae. An effect has been reported neither for other pathogens, nor for other neurological sequelae. Therefore, since HIB-meningitis is rare due to vaccination nowadays, the available evidence is not strong enough to support routine use of dexamethason in acute bacterial meningitis. [51,52] The choice for antibiotic treatment should be based on the epidemiology of potential pathogens related to the patient's age and predisposing factors. Before identification of the pathogen, empirical treatment should be started with either a third generation cephalosporin, in combination with amoxicillin in infants younger than two months old to cover the more prevalent *Listeria monocytogenes* and *Streptococcus agalactiae*. [53,54] Meningitis caused by *Neisseria meningitidis* and penicillin-susceptible *Streptococcus pneumoniae* strains should be treated with penicillin G. In penicillin-resistant pneumococcal strains, a third generation cephalosporin and vancomycin are indicated. [54,55]

Several factors have been identified as being associated with the prognosis of bacterial meningitis. The risk of complications depends on the causative microorganism (Table 2). [39] Of all pathogens, *S. pneumoniae* is most frequently associated with death and neurological sequelae (15% and 36%, respectively), but an increased risk of hearing impairment has not been proven. [39,41,42,56] Clinical characteristics related to a higher risk of neurological sequelae or death are a male gender, young age (< 12 months) and a disturbed consciousness, focal neurological signs and seizures at examination. [40,41,56-63] Controversial reports exist on the relationship between the duration of complaints before admission and the prognosis. [40,57,60,62-65] The presence of ataxia or vestibular disturbance is associated with a higher risk of hearing impairment. [44] Seizures during the acute phase of meningitis resulting from systematic metabolic disturbances do not mean an increased risk of late seizures, in contrast to those resulting from direct brain involvement. [40] Low CSF glucose levels or a low glucose CSF/blood ratio during the acute phase of meningitis is associated with late seizures and persistent neurological sequelae. [40,41,56,58,59,61,63,66] Although not confirmed in all studies, a low CSF leukocyte count and a high protein level may also be related to neurological sequelae or death. [59,62,63] Transient neurological disorders during the acute phase of the disease are not associated with an increased risk of late seizures, in contrast to persistent neurological deficits. The presence of hearing impairment is not related to the incidence of late seizures. [40] Only a few studies have evaluated the independent prognostic value of variables by multivariate analysis. [57,59,60,63,66] The combination of independent prognostic variables into a scoring rule allows classification of patients into increased risk categories. Such a rule provides the physician with a rationale for parental counselling on the prognosis of their child in an early phase of the disease and to characterise the clinical condition of patients for clinical trials on new therapy (aim 5 and 6).

Quality-of-life measurement

To describe the consequences of a disease and the effects of treatment, mortality or survival time used to be important measures. Due to improving medical care, morbidity and the psychological and social consequences of a disease have become more important. The World Health Organisation defined 'health' as 'a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity'. [67] This definition was the basis of the notion of 'Quality-of-life' (QoL), including physical, mental, social, emotional and behavioural components of well being and functioning. [68] Within the context of evaluating effects of disease and medical care, the quality-of-life related to disease, or treatment ('health-related quality-of-life' (HRQoL), or 'health status') are preferably included. It should be noted that HRQoL does not consider the determinants of quality-of-life that are not directly related to health or treatment. It merely addresses one's physical, psychological and social *functioning* rather than the broader 'well-being'. At the start of this study, no other outcome measure than disease-related mortality and morbidity, including the broader aspects of quality-of-life, was available for children with bacterial meningitis.

HRQoL can be assessed by measuring a subject's functioning related to the functional status, disease and treatment related physical and mental symptoms, and social consequences. HRQoL instruments generally address several dimensions, covering the main domains of health-related quality-of-life, such as motor function, self-care, emotional state and pain. Several types of instruments are available for measuring HRQoL. [68,69] *Generic* instruments are used in patients with a broad range of diseases and in healthy persons as well, and hence allow for the comparison of HRQoL consequences of different diseases. Generic measures comprehensively cover the three domains of HRQoL (physical, mental and social). *Disease-specific* instruments are focussed on the disease-specific consequences on HRQoL and are generally more sensitive for small changes (over time within one person or between groups at one moment) within a disease. For meningitis, no such disease-specific instrument is available.

Most health status measures are descriptive, yielding a score on each of the dimensions of the instrument. Health status is characterised by a profile of scores across the different dimensions. Using such profile scores, effects of treatment on each of the dimensions can be estimated separately. If an intervention affects the dimensions differently (e.g. increasing the score on one dimension, but decreasing another one), problems arise in drawing conclusions on the treatment effect. To compare the combined consequences for health status and survival time into one outcome measure, the profile scores need to be summarised. Such summary scores are obtained by an additional step, in which the health status descriptions are valued by a representative sample of the general population (including patients). Only a few instruments allow for a link between descriptive profiles and a one-dimensional preference score (e.g. Health Utilities Index and EQ-5D). [70-72] Such a preference score can be regarded as a quality weight, scaled on a continuum from zero (death) to one (perfect health), reflecting the relative

severity of the sub-optimal health state compared to perfect health and death. Initially, the Health Utilities Index (HUI) has been developed in the field of paediatric oncology, but has been proven to be applicable to other diseases as well. [71] The EQ-5D has been designed for various groups of diseases, and for persons over 12 years of age. [70]

To include the final consequences of diagnostic procedures, in terms of an increase or decrease of adverse outcomes in our decision rule on diagnostic and therapeutic strategies in children with meningeal signs, we needed preference scores for permanent disabling health states caused by sequelae of bacterial meningitis. [73-75] Optimal estimation of these scores can theoretically be achieved by a prospective descriptive health status assessment of a sufficiently large representative sample of children and parents of children with permanent sequelae after meningitis, followed by a valuation of the resulting health state descriptions. Our study, based on retrospective data, did not allow for an empirical description estimation of the health states associated with permanent sequelae after meningitis. Therefore, an expert panel evaluated representative narrative health-state descriptions of outcomes of bacterial meningitis in order to assess preference scores and to determine which instrument was most appropriate for eliciting preference scores for health states after bacterial meningitis (aim 7).

Economic evaluation of clinical practice

In the evaluation of clinical care, the economic evaluation of diagnostic or therapeutic interventions is of growing interest. Four standard types of economic evaluations exist. [73,76-78] A *cost minimisation* analysis provides information on the absolute cost difference between two strategies, neglecting the health effects. This type of analysis can be used in comparing strategies with a similar outcome with regard to mortality or morbidity. *Cost-effectiveness* analysis incorporates the health benefits in natural units, such as life years saved, achieved clinical endpoints, or improvement in health expressed in e.g. units of blood pressure. In this analysis, the benefits of two interventions expressed by similar units are compared. *Cost-utility* analysis involves measuring the effect on the quantitative and qualitative aspects of health (morbidity and mortality) using a measure such as quality-adjusted life-years. In principle, this type of analysis allows for a comparison of costs and effects between various diseases. In *cost-benefit* analysis, the health benefits are expressed in monetary values. By valuing all costs and benefits in the same units, the net cost can be estimated and comparisons between interventions can be made. Controversies, however, remain about valuing methods of effects in monetary terms. [76] Therefore, a cost-utility analysis is generally preferred in economic evaluations. [73,79]

Economic investigation generally consists of several steps. [80] The first step involves definition of the study perspective and time-horizon. The costs to be

included in the analysis depend on the perspective of the study, e.g. the society, the insurance companies, the general public or the patient (consumer). The basic principle of medical economic studies is the societal perspective [73,80], such that medical and non-medical costs indirectly and directly related to the intervention are necessarily included. The time span of the study should be defined such that all cost consequences related to the intervention at issue are included in the analysis. Further steps involve the definition of the costs categories (direct and indirect medical and non-medical costs), identification of resources within each category (e.g. nursing days, laboratory tests), their frequency use and the estimation of their unit costs. Unfortunately, discrepancies still remain in the methods employed by those conducting economic studies. [81] Additionally, epidemiology of diseases and the clinical practice may vary between countries and institutions. Consequently, the ability to draw generalisations from cost-effectiveness analysis results is usually rather limited. [73,82]

A diagnostic strategy can influence total costs by a large reduction of the number of cheap tests, a small reduction of the number of expensive tests or the prevention of an expensive treatment. In general, diagnostic tests serve to rule out the necessity of therapeutic interventions. Intuitively, one can assume that a decrease in costs associated with a reduction in treatment (hospitalisation in particular) will outweigh the higher costs associated with the increase of diagnostic tests in patients. Performing diagnostic tests more frequently, however, will result in more false positives as well, leading to inappropriate follow-up testing and treatment. [83,84] The question is whether the introduction of a new diagnostic strategy will lead to a cost-reduction and what aspects contribute to these cost changes (aim 8).

Figure 1 Case descriptions of children presenting with meningeal signs

Case 1
A six year-old boy was referred to the paediatric emergency department by the general practitioner for neck stiffness. He had a 1-day history of fever up to 40 °C, vomiting, drowsiness, abdominal pain, headache and pain in neck. He refused to eat, was coughing and complained about throatache. Micturation and defecation were normal. On examination, a feverish, non-toxic child was seen. He was alert, well circulated and hydrated. He had a temperature of 39.8 °C, a pulse of 120 beats per minute and a respiration frequency of 36 breaths per minute. Nuchal rigidity was detected when the neck was flexed. Petechiae were absent. At pulmonary auscultation, symmetrical respiration sounds were heard, without rales. Additional laboratory tests were performed under suspicion of meningitis or septicaemia. In peripheral blood 39 × 10^9 leukocytes/l were present, with 77% segmented neutrophils and 9% bands; the serum C-reactive protein concentration was 189 mg/l. Acid-base balance of blood showed a pH of 7.42, a pCO2 of 4.7 kPa, an actual bicarbonate of 23.1 mmol/l, a base-excess of –0.2 mmol/l and a saturation of 94%. In cerebrospinal fluid (CSF) 3 cells/ µl were present (no polymorphonuclear cells), protein concentration was 0.33 g/l and glucose concentration 4.1 mmol/l (CSF/blood glucose ratio 0.64). The gram stain smear of CSF was negative for bacteria. Chest radiograph showed a segmental pneumonia of the right upper lobe. The boy was hospitalised and treated with antibiotics for pneumonia. Cultures of blood and CSF remained sterile. Control visit within two weeks showed uneventful recovery.

Case 2
A 14 month-old boy was referred to the paediatric emergency department by the general practitioner for irritability and neck stiffness. He had a 3-day history of fever, feeding problems, drowsiness. He had no history of vomiting; micturation and defecation were normal. On examination the child had a toxic appearance and was irritable. Nuchal rigidity was present. He had a temperature of 40.4 °C, a pulse of 168 beats per minute, respiration frequency of 32 breaths per minute, blood pressure of 120/80 mm Hg, and a cutaneous oxygen saturation of 99%. His reaction to pain stimuli was decreased, and his peripheral perfusion impaired. Petechiae were absent. Based on this presentation, meningitis was suspected. Additional laboratory tests showed 8 × 10^9 leukocytes/l, with 43% segmented neutrophils and 3% bands in peripheral blood and a C-reactive protein concentration of 228 mg/l in serum. In cerebrospinal fluid (CSF) 700 cells/ µl were present (80% polymorphonuclear cells), the protein concentration was 2.0 g/l and the glucose concentration 0.5 mmol/l (CSF/blood glucose ratio 0.1). Microscopic CSF analysis revealed multiple gram stain positive cocci. The boy was hospitalised and treated with antibiotics for bacterial meningitis intravenously. *Streptococcus pneumoniae*, sensitive for penicillin were isolated from CSF and blood. He was discharged without neurological deficits. During follow-up at the outpatient department, he had a normal psychomotor development. Brainstem response audiometry after 6 weeks revealed a hearing loss of 80 dB in both ears. Now, at the age of 5 years, he uses a hearing aid for both ears and visits a special school for hearing disabled children.

References

1. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
2. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr 1990;29:254-5, 258-61.
3. Gururaj VJ, Russo RM, Allen JE, Herszkowicz R. To tap or not to tap.. What are the best indicators for performing a lumbar puncture in an outpatient child? Clin Pediatrics 1973;12:488-493.
4. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
5. Vincent J, Thomas K, Mathew O. An improved clinical method for detecting meningeal irritation. Arch Dis Child 1993;68:215-8.
6. Verghese A, Gallemore G. Kernig's and Brudzinski's signs revisited. Rev Infect Dis 1987;9:1187-92.
7. Riordan FA, Thomson AP, Sills JA, Hart CA. Bacterial meningitis in the first three months of life. Postgrad Med J 1995;71:36-8.
8. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
9. Joffe A, McCormick M, DeAngelis C. Which children with febrile seizures need lumbar puncture? A decision analysis approach. Am J Dis Child 1983;137:1153-6.
10. Offringa M, Beishuizen A, Derksen-Lubsen G, Lubsen J. Seizures and fever: can we rule out meningitis on clinical grounds alone? Clin Pediatr (Phila) 1992;31:514-22.
11. Maxson S, Jacobs RF. Viral meningitis. Tips to rapidly diagnose treatable causes. Postgrad Med 1993;93:153-6, 159-60, 163-6.
12. Saywer MH. Enterovirus infections: diagnosis and treatment. Ped Inf Dis J 1999;18:1033-1040.
13. Conyn-van Spaendonck MA, Veldhuijzen IK, Suijkerbuijk AW, Hirasing RA. Significant decline of the number of invasive Haemophilus influenzae infections in the first 4 years after introduction of vaccination against H. influenzae type B in children [in Dutch, English summary]. Nederlands Tijdschrift voor Geneeskunde 2000;144(22):1069-73.
14. van Alphen L, Spanjaard L, van der Ende A, Dankert J. Absence of Haemophilus influenzae type b meningitis in the Netherlands in twice vaccinated children [in Dutch, English summary]. Ned Tijdschr Geneeskd 1995;139:880-884.
15. Kornelisse RF, de Groot R, Neijens HJ. Bacterial meningitis: mechanisms of disease and therapy. Eur J Ped 1995;154:85-96.
16. Hurst MK, Yoder BA. Detection of bacteremia in young infants: is 48 hours adequate? Pediatr Infect Dis J 1995;14:711-3.
17. Anttila M. Clinical criteria for estimating recovery from childhood bacterial meningitis. Acta paediatr 1994;83:63-67.
18. Rodewald LE, Woodin KA, Szilagyi PG, Arvan DA, Raubertas RF, Powell KR. Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatr 1991;119:363-9.
19. Spanos A, Harrell FE, Jr., Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. JAMA 1989;262:2700-7.
20. Ramers C, Billman G, Hartin M, Ho S, Saywer M. Impact of a diagnostic cerebrespinal fluid enterovirus polymerase chain reaction test on patient management. JAMA 2000;283:2680-2685.
21. Ahmed A, Brito F, Goto C, Hickey SM, Olsen KD, Trujillo M, et al. Clinical utility of the polymerase chain reaction for diagnosis of enteroviral meningitis in infancy. J Pediatr 1997;131:393-7.
22. Olukoga AO, Bolodeoku J, Donaldson D. Cerebrospinal fluid analysis in clinical diagnosis. J Clin Pathol 1997;50:187-192.
23. Bonadio WA. The cerebrospinal fluid: physiologic aspects and alterations associated with bacterial meningitis. Pediatr Infect Dis J 1992;11:423-31.
24. Carraccio C, Blotny K, Fisher MC. Cerebrospinal fluid analysis in systemically ill children without central nervous system disease. Pediatrics 1995;96:48-51.
25. Deivanayagam N, Ashok TP, Nedunchelian K, Ahamed SS, Mala N. Evaluation of CSF variables as a diagnostic test for bacterial meningitis. J Trop Pediatr 1993;39:284-7.

26.Hoen B, Viel JF, Paquot C, Gerard A, Canton P. Multivariate approach to differential diagnosis of acute meningitis. Eur J Clin Microbiol Infect Dis 1995;14:267-74.
27.Hansson LO, Axelsson G, Linne T, Aurelius E, Lindquist L. Serum C-reactive protein in the differential diagnosis of acute meningitis. Scand J Infect Dis 1993;25:625--630.
28.Lembo RM, Marchant CD. Acute phase reactants and risk of bacterial meningitis among febrile infants and children. Ann Emerg Med 1991;20:36-40.
29.Sormunen P, Kallio MJT, Kilpi T, Peltola H. C-reactive protein is useful in distinguishing Gram stain-negative bacterial meningitis from viral meningitis in children. J Pediatr 1999;134:725-729.
30.Dulkerian SJ, Kilpatrick L, Costarino AT, Jr., McCawley L, Fein J, Corcoran L, et al. Cytokine elevations in infants with bacterial and aseptic meningitis. J Pediatr 1995;126:872-6.
31.Gerdes LU, Jorgensen PE, Nexo E, Wang P. C-reactive protein and bacterial meningitis: a meta-analysis. Scan J CLin Lab Invest 1998;58:383-394.
32.Lebel MH, McCracken GH, Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989;83:161-167.
33.Knottnerus JA, Leffers JP. The influence of referral patterns on the characteristics of diagnostic tests. J Clin Epidemiol 1992;45:1143-1154.
34.Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
35.Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-9.
36.Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, Kraayenoord S, et al. The development and applicability of a problem oriented patient classification system in a pediatric outpatient clinic. Abstract. In: The 16th Annual meeting of the European Society for Paediatric Infectious Diseases; Bled, Slovenia; 1998.
37.Derksen-Lubsen G, Jongkind CJ, Kraayenoord S, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics I. [in Dutch, English summary]. Tijdschr Kindergeneesk 1996;64:93-98.
38.Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
39.Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993;12:389-94.
40.Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990;323:1651-7.
41.Fortnum HM. Hearing impairment after bacterial meningitis: a review. Arch Dis Child 1992;67:1128-33.
42.Fortnum HM, Davis AC. Hearing impairment in children after bacterial meningitis: incidence and resource implications. Br J Audiol 1993;27:43-52.
43.Davis A, Wood S. The epidemiology of childhood hearing impairment: factors relevant to planning of services. Br J Audiology 1992;26:77-90.
44.Kaplan SL, Catlin FI, Weaver T, Feigin RD. Onset of hearing loss in children with bacterial meningitis. Pediatrics 1984;73:575-8.
45.Richardson MP, Reid A, Tarlow MJ, Rudd PT. Hearing loss during bacterial meningitis. Arch Dis Child 1997;76:134-8.
46.Jayarajan V, Rangan S. Delayed deterioration of hearing following bacterial meningitis. Journal of Laryngology and Otology 1999;113:1011-1014.
47.Külahli I, Öztürk M, Bilen C, Cüreoglu S, Merhametsiz A, Çagil N. Evaluation of hearing loss with auditory brainstem responses in the early and late period of bacterial meningitis in children. J Laryngol Otol 1997;111:223-227.
48.Sell SH. Long term sequelae of bacterial meningitis in children. Pediatr Infect Dis 1983;2:90-3.
49.Grimwood K, Anderson VA, Bond L, Catroppa C, Hore RL, Keir EH, et al. Adverse outcomes of bacterial meningitis in school-age survivors. Pediatrics 1995;95:646-56.
50.Grimwood K, Anderson P, Anderson V, Tan L, Nolan T. Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. Arch Dis Child 2000;83:111-116.
51.McIntyre PB, Berkey CS, King SM, Schaad UB, Kilpi T, Kanra GY, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. JAMA 1997;278:925-31.

52.Prasad K, Haines T. Dexamethasone treatment for acute bacterial meningitis: how strong is the evidence for routine use? J Neurol Neurosurg Psychiatry 1995;59:31-7.
53.Derksen-Lubsen G, Moll HA, Büller HA. Compendium kindergeneeskunde. Diagnostiek en behandeling. second ed. Houten, The Netherlands: Bohn Stafleu Van Loghum; 2000.
54.Saez-Llorens S, McCracken GHJ. Antimicrobial and anti-inflammatory treatment of bacterial meningitis. Infectious disease clinics of North America 1999;13:619-636.
55.Klugman KP, Madhi SA. Emergence of drug resistance. Impact on bacterial meningitis. Inf Dis Clinics of North America 1999;13:637-646.
56.Bohr VA, Rasmussen N. Neurological sequelae and fatality as prognostic measures in 875 cases of bacterial meningitis. Dan Med Bull 1988;35:92-95.
57.Grimwood K, Nolan TM, Bond L, Anderson VA, Catroppa C, Keir EH. Risk factors for adverse outcomes of bacterial meningitis. J Paediatr Child Health 1996;32:457-462.
58.Woolley AL, Kirk KA, Neumann AM, Mc Willams SM, Freind D, Wiatrak BJ. Risk Factors for Hearing Loss From Meningitis in Children. Arch Otolaryngol Head Neck Surg 1999;125:509-514.
59.Kornelisse RF, Westerbeek CM, Spoor AB, van der Heijde B, Spanjaard L, Neijens HJ, et al. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis 1995;21:1390-7.
60.Akpede GO, Akuhwa RT, Ogiji EO, Ambe JP. Risk factors for an adverse outcome in bacterial meningitis in the tropics: a reappraisal with focus on the significance and risk of seizures. Ann Trop Paediatr 1999;19:151-159.
61.Aronin SI, Peduzzi P, Quagliarello J. Community Acquired Bacterial Meningitis: Risk Stratification for Adverse Clinical Outcome and Effect of Antibiotic Timing. Ann Intern Med 1998;129:862-869.
62.Kaaresen PI, Flaegstad T. Prognostic factors in childhood bacterial meningitis. Acta Paediatr 1995;84:873-8.
63.Valmari P, Makela M, Kataja M, Peltola H. Multivariate prognostication in bacterial meningitis of childhood. Scand J Infect Dis 1987;19:29-34.
64.Kilpi T, Anttila M, Kallio MJ, Peltola H. Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. Pediatr Infect Dis J 1993;12:184-8.
65.Radetsky M. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. Pediatric Infectious Disease Journal 1992;11(9):694-8; discussion 698-701.
66.Hoen B, Viel JF, Gerard A, Dureux JB, Canton P. Mortality in pneumococcal meningitis: a multivariate analysis of prognostic factors. Eur J Med 1993;2:28-32.
67.World Health Organization. Constitution of the World Health Organization. Geneva; 1948.
68.Pal DK. Quality of life assessment in children: a review of conceptual and methodological issues in multidimensional health status measures. J Epidemiol Community Health 1996;50:391-6.
69.Jenney ME. Theoretical issues pertinent to measurement of quality of life. Med Pediatr Oncol 1998;Suppl:41-5.
70.Dolan P. Modeling valuations for the EuroQol health states. Med Care 1997;35:1095-1108.
71.Feeny DH, Furlong WJ, Barr RD. Multiattribute approach to the assessment of health-related quality of life: Health Utilities Index. Med Pediatr Oncol 1998;Suppl:54-9.
72.Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702-22.
73.Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. second edition. 2nd ed. Oxford: Oxford University Press; 1997.
74.Palmer S, Byford S, Raftery J. Types of economic evaluation. BMJ 1999;318:1349.
75.Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980;302:1109-1117.
76.Detsky AS, Naglie IG. A clinican's guide to cost-effectiveness analysis. Ann Int Med 1990;113:147-154.
77.Bonsel GJ, Rutten FFH, Uyl-de Groot CA. Economic evaluation alongside cancer trials: Methodological and practical aspects. Eur J Cancer 1993;29A, suppl. 7:S10-S14.
78.Weinstein MC. Economic assessments of medical practices and technologies. Med Decis Making 1981;1:309-330.

79. Schulman KA, Linas BP. Pharmacoeconomics: state of the art in 1997. Annu Rev Public Health 1997;18:529-548.
80. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Manual for cost evaluation, methods, guidelineprices for economic evaluation in health care. [In Dutch]. Amstelveen, The Netherlands: College voor zorgverzekeringen; 2000.
81. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. Jama 1996;276(15):1253-8.
82. Mason J. The generalisability of pharmacoeconomic studies. Pharmacoeconomics 1997;11:503-514.
83. DeKay ML, Asch DA. Is the defensive use of diagnostic tests good for patients, or bad? Med Decis Making 1998;18:19-28.
84. Kassirer JP. Our stubborn quest for diagnostic certainty. A cause of excessive testing. N Engl J Med 1989;320:1489-1491.

Outline of the thesis and aims of the study

1.2

The overall aim of this thesis is to contribute to our knowledge of diagnoses and prognosis of *children with meningeal signs*. A diagnostic study on bacterial meningitis in children presenting with meningeal signs at the emergency department is performed and predictors of neurological sequelae and the health-related quality-of-life after bacterial meningitis were determined.

The specific aims are:

1. To describe the diagnoses in children visiting the emergency department with meningeal signs.
2. To derive and validate a scoring rule for the indication of a lumbar puncture using independent predictors from patient history, physical examination and blood laboratory tests.
3. To derive and validate a diagnostic decision rule, using cerebrospinal fluid indices and the patient's clinical profile, to guide decisions on empirical antibiotic treatment of bacterial meningitis.
4. Prospective validation of the diagnostic decision rule in children with meningeal signs
5. To describe the major neurological sequelae after childhood bacterial meningitis.
6. To assess independent predictors of neurological sequelae in children with bacterial meningitis
7. To obtain preference scores for quality-of-life of health states associated with neurological sequelae after bacterial meningitis.
8. To perform an economical evaluation of the diagnostic decision rule using cost minimisation and cost-utility analyses.

Chapter 2 of this thesis focuses on the diagnostic aspects of children with meningeal signs. In *chapter 2.1* the differential diagnosis in children suspected of having bacterial meningitis because of meningeal signs, and the presenting symptoms and signs, are discussed. As a first step in the diagnostic process we study in *chapter 2.2* the clinical signs and symptoms of a patient at the emergency department, that are independently related to the presence of bacterial meningitis. With these predictors, a clinical score is developed that may help the physician in decisions on whether or not to perform a lumbar puncture. Subsequently, in *chapter 2.3*, indices from the cerebrospinal fluid (CSF) are identified, that contribute to the discrimination between presence or absence of bacterial meningitis, in addition to the clinical signs and symptoms. These CSF variables are combined with the previously derived clinical score to formulate a diagnostic decision rule, to guide decisions on whether empirical treatment should be initiated or not. The prospective application of this diagnostic decision rule as described in the previous two chapters (2.2 and 2.3) is evaluated in *chapter 2.4* in order to predict the performance of the rule in new patients from different hospitals.

In *chapter 3*, the prognosis of children with bacterial meningitis, presenting with meningeal signs is addressed. *Chapter 3.1* describes the long-term prognosis of bacterial meningitis in these children. In *chapter 3.2*, potential predictors of neurological sequelae after bacterial meningitis are assessed and a scoring rule is developed to classify patients with increased risk of mortality and morbidity after bacterial meningitis. *Chapter 3.3* concerns the measurement of health-related quality-of-life of children with neurological sequelae after bacterial meningitis. Two instruments (EQ-5D and Health Utility Index) available for measuring health-related quality-of-life are compared in terms of feasibility, reliability, and the value obtained for the preference scores for the health states under evaluation.

Chapter 4 describes the economic evaluation of the diagnostic decision rule. In *chapter 4.1* the potential costs associated with the application of the decision rule are estimated, on the assumption that the rule will lead to similar morbidity and mortality rates as in current clinical practice, but with less intervention. In *chapter 4.2*, we design a hypothetical model to assess the consequences of adequate diagnosis and treatment in patients with meningeal signs in terms of health-related quality-of-life and costs. Changes in costs and health-related quality-of-life due to changes in diagnostic or therapeutic strategies are evaluated in a cost-utility analysis.

In *chapter 5* the methodological aspects of this study are discussed in view of the prevailing ideas on diagnostic research.

Finally, in *chapter 6* the results of previous studies are summarised and suggestions for future studies are put forward.

Diagnostic procedures in children with meningeal signs

Signs of meningeal irritation at the emergency department: How often bacterial meningitis?

2.1

Rianne Oostenbrink, Karel GM Moons, Chantal CW Theunissen, Gerarda Derksen-Lubsen, Diederick E Grobbee, Henriëtte A Moll
Pediatric Emerg Care, in preparation

Abstract

Although signs of meningeal irritation are highly indicative of meningitis, they are not pathognomonic. In this study we describe the final diagnoses in children with signs of meningeal irritation and we assess the frequency of bacterial meningitis related to specific signs of meningeal irritation.

Information was collected from records of 326 patients (aged 1 month to 15 years) who visited the emergency department of the Sophia Children's Hospital between 1988 and 1998 with signs of meningeal irritation, assessed by either the general practitioner or the paediatrician.

Bacterial meningitis was diagnosed in 99 patients (30%), viral or aseptic meningitis in 43 (13%). Other diagnoses were pneumonia (8%), other serious bacterial infections (2%) and upper respiratory tract infections or other self-limiting diseases (46%). Presence of one of the signs of meningeal irritation assessed by the paediatrician was related to bacterial meningitis in 39%. Specific tests eliciting meningeal irritation, such as Brudzinski and Kernig sign, were not related to a higher frequency of bacterial meningitis than neck stiffness and the tripod phenomenon. In children ≤ 1 year, bacterial meningitis is more frequently related to presence of irritability and a bulging fontanelle.

In conclusion, bacterial meningitis is present in 30% of children with signs of meningeal irritation. Presence of meningeal irritation as assessed by the paediatrician is related to bacterial meningitis in 39%. By using more specific tests for signs of meningeal irritation a better prediction of bacterial meningitis was not achieved.

Introduction

Signs of meningeal irritation are considered highly indicative of meningitis. [1] These signs include neck stiffness, tripod phenomenon and the specific clinical tests evoking meningeal irritation, such as Kernig sign and Brudzinski nape of the neck and contralateral leg sign (Brudzinski I and II, respectively). [2] All these tests aim to stretch the inflamed nerve roots and meninges of the cervical region by flexion of the neck, causing protective muscle spasm manifesting as neck stiffness. [3] The presence of meningeal irritation, however, is not pathognomonic

for meningitis. In about 20% of children with meningitis, signs of meningeal irritation are absent. [4-6] Studies among children, in whom a lumbar puncture was performed, have reported a 40% prevalence of meningitis (bacterial meningitis in 8% and aseptic meningitis in 32%), whereas in those with normal cerebrospinal fluid findings the most common diagnoses were pneumonia, pharyngo-tonsillitis, urinary tract infections and gastro-enteritis. [7 8] These studies, however, described the frequency of the different diagnoses or clinical features in children that all had undergone a lumbar puncture. Clinical practice, in contrast, starts with a child with signs of meningeal irritation as reason for consultation, before any diagnostic procedures have been performed. To our knowledge, frequencies of final diagnoses in children selected on the clinical profile 'signs of meningeal irritation' have never been studied.

The *objective of this study* is to determine the frequency of diagnoses in children with signs of meningeal irritation as reason for consultation in a large paediatric emergency department. In addition, the frequency of bacterial meningitis in children with positive results on tests evoking meningeal irritation is investigated.

Methods

Patients

We collected routinely documented information from records of children aged from one month to 15 years, who visited the emergency department of the Sophia Children's Hospital between 1988 and 1998 with signs of meningeal irritation. Patients with a history of severe neurological diseases, or ventricular drainage, or those referred from other hospitals were excluded. The latter were excluded, since in these patients treatment may have been initiated already and influenced the clinical signs at examination. The Sophia Children's University Hospital Rotterdam in The Netherlands has a catchment area of nearly two million inhabitants. The general paediatric emergency department is open 24 hours a day, and receives 2,500 new patients yearly (± 90% basic paediatric care); either referred by a general practitioner (70%) or self-referred (30%).

Since 1988 a problem-oriented patient classification system is applied at the outpatient and emergency department of the Sophia Children's Hospital. In brief, every medical problem at referral is characterised in a matrix by an internal organ system or disease entity, and by either a complaint or symptom, abnormal laboratory result or (presumed) diagnosis. The problem list contains 18 main categories of internal organ systems or disease entities with a total of 144 items. For each patient, at first referral the main problem is prospectively coded and eventually linked to a final diagnosis according to the international classification of diseases (ICD-9). In a sample, the coding system was complete for 95% of the visits. 'Meningeal signs' is a defined code, applied to children referred by the general practitioner for (suspected) signs of meningeal irritation or in whom the paediatrician has assessed meningeal irritation. For further details on this

classification system, we refer to previous publications. [9 10] To ensure the enrolment of all patients with signs of meningeal irritation, we compared the hospital problem oriented classification system data to all patients with fever as documented in the emergency department log.

Definitions
Meningeal irritation as assessed by the paediatrician at the emergency department was defined as presence of either one or more of the following six symptoms: neck stiffness, Brudzinski nape of the neck or contralateral leg sign, Kernig sign and the tripod-phenomenon in children > 1 year, and one of the previous signs or irritability or a bulging fontanelle in children ≤ 1 year. [2 3] In children with missing information on some tests, but with at least one of these signs present, meningeal irritation was considered present. Fever (body temperature ≥ 38.0°C) could be present or absent.

The final exclusive diagnosis was determined either by a reference standard (bacteriologic cultures of blood, spinal fluid, urine, etc.), or based on a combination of symptoms and signs agreed upon by three independent paediatricians (consensus diagnosis). *Bacterial meningitis* was defined as the presence of elevated leukocyte count (> 5 cells/μl) in cerebrospinal fluid (CSF) and a positive pathogenic bacterial culture of CSF and/or blood [1 4 7]. *Viral meningitis* was defined as the presence of elevated CSF leukocyte count with a positive viral culture of CSF, blood or stool [1 4 7]; *aseptic meningitis* was defined as an elevated CSF leukocyte count of a non-traumatic lumbar puncture, without any bacterial or viral isolate. Aseptic meningitis in a child who recently used antibiotics was considered as a pre-treated case of meningitis. [11]

If lumbar puncture or follow-up ruled out meningitis, the following differential diagnoses were distinguished:
Septicaemia, defined as a positive bacterial blood culture with symptoms of generalised infection and signs of hypoperfusion. [1]
Pneumonia, defined as presence of five clinical symptoms according to the WHO criteria [12] or an infiltrate on the chest radiograph with one of the clinical signs.
Upper respiratory tract infection, defined as presence of fever with signs of rhinitis (nasal secretion), pharyngitis (redness, swollen tonsils either with or without purulent secretion) or acute otitis media (red or bulging eardrum). [13]
Urinary tract infection, defined as urine monoculture ≥ 10^5 bact/ml (urine collected by bag) with clinical symptoms (fever, toxic-appearance, lethargy, irritability, vomiting, dysuria or changed voiding pattern) and abnormal microscopic urinalysis (> 20 leukocytes per high power field in centrifuged specimen). [14 15]
Gastro-enteritis, defined as diarrhoea and vomiting without clinical indication for parenteral diarrhoea, either with or without presence of bacterial or viral micro-organism isolated from stool.
Other causes included self-limiting non-specified viral infections and non-infectious causes, like trauma, torticollis and myalgia.

Analysis

We estimated the prevalence and 95% confidence intervals (95% CI) of the final diagnoses in our study population. Additionally, the frequency of bacterial meningitis among children with a positive test result on various tests evoking meningeal irritation was estimated. Differences were tested by Chi-square analysis.

Table 1 Characteristics of the study population (n=326).

Characteristic	Number (%)[§]
Male gender	206 (63%)
Age (years)[†]	2.2 (0.7-5.2)
Referral pattern[‡]	
General practitioner	275 (84%)
Self referral	26 (8%)
Other	8 (2.4%)
Meningeal irritation assessed by general practitioner (GP)	203 (62%)
Meningeal irritation assessed by paediatrician	256 (79%)
Meningeal irritation assessed by GP and paediatrician	133 (41%)
Fever (≥38.0°C)	
In history	309 (95%)
At examination	276 (85%)
No fever in history nor at examination	12 (4%)
Body temperature at examination (°C)[*]	39.2 (1.0)
Hospitalisation	217 (67%)

[§]Values represent absolute numbers and percentage between parentheses, otherwise if stated

[†]median (25th and 75th percentiles)

[‡]in 17 patients the referral pattern was unknown

[*]mean (standard deviation)

Results

We included 326 consecutive patients with (suspected) signs of meningeal irritation either assessed by the general practitioner or by the paediatrician. In a comparison of the hospital problem oriented classification system to the emergency department log, three patients appeared to be missed. The general characteristics of all patients are provided in Table 1. In 133 of the 203 children referred by the general practitioner for signs of meningeal irritation, the paediatrician confirmed this finding. The paediatrician also assessed meningeal irritation in the 80 children referred for other reasons and in the self-referrals. The final diagnoses of the children are presented in Table 2. Bacterial meningitis was diagnosed in 30% (95% CI: 25 - 35%), viral or aseptic meningitis in 13% (95% CI: 10 - 17%). A lumbar puncture had been performed in 256 of the 326 patients (79%). In eight patients the lumbar puncture was traumatic, but none of them was excluded from the study. Bacterial cultures proved a bacterial meningitis in one of them; in the seven patients with negative cultures we concluded another diagnosis based on the presence of clinical symptoms and additional diagnostic tests. In 11 children with signs of meningeal irritation at examination, a lumbar puncture had been withheld. Almost all of them (n = 9) had neck stiffness as the

only meningeal sign. None of the 70 children without a lumbar puncture appeared to have bacterial meningitis during follow-up, which involved an outpatient department visit or telephone call by one of the paediatricians or a renewed referral within 14 days after discharge. In 18 of the 27 patients with pneumonia as final diagnosis a lumbar puncture had been performed (66%, Table 2), and in all 8 children with a septicaemia, urinary tract infection or bacterial gastro-enteritis. In children with upper respiratory tract infections or other self-limiting diseases a lumbar puncture had been performed in 88 (59%).

Table 2 Diagnoses in children with signs of meningeal irritation

Diagnosis	Number (%)[§]	Number of lumbar punctures[§]
Meningitis		
Bacterial	99 (30%)	99
Viral/aseptic	43 (13%)	43
Pneumonia	27 (8%)	18
Other bacterial infection[†]	8 (3%)	8
Self limiting diseases[‡]	149 (46%)	88
Total	326 (100%)	256 (79%)

[§]Values represent absolute numbers and percentages between parentheses.
[†]other bacterial infection include septicaemia, urinary tract infection, bacterial gastro-enteritis
[‡]self-limiting diseases included upper respiratory tract infection, non-specified viral infection and non-infectious causes like myalgia, torticollis

Of the 203 patients referred by the general practitioner because of signs of meningeal irritation, 49 indeed had bacterial meningitis (24%; 95% CI: 18 - 30%). The paediatrician assessed meningeal irritation (presence of one of the six signs of meningeal irritation) in 256 children, of whom 99 had bacterial meningitis (39%; 95% CI: 33 - 45%). Among the latter group, Table 3 shows the frequency of bacterial meningitis for the six signs of meningeal irritation separately. Bacterial meningitis was present in 42% of the children with neck stiffness, and in 30% and 36% of those with a positive Kernig or one of the Brudzinski signs, respectively. In 31 of all children with signs of meningeal irritation, both the Kernig sign and neck stiffness were present; nine of these children had bacterial meningitis (29%; 95% CI: 14 - 48%). Combination of one of the Brudzinski signs with neck stiffness was present in 41 children, of whom 15 had bacterial meningitis (37%; 95% CI: 22 - 53%).

Table 3 Frequency of bacterial meningitis related to specific signs of meningeal irritation among children with meningeal irritation assessed by the paediatrician

Positive sign	Children ≤ 1 year (n = 88)	Children > 1 year (n = 168)	All children (n = 256)
Neck stiffness	18/56 (32%)	64/141 (45%)	82/197 (42%; 35 - 49%)
Kernig sign	0/5 (0%)	10/28 (36%)	10/33 (30%; 16 - 49%)
Brudzinski sign I or II	1/8 (13%)	15/36 (42%)	16/44 (36%; 22 - 52%)
Tripod phenomenon	not applicable	4/22 (18%)	4/22 (18%; 5 - 40%)
Irritability at manipulation of head or legs	12/37 (32%)	not applicable	12/37 (32%; 18 - 50%)
Bulging fontanelle	11/34 (32%)	not applicable	11/34 (32%;17 - 51%)
At least one sign of meningeal irritation	23/88 (26%)	76/168 (45%)	99/256 (39%; 33 - 45%)

In a separate analysis of children younger and older than one year with signs of meningeal irritation, the frequency of bacterial meningitis was 26% (95% CI: 17 - 37%) and 45% (95% CI: 38 - 53%), respectively (Table 3). In children aged ≤ 1 year, bacterial meningitis was present in 32% of the children with a bulging fontanel or in those with irritability. These frequencies were much higher than for the Kernig or Brudzinski signs in this age group.

Among all included patients, we evaluated whether the prevalence of bacterial meningitis differed among patients with and without fever. Children with bacterial meningitis had a mean temperature of 39.3 °C (95% CI: 39.1 - 39.5 °C), those without 39.2°C (95% CI: 39.1 - 39.3 °C). In the 314 children with either fever at presentation or in history, bacterial meningitis was diagnosed in 99 (32%; 95% CI: 26 - 37%). None of the 12 children with neither fever in history nor at presentation had bacterial meningitis (0%; 95% CI: 0 - 27%).

Discussion

In this study of 326 children with signs of meningeal irritation, bacterial meningitis was present in 30% and viral meningitis in 13%. Upper respiratory tract infection and other self-limiting infections, however, were commonly diagnosed in these children. The presence of signs of meningeal irritation in children without meningitis can be explained by nuchal spasm associated with cervical lymphadenitis in case of upper respiratory infections. [7 8] Also pneumonia, diagnosed in 8% of our population, is known to elicit meningism by pleural irritation. [16] In almost 80% of the children with signs of meningeal irritation at physical examination a lumbar puncture has been performed. In 59% of the patients with self-limiting diseases a lumbar puncture has been performed, that may be judged unnecessary afterwards. Missing the diagnosis bacterial meningitis, however, is not acceptable. Therefore, these 'unnecessary' punctures are unavoidable until another clinical or laboratory test will be available to reliably exclude the possibility of bacterial meningitis. In a future study we will evaluate clinical characteristics in a child with signs of meningeal irritation that may be associated with the presence of meningitis, in order to improve the basis for well-founded decisions on the management of these children.

Presence of one of the six signs of meningeal irritation as assessed by the paediatrician, was related to bacterial meningitis in 39%. The frequency of other diagnoses than bacterial meningitis is still very high among patients with meningeal irritation (61%). Since some signs of meningeal irritation may be stronger related to bacterial meningitis than other [2 6 8 17], we evaluated the frequency of bacterial meningitis among children with positive results on each of the six evaluated tests evoking meningeal irritation separately (Table 3). None of the separate signs, however, showed a significantly higher frequency of bacterial meningitis than another. Furthermore, the combination of presence of neck stiffness with either Kernig or Brudzinski sign was not stronger related to bacterial

meningitis than presence of neck stiffness alone. Since in the presentation of young children with meningitis specific signs of meningeal irritation are often absent, we evaluated children younger and older than one year separately. [6 8] Indeed, in children ≤ 1 year with signs of meningeal irritation, the frequency of bacterial meningitis was lower than in older ones. In children ≤ 1 year, a bulging fontanelle and irritability seem to be related to bacterial meningitis more frequently. Kernig and Brudzinski signs were often absent or not assessed in these children.

Since fever is often associated with bacterial meningitis [1 8], we evaluated its relation to bacterial meningitis. The mean body temperature at physical examination was not significantly different between children with and without meningitis. Absence of fever was related to the absence of bacterial meningitis in this study. The latter, however, is based on a very small group (n = 12) and therefore should be interpreted with care.

It should be noted that in this study selection of patients is based on suspicion of having meningitis because of (referral for) signs of meningeal irritation at a general paediatric emergency department. This is conform clinical practice though in contrast to other studies, which selected their study population on the presence of a lumbar puncture result or diagnosis. [6-8 17] Patient selection on the presence of lumbar puncture or diagnosis, however, often leads to a biased selection of the most evident or more severe cases of meningitis. The selection of our patient population corresponds more to clinical practice, in which the physician is faced with a patient in whom the diagnosis is not yet known and choices towards diagnostic tests and treatment has to be made.

In order to appreciate the present results, some limitations of this study need to be discussed. First, due to our study design, our population of patients with signs of meningeal irritation does not include all cases of bacterial meningitis, since other reasons for encounter that are indicative for meningitis (such as a predominance of convulsions, coma, etc.) are not included. [1] Secondly, presence or absence of the six signs of meningeal irritation were not always documented for each patient. Documentation of neck stiffness was most frequently completed in this study (87%) but Kernig and Brudzinski signs were often not included by the paediatrician in the clinical evaluation in this study (about 40% missing). Presence or absence of the bulging fontanelle and irritability (for ≤ 1 years only) was not documented in 17% and 51% respectively. Because of these missing variables, the analysis of the separate signs of meningeal irritation is based on small numbers and conclusions should be drawn with care. The missing of these data, however, reflects clinical practice. Apparently, Brudzinski and Kernig signs are not applied frequently to young children or are difficult to interpret. Since it is not known whether these missings result from the sign being negative or not evaluated, only the presence of bacterial meningitis in presence of the separate signs of meningeal irritation could be evaluated. Finally, not all children in this study had a lumbar puncture performed, which may bias the frequencies of the

diagnoses in this study as we assessed. For bacterial meningitis this is unlikely, since we included the follow-up (outpatient visits or telephone call) for determining the final diagnosis. Though, we may have missed some viral or aseptic meningitis cases. Viral or aseptic meningitis in children aged 1 month or more, however, is a self-limiting disease with a fair prognosis and therefore the importance of truly setting this diagnosis is questionable. [18]

In conclusion, in a population of children aged from 1 month to 15 years referred because of signs of meningeal irritation or with meningeal irritation at physical examination at the paediatric emergency department, the frequency of bacterial meningitis is 30%. Other frequent diagnoses are pneumonia, upper respiratory tract infections and self-limiting viral infections. Presence of one of the signs of meningeal irritation at physical examination is related to bacterial meningitis in 39%, which is not increased by using specific tests such as the Brudzinski or Kernig sign, evoking meningeal irritation. Further evaluation of clinical characteristics that are predictive for the presence of bacterial meningitis, additional to signs of meningeal irritation will improve the basis of well-founded decisions for the performance of lumbar punctures in children with meningeal irritation.

References

1 Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
2. Verghese A, Gallemore G. Kernig's and Brudzinski's signs revisited. Rev Infect Dis 1987;9:1187-92.
3. Vincent J, Thomas K, Mathew O. An improved clinical method for detecting meningeal irritation. Arch Dis Child 1993;68:215-8.
4. Oliver LG, Harwoord-Nuss AL. Bacterial meningitis in infants and children: a review. J Emerg Med 1993;11:555-564.
5. Granier S, Owen P, Stott NCH. Recognizing meningococcal disease: the case for further research in primary care. Br J Gen Pract 1998:1167-1171.
6. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
7. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
8. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr (Phila) 1990;29:254-5, 258-61.
9. Derksen-Lubsen G, Jongkind CJ, Kraayenoord S, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics I. [in Dutch, English summary]. Tijdschr Kindergeneesk 1996;64:93-98.
10. Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, Kraayenoord S, et al. The development and applicability of a problem oriented patient classification system in a pediatric outpatient clinic. Abstract. In: The 16th Annual meeting of the European Society for Paediatric Infectious Diseases; Bled, Slovenia; 1998.
11. Walsh-Kelly C, Nelson DB, Smith DS, Losek JD, Melzer-Lange M, Hennes HM, et al. Clinical predictors of bacterial versus aseptic meningitis in childhood. Ann Emerg Med 1992;21:910-4.
12. World Health Organization. The management of acute respiratory infections in children. Practical guidelines for outpatient care. Geneva: WHO, 1995.
13. Heikkinen T, Ruuskanen O. Signs and symptoms predicting acute otitis media. Arch Pediatr Adolesc Med 1995;149:26-29.

14. Hoberman A, Wald ER. Urinary tract infections in young febrile children. Pediatr Infect Dis J 1997;16:11-7.
15. Oostenbrink R, van der Heijden AJ, Moons KGM, Moll HA. Prediction of vesico-ureteric reflux in childhood urinary tract infection: a multivariate approach. Acta Paediatr 2000;89:1-5.
16. Nussinovitch M, Cohen HA, Frydman M, Varsano I. Cerebrospinal fluid pleocytosis in children with pneumonia but lacking evidence of meningitis. Clin Pediatr (Phila) 1993;32:372-3.
17. Attia J, Hatala R, Cook DJ, Wong JG. Does this adult patient have acute meningitis? JAMA 1999;282:175-181.
18. Rotbart HA. Enteroviral infections of the central nervous system. Clin Infect Dis 1995;20:971-81.

Prediction of bacterial meningitis in childhood: Reduction of lumbar punctures.

2.2

Rianne Oostenbrink, Karel GM Moons, A Rogier T Donders, Diederick E Grobbee, Henriëtte A Moll
Acta Paediatrica, in preparation

Abstract

Physicians have a low threshold to perform a lumbar puncture to ascertain the diagnosis in patients with meningeal signs, because of the serious consequences of missing bacterial meningitis. The aim of this study was to derive and validate a clinical rule to predict bacterial meningitis in children with meningeal signs, in order to guide decisions on the performance of lumbar punctures.

Information was collected from records of patients (aged 1 month to 15 years) consulting the emergency department of the Sophia Children's Hospital between 1988 and 1998 with meningeal signs. Bacterial meningitis was defined as cerebrospinal fluid (CSF) leukocyte count > 5 cells/μl with a positive bacterial culture of CSF or blood. The diagnostic value of predictors was judged using multivariate logistic modelling and area under the receiver operating characteristic curves (ROC-area).

In the derivation set (286 patients, years 1988 - 1995) the duration of the main complaint, vomiting, meningeal irritation, cyanosis, petechiae and disturbed consciousness were independent clinical predictors of bacterial meningitis. The ROC-area of this model was 0.92. The only independent predictor from subsequent laboratory tests was serum C-reactive protein concentration, increasing the ROC-area to 0.95. Without missing a single case, this final model identified 99 patients (35%) without bacterial meningitis. Validation on 74 consecutive patients of subsequent three years (1996 - 1998) yielded similar results.

In conclusion, this prediction rule identifies about 35% of the patients with meningeal signs in whom a lumbar puncture can be withheld without missing one case of bacterial meningitis. For the individual patient this prediction rule is valuable to decide whether or not to perform a lumbar puncture.

Introduction

A child with meningeal signs is suspected of having bacterial meningitis, a serious disease that needs immediate treatment. [1,2] Because of the serious consequences of missing this diagnosis, physicians have a low threshold to perform a lumbar puncture. In a substantial part of patients with meningeal signs, however, bacterial meningitis is absent and a lumbar puncture may be considered unnecessary in retrospect. [3,4] Given patient burden and the risk of

side effects, a decrease in the number of unnecessary lumbar punctures is desirable.

Previous studies have shown that clinical signs like meningeal irritation, vomiting, headache and fever are associated with the presence of bacterial meningitis and may be useful in early prediction of meningitis. [2,3,5-8] These studies, however, all selected their patients on the availability of results of a lumbar puncture. Such a patient selection often leads to a biased selection of the most evident cases of meningitis, resulting in a potential overestimation of the diagnostic value of tests that are applied in practice to all patients with meningeal signs. [9-11] In this study, therefore, patients were selected on the presence of meningeal signs conform clinical practice. In this group of patients, independent predictors of bacterial meningitis have never been established.

The *objective of this study* is to determine whether easy obtainable results from clinical evaluation and subsequent tests can predict the presence or absence of bacterial meningitis in children with meningeal signs. A scoring rule was developed and validated to identify a subgroup of patients with a low risk of bacterial meningitis, in whom a lumbar puncture can be withheld, without missing any case of meningitis.

Methods

Patients aged from 1 month up to 15 years, visiting the emergency department of the Sophia Children's Hospital in Rotterdam, the Netherlands between 1988 and 1998 with meningeal signs were eligible. These patients were identified using a problem oriented patient classification system, as has been applied at the outpatient department of the Sophia Children's Hospital since 1988. [12] For each patient the main reason for consulting the outpatient department is prospectively coded by one of the paediatricians (n = 5). The code 'meningeal signs' applies to patients with pain in the neck in history, or with meningeal irritation assessed by either the general practitioner or the paediatrician. Meningeal irritation was defined as presence of Brudzinski sign I or II, Kernig sign, tripod phenomenon or neck stiffness in children > 1 year, and in children ≤ 1 year one of the previous signs or irritability during manipulation of head or legs by the paediatrician or a bulging fontanelle. [4,13] In children with missing information on some tests, but with at least one positive sign, meningeal irritation was considered present. Patients with a history of severe neurological disease or ventricular drain were excluded. Patients referred from other hospitals were additionally excluded, since in these patients treatment may have been initiated already and influenced the clinical signs at presentation. Data obtained from patients between 1988 and 1995 were used to derive a prediction model (derivation set). This model was evaluated on data from patients between 1996 and 1998 (validation set).

Data from patient history and physical examination were collected by review of

the patient charts. The paediatric patient record has a standardised format, including general characteristics, the patient's history of the main problem and complaints of main organ systems and the findings at physical examination. For consciousness four levels were distinguished: alert – reaction to voice – reaction to pain - no reaction. Disturbed consciousness was considered in case of reaction to pain only, or no reaction at all. Data from laboratory tests of cerebrospinal fluid (CSF), blood, stool and urine specimens were retrieved from the computer-documented hospital information system.

The outcome diagnosis was the presence or absence of bacterial meningitis. Its presence was defined as a leukocyte count of > 5 cells/µl in CSF, with positive bacterial cultures of CSF or blood. [1] Patients with antibiotics used before the lumbar puncture were considered to have a pre-treated bacterial meningitis in case of an increased CSF leukocyte count with negative bacterial cultures and subsequent hospitalisation and treatment with antibiotics for at least 7 days. [14] Elevated CSF leukocyte count with viral growth in CSF or faeces or positive viral serology was considered as a case of viral meningitis and absence of any isolated pathogen as a case of aseptic meningitis. [15] Final diagnoses other than meningitis were determined by either bacterial cultures of blood, urine, stool, or ear, nose, or throat specimens, or based on a consensus diagnosis. [4]

In the derivation set, we first quantified the association between the presence and absence of bacterial meningitis and each potential diagnostic determinant using univariate logistic regression analyses. Continuous variables were analysed on a linear and on a transformed scale (logarithmic, quadratic, root or exponential), if clinically plausible, and the best transformation was used in further analyses. We assessed the independent contribution of determinants with univariate associations (p-value < 0.15) by multivariate logistic regression analyses. In accordance to the chronology in which data are documented in clinical practice [9], we first included determinants from patient history and physical examination. The 'clinical evaluation model' was reduced by excluding predictors from the model with p-values > 0.10, since variables with a p-value ≤ 0.10 were considered to be independently related to bacterial meningitis, only. [16] Then, all univariate correlates obtained from laboratory tests were added to the reduced 'clinical evaluation model'. Laboratory variables with a p-value ≤ 0.10 were considered to additionally contribute to the prediction of bacterial meningitis and thus remained in the final model. Reliability of all models was estimated using the Hosmer & Lemeshow test [17], and their ability to discriminate between patients with and without bacterial meningitis using the area under the receiver operation characteristic curve (ROC-area). Differences in the discriminative value between the models were estimated by differences in ROC-area, taking into account the correlation between models as they were based on the same cases. [18,19]

Since multivariate analysis requires all data to be present in all patients [16], we used imputation techniques as available in SOLAS (version 1.1) to fill in missing values of some variables by a (theoretical) value, without disturbing the

relationship between the variables as observed in the data. This allowed to include all patients in the analysis (increased statistical efficiency) and reduced bias since missing may not occur at random (e.g. a record of a seriously sick patient may be more complete than that of a less sick patient) such that the 'complete cases' would reflect a selected sample of children with meningeal signs. [20] Variables with a high percentage of missing data (> 50%) before imputation were excluded from the analysis. To account for uncertainties in imputed data [20,21], the imputation was repeated five times (i.e. multiple imputation), and one prediction model was estimated, as described above, from each of the five imputed datasets. Averaging the regression coefficients and standard errors of the logistic models estimated of the five datasets resulted in one prediction model. [21]

The final model was then transformed into a clinical prediction rule. The coefficient of each variable in the model was multiplied by 2.5 and then rounded to the nearest (half) integer. By assigning points for each variable present and adding the results, a score was obtained for each individual patient. The ROC-area of this score was estimated. The derived prediction rule was then applied to the patients in the validation set, and the performance of the rule (ROC-area) and the percentage of correctly predicted patients was compared with the derivation set.

Table 1 General characteristics of derivation and validation set.

	Derivation set (n=286)	Validation set (n=74)
Male gender	61%	68%
Age (years)*	3.5 (3.4)	4.0 (3.9)
Age ≤ 6 months	37 (13%)	13 (18%)
Age from 6 months to 2 years	92 (32%)	16 (22%)
Age from 2 years to 6 years	98 (34%)	26 (35%)
Age > 6 years	59 (21%)	19 (26%)
Referral pattern		
General practitioner	80%	78%
Self referral	12%	12%
Other specialist	2%	4%
Fever in history	93%	88%
Body temperature at examination (°C)*	39.1 (1.1)	38.9 (1.1)
Pain in the neck in history	46%	49%
Suspected meningeal signs at referring physician	56%	60%
Meningeal irritation at paediatrician	73%	65%
Diagnosis		
Bacterial meningitis	29%	20%
Viral/aseptic meningitis	12%	12%
Pneumonia	7%	11%
Other bacterial infections†	3%	2%
Self limiting diseases‡	49%	55%

*mean (standard deviation)
†other bacterial infections included septicaemia, urinary tract infections, gastro-enteritis
‡self-limiting diseases are upper respiratory tract infections, non-specified viral infection and myogenic torticollis

Results

The derivation set comprised 286 consecutive patients, the validation set 74. There were no differences between the derivation and validation set (Table 1). Bacterial meningitis was diagnosed in 29% (95% CI: 24 - 35%) of the patients of the derivation set (five pre-treated before lumbar puncture) and in 20% (95% CI: 12 - 31%) of the validation set. A lumbar puncture had been performed in 210 (73%) and 47 (64%) children of the derivation and validation set, respectively. None of the 103 children without lumbar puncture developed bacterial meningitis during follow-up, which involved an outpatient department visit or telephone call by one of the paediatricians (in training) within 14 days after discharge.

Table 2 Univariate correlates ($p < 0.15$) of bacterial meningitis (BM) (derivation set, n = 286) (numbers are percentages, unless stated otherwise)

Variable	Number of subjects available (%)	BM present (n=84) %	BM absent (n=202) %
Patient history			
Male gender	286 (100%)	50	66
Temperature (highest) measured at home(°C)*	212 (74 %)	39.8 (1.3)	39.5 (1.2)
Fever	283 (99%)	100	91
Duration of fever (days)*	271 (95%)	2.3 (2.0)	1.8 (2.0)
Duration of the main complaint (days)*	276 (97%)	2.1 (1.7)	1.8 (2.4)
Pain in the neck in history	233 (81%)	46	57
Head ache	180 (63%)	49	56
Acute deterioration	276 (97%)	33	9
Drowsiness	201 (70%)	70	36
Vomiting	256 (90%)	74	23
Increased crying	256 (90%)	15	27
Coughing	212 (74%)	35	43
Complex convulsions	286 (100%)	6	1
Physical examination			
Rectal temperature (°C)§	279 (98%)	39.4 (0.9)	39.1 (1.2)
Disturbed consciousness	286 (100%)	63	6
Impaired peripheral perfusion	210 (73%)	49	20
Cyanosis	286 (100%)	12	0
Petechiae or ecchymoses	286 (100%)	21	3
Enlarged cervical lymphenodes	253 (88%)	32	48
Throat infection	267 (93%)	23	38
Rhinitis	257 (90%)	32	42
Otitis	243 (85%)	0	5
Meningeal irritation	286 (100%)	100	61
Focal neurological disorders	286 (100%)	23	10
Haematology/blood chemistry			
Leukocyte count ($\times 10^9$/l)*	264 (92%)	17.0 (8.8)	15.0 (8.0)
Absolute neutrophil count ($\times 10^9$/l)*	213 (74%)	13.1 (8.3)	10.5 (7.3)
Thrombocyte count ($\times 10^9$/l)*	255 (89%)	257 (144)	319 (128)
Serum CRP (mg/l)*	145 (51%)	166 (94)	69 (82)
Actual bicarbonate (mmol/l)*	196 (69%)	20.0 (3.9)	21.3 (3.7)
Base excess (mmol/l)*	196 (69%)	-3.0 (4.0)	-2.1 (3.9)

*Mean (standard deviation)

Univariate correlates ($p < 0.15$) of bacterial meningitis in the derivation set are presented in Table 2. In all children with bacterial meningitis fever in history and meningeal irritation assessed by the paediatrician were both present. The age of children with bacterial meningitis (3.6 years, 95% CI: 2.8 - 4.3) did not significantly differ from children without (3.5 years, 95% CI: 3.0 - 4.0).

Independent predictors of the presence of bacterial meningitis obtained from patient history and physical examination were the duration of the main complaint and vomiting in history and meningeal irritation, cyanosis, petechiae and disturbed consciousness at physical examination (Table 3). The ROC-area was 0.92 (95% CI: 0.89 - 0.95). Including age did not improve this model, nor a subgroup analysis on children younger and older than 1 year, separately. Serum CRP was the only laboratory predictor with added value beyond the independent predictors in the 'clinical evaluation' model and increased the ROC-area to 0.95 (95% CI: 0.92 - 0.97): an increase of 0.02 (95% CI: 0.01 - 0.04). All models had a good fit (p-value > 0.10).

Table 3 Independent predictors for bacterial meningitis

Variable	Clinical evaluation model OR (95% CI)	Clinical evaluation + laboratory model OR (95% CI)	Contribution to score*
Patient history			
Duration of the main complaint (per day)¶	1.5 (1.2 - 1.9)	1.5 (1.2 - 1.9)	1
Vomiting	2.4 (1.0 - 5.4)	2.3 (0.9 - 5.5)	2
Physical examination			
Meningeal irritation	25.0 (3.2 - 197.5)	21.1 (2.6 - 172.4)	7.5
Cyanosis	24.0 (2.0 - 289.4)	13.0 (1.1 – 151.3)	6.5
Petechiae or ecchymoses	7.5 (2.2 - 25.6)	4.9 (1.4 - 17.9)	4
Disturbed consciousness	22.2 (9.4 - 52.4)	21.8 (8.6 - 55.2)	8
Laboratory tests			
Serum CRP (per 10 mg/l)†	–	1.1 (1.0 - 1.1)	0.1
ROC-area (95% CI) in derivation set	0.92 (0.89 - 0.95)	0.95 (0.92 - 0.97)	0.94 (0.91 - 0.97)
ROC-area (95% CI) in validation set	0.92 (0.86 - 0.98)	0.92 (0.86 - 0.98)	0.92 (0.86 - 0.98)

*Based on 'clinical evaluation + laboratory model'
OR = odds ratio, CI = confidence interval, ROC = receiver operating characteristic
¶duration of the main complaint rounded off to half days, with a maximum of 7 points
†points assigned to serum CRP: 0.1 point per 10 mg/l increase, thus 0 - 9 mg/l: 0 points; 10 - 19 mg/l: 0.1 points; etc, with a maximum of 2 points

Using the scores assigned to each predictor after transformation of the final model (final column of Table 3) the following rule was derived:

$$\text{Score} = 1 \times \text{duration main complaint (days)} + 2 \times \text{vomiting} + 7.5 \times \text{meningeal irritation} + 6.5 \times \text{cyanosis} + 4 \times \text{petechiae} + 8 \times \text{disturbed consciousness} + 0.1 \times \text{serum CRP (per 10 mg/l)}$$

The total score in our patients in the derivation set ranged from 0.5 to 31.0 points. The ROC-area of the score was 0.94 (Table 3). Using the total scores, patients were divided into five groups and the frequency of meningitis in each group was computed (Table 4). Bacterial meningitis was absent in all patients with a score < 9.5 and present in almost all patients with a score ≥ 20. The threshold value < 9.5 identified 99 patients without bacterial meningitis (35%; 95% CI: 29 - 40%), without missing one case of bacterial meningitis.

Table 4 Frequency of bacterial meningitis (BM) related to the score (based on final model)

Risk score	Derivation set (n = 286)		Validation set (n = 74)	
(points)	BM present	BM absent	BM present	BM absent
0 - 4.9	0	64 (100%)	0	20 (100%)
5.0 - 9.4	0	35 (100%)	0	14 (100%)
9.5 - 14.9	17 (16%)	88 (84%)	3 (15%)	17 (85%)
15.0 - 19.9	24 (63%)	14 (37%)	4 (44%)	5 (56%)
≥ 20.0	43 (98%)	1 (2%)	8 (73%)	3 (27%)

Both models and the prediction rule were applied to the validation set to estimate future performance of the rule. The ROC-areas of all three models were 0.92 (95% CI: 0.86 - 0.98) (Table 3), suggesting nearly identical performance compared to the derivation set. The threshold value of 9.5 identified 34 (46%; 95% CI: 34 - 58%) of the patients in the validation set without bacterial meningitis. In the validation set, 47 lumbar punctures had been performed actually; 36 of these were indicated by the prediction rule. Four lumbar punctures were additionally indicated by the rule in 27 patients without an actual lumbar puncture. Considering the number of lumbar punctures as actually performed, the net benefit of the prediction rule would be 7 (47 - (36 + 4)) of 47 lumbar punctures (15%; 95% CI: 6 - 28%).

Discussion

We have shown that physicians can very well predict the presence or absence of bacterial meningitis in children with meningeal signs using a few patient characteristics, such as the duration of the main complaint, vomiting, meningeal irritation, cyanosis, petechiae, disturbed consciousness and serum CRP. The application of this rule in practice decreases the diagnostic burden and risk for side effects for the patient, as well as the measurement costs. In particular, with this rule a lumbar puncture can correctly be withheld in about 35% of children presenting with meningeal signs, leading to a 15% net reduction of lumbar punctures. This net benefit, however, depends on the actual number of lumbar punctures currently applied, and will vary among hospitals.

Most physicians will perform a lumbar puncture in any child with signs of meningeal irritation. Indeed, in our model, meningeal irritation appeared to be one of the strongest predictors. To distinguish between bacterial and viral / aseptic meningitis or other diseases that may present with meningeal signs, however, other clinical characteristics as present in our model have added value.

The relative importance of a variable on the risk of bacterial meningitis is indicated by the value of the score assigned to each predictor. For instance a patient with vomiting and meningeal irritation obtains 9.5 points (2 + 7.5) and has an estimated probability of bacterial meningitis of 16% (Table 3, score 9.5 - 14.9). Additional presence of a disturbed consciousness increases the score to 17.5 (9.5 + 8), which is related to a 63% probability of bacterial meningitis. Inclusion of serum CRP in our rule suggests that CRP results are necessarily available, before drawing conclusions. CRP, however, has a positive score in the rule and thus always increases the total score. Therefore, patients with a score above 9.5 based on clinical variables only (i.e. before knowing serum CRP) will receive an indication for lumbar puncture, irrespectively of the CRP level. These patients are probably the evident cases of bacterial meningitis, in whom further diagnostic tests are quite straightforward. To include serum CRP is valuable in the less evident cases (with clinical score < 9.5), in particular.

We have chosen a threshold value for the total score that will not miss a single case of bacterial meningitis. A higher threshold for the risk score may lead to a larger reduction in lumbar punctures, but also increases the risk of missing a case of bacterial meningitis, which is unacceptable. The defined threshold value of 9.5 has not missed one case of bacterial meningitis in both the derivation and validation set. Since the validation set comprises a random sample of patients to whom the prediction rule will be applied in future, this validation reflects the future performance of the rule. Nevertheless, the purpose of the prediction rule is to *guide* decisions into practice, and not to replace clinical judgement.

It may seem controversial that meningeal irritation at physical examination is part of our inclusion criteria and included as a predictor in our prediction rule as well. Patient inclusion, however, has been based on the presence of either one of the three characteristics (pain in the neck, referral for meningeal signs or meningeal irritation at physical examination). Presence of meningeal irritation at physical examination appears to be independently related to an increased risk of bacterial meningitis, in contrast to pain in neck in history or referral because of meningeal signs.

In accordance with clinical practice, the value of diagnostic tests (i.e. findings of clinical examination and laboratory tests) should be assessed in patients with disease suspicion, defined by signs and symptoms, as the final diagnosis is still unknown at this stage. [11] Therefore, we have studied patients suspected of bacterial meningitis, characterised by signs as described above. Because of this way of patient selection, we cannot directly compare our results to previous reported prediction models, as these studies are based on patients selected on their proven presence or absence of meningitis (bacterial, viral or aseptic). Furthermore, the characteristics of our study population, such as age and pathogen type are determined by the clinical presentation. This selection of patients, however, does not affect the applicability of the rule in future patients, as long as they are also selected on their clinical presentation of 'meningeal signs'. It

should be noted, however, that the diagnostic prediction rule does not apply to all patients suspected of meningitis, since patients with a dominance of other symptoms of meningitis (such as convulsions, coma, etc.) are not included in our study population. [1,5,6]

To further appreciate the present results some aspects need to be discussed. First; the study partly includes the period in which bacterial meningitis caused by *Haemophilus influenzae* (HIB) was still present, although almost eradicated by vaccination nowadays. [22] An analysis with exclusion of the HIB cases (n = 32), however, did not alter the results and yielded the same rule. The rule has proven to perform well in the validation set, in which no cases of HIB meningitis were present. Second; this study has been performed at a paediatric university hospital with about 2,500 new patients visiting the paediatric emergency department yearly and of whom 90% need basic paediatric care. [23] Therefore we think that the derived prediction rule is also applicable for general hospitals. Third; this study has been based on routinely documented information, in which not all data were available for each patient. Although formal criteria do not exist, we initially chose to exclude all diagnostic variables from the analysis with a large proportion of missing data, since imputation of variables with 50% missing data or more would be too in-stable. Moreover, missing data of such variables may indicate that they are difficult to document in clinical practice and therefore are not preferred in an easy and widely applicable prediction rule. Finally, in some children the reference standard (lumbar puncture) for the outcome bacterial meningitis was missing, which may have lead to a certain verification bias. [24] Bacterial meningitis, however, is a serious and rapidly progressing disease without treatment. [1] Since none of the children without a lumbar puncture developed bacterial meningitis during follow-up, no cases of bacterial meningitis were missed. We may have misdiagnosed some cases of viral or aseptic meningitis, since these are not fatal if left untreated. This misclassification, however, will not affect our results, since we aimed to distinguish between the presence or absence of *bacterial* meningitis. We presumed that a lumbar puncture is performed to detect bacterial meningitis. Hence, by using our rule, a lumbar puncture will be withheld in some children with a viral or aseptic meningitis (n = 9 out of 44; 20% in this study), such that this diagnosis is missed. We believe that this is acceptable, since viral and aseptic meningitis have a fair prognosis in children > 1 month and do not need specific treatment. [25] This point of view may change in the future, when antiviral treatment for enteroviral meningitis becomes available. Ascertaining the diagnosis viral meningitis may be additionally important to inform parents or for epidemiological reasons.

The predictors of our rule have also been reported by other studies on the clinical characteristics of children with meningitis, although the independent contribution of serum CRP to the diagnostic accuracy has not been described before. [2,5,7,8,26] It may be surprising that in our study presence of fever in history and leukocyte count in blood did not contribute to the diagnosis bacterial meningitis, since they are known to be predictors for serious bacterial infections. [26,27] We, however,

have evaluated whether the predictors could distinct between bacterial meningitis and 'non-bacterial meningitis' (the latter including viral/aseptic meningitis, other serious bacterial infections and self-limiting diseases). Apparently, fever or leukocyte count does not differ between these two. Additionally, if we consider laboratory tests separately from the clinical evaluation model, also thrombocyte count, glucose level and actual bicarbonate concentration in blood are associated with bacterial meningitis. These tests, however, have no additional value beyond patient history and physical examination and thus can be omitted in the diagnostic process. [9] Furthermore, it should be noted that the aim of this study was to derive a prediction rule for identifying those patients presenting with meningeal sings in whom a lumbar puncture can correctly be withheld for ruling out bacterial meningitis. Hence, we did not yet analyse the additional diagnostic value of variables obtained from CSF laboratory tests.

In conclusion, this is the first study on the predictive value of clinical parameters to estimate the presence or absence of bacterial meningitis among patients consulting the emergency department with meningeal signs. A prediction rule including duration of the main complaint and presence of vomiting in history, presence of meningeal irritation, cyanosis, petechiae and disturbed consciousness at physical examination, and serum CRP concentration, is an easy applicable tool for physicians to guide their decision whether or not to perform a lumbar puncture in the individual patient. In patients with meningeal signs, a lumbar puncture can be withheld in 35% without missing one case of bacterial meningitis.

References

1. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
2. Walsh-Kelly C, Nelson DB, Smith DS, Losek JD, Melzer-Lange M, Hennes HM, et al. Clinical predictors of bacterial versus aseptic meningitis in childhood. Ann Emerg Med 1992;21:910-4.
3. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr 1990;29:254-5, 258-61.
4. Oostenbrink R, Theunissen CCW, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Signs of meningeal irritation at the emergency department; how often bacterial meningitis? Ped Emerg Care, in preparation 2001.
5. Riordan FA, Thomson AP, Sills JA, Hart CA. Bacterial meningitis in the first three months of life. Postgrad Med J 1995;71:36-8.
6. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
7. Hoen B, Viel JF, Paquot C, Gerard A, Canton P. Multivariate approach to differential diagnosis of acute meningitis. Eur J Clin Microbiol Infect Dis 1995;14:267-74.
8. Gerdes LU, Jorgensen PE, Nexo E, Wang P. C-reactive protein and bacterial meningitis: a meta-analysis. Scan J CLin Lab Invest 1998;58:383-394.
9. Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
10. Knottnerus JA, Leffers JP. The influence of referral patterns on the characteristics of diagnostic tests. J Clin Epidemiol 1992;45:1143-1154.

11. van der Schouw YT, van Dijk R, Verbeek ALM. Problems in selecting the adequate patient population from existing data files for assessment studies of new diagnostic tests. J Clin Epidemiol 1995;48:417-422.
12. Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, Kraayenoord S, et al. The development and applicability of a problem oriented patient classification system in a pediatric outpatient clinic. Abstract. In: The 16th Annual meeting of the European Society for Paediatric Infectious Diseases; Bled, Slovenia; 1998.
13. Vincent J, Thomas K, Mathew O. An improved clinical method for detecting meningeal irritation. Arch Dis Child 1993;68:215-8.
14. Rodewald LE, Woodin KA, Szilagyi PG, Arvan DA, Raubertas RF, Powell KR. Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatr 1991;119:363-9.
15. Maxson S, Jacobs RF. Viral meningitis. Tips to rapidly diagnose treatable causes. Postgrad Med 1993;93:153-6, 159-60, 163-6.
16. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
17. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, Inc; 1989.
18. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
19. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-843.
20. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255-1264.
21. Little RA. Regression with missing X's: A review. J Am Stat Assoc 1992;87:1227-1237.
22. van Alphen L, Spanjaard L, van de Ende A, Dankert J. Absence of Haemophilus influenzae type b meningitis in the Netherlands in twice vaccinated children [In Dutch, English summary] Ned Tijdschr Geneeskd 1995;139:880-884.
23. van Steensel-Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, Dekker A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics II. [In Dutch, English summary]. Tijdschr Kindergeneesk 1996;64:99-104.
24. Begg CB. Biases in the assessment of diagnostic tests. Stat Med 1987;6:411-23.
25. Rotbart HA. Enteroviral infections of the central nervous system. Clin Infect Dis 1995;20:971-81.
26. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH, Jr., Powell KR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. Ann Emerg Med 1993;22:1198-210.
27. Hewson PH, Humphries SM, Roberton DM, McNamara JM, Robinson MJ. Markers of serious illness in infants under 6 months old presenting to a children's hospital. Arch Dis Child 1990;65:750-6.

Children with meningeal signs: when to start empirical antibiotic treatment?

2.3

Rianne Oostenbrink, Karel GM Moons, Minke J Twijnstra, Diederick E Grobbee, Henriëtte A Moll

Submitted for publication

Abstract

We developed a decision rule, including cerebrospinal fluid (CSF) indices and clinical characteristics to decide whether or not empirical antibiotic treatment should be started in children with meningeal signs.

In 227 children (aged 1 month to 15 years) visiting the paediatric emergency department with meningeal signs, the added value of early obtainable (CSF) indices to predict bacterial meningitis was judged using multivariable logistic modelling. Bacterial meningitis was defined as CSF leukocyte count > 5 cells/μl with a positive bacterial culture of CSF or blood.

Independent predictors of bacterial meningitis from early obtainable CSF indices were the CSF polymorphonuclear leukocyte count and the CSF/blood glucose ratio. The diagnostic value of this CSF model was 0.93. Applying the model together with clinical characteristics, absence of bacterial meningitis was early predicted in 69 of the 227 patients (30%), such that treatment could correctly be withheld.

In conclusion, the decision rule including clinical characteristics and CSF indices, is a useful tool for decisions on therapeutic interventions in clinical practice and will optimise their use.

Introduction

A delayed diagnosis and treatment of bacterial meningitis worsens its prognosis. Consequently, physicians have a low threshold to perform a lumbar puncture in patients suspected of having meningitis. Moreover, patients with an increased cell count in cerebrospinal fluid (CSF) are commonly treated for bacterial meningitis until the CSF culture result becomes available (after 48 - 72 hours). [1-3] Patients with meningeal signs, however, may still suffer from other diagnoses than bacterial meningitis. [4-6] Early discrimination of bacterial meningitis from other diseases can prevent unnecessary hospitalisation and potential side effects of empirical antibiotic treatment.

Previous studies have assessed several characteristics from clinical evaluation or laboratory tests that may predict bacterial meningitis. [7-10] These studies, however, selected their patients on the diagnosis (proven bacterial, viral and/or aseptic meningitis) or on the presence of a lumbar puncture. Such a patient selection may lead to bias towards the more evident cases of meningitis and thus to an overestimation of the diagnostic value of tests that in practice will be applied to all patients *suspected* of having meningitis. [11-13] Moreover, in practice the physician is faced with a patient with meningeal signs in whom the diagnosis is not known yet. [11] In accordance to clinical practice, we therefore selected in this study children by their clinical presentation.

In a previous study we derived and validated on 360 children with meningeal signs a prediction rule based on clinical signs and symptoms, that enables to determine the indication for lumbar puncture. [14] The *aim of the present study* was to evaluate in those patients with an indication for lumbar puncture whether early available CSF indices can predict the presence or absence of bacterial meningitis, before the CSF culture becomes available. Such predictors could then be used to determine whether or not empirical antibiotic treatment should be started.

Patients and methods

Patients

All patients aged from 1 month up to 15 years, visiting the emergency department of the Sophia Children's Hospital in Rotterdam, the Netherlands between 1988 and 1998 with meningeal signs, were eligible. 'Meningeal signs', as documented by a prospective problem oriented patient classification system [15], was defined as presence of pain in the neck in medical history, or presence of meningeal irritation as assessed by either the general practitioner or the paediatrician. Meningeal irritation was defined as presence of Brudzinski sign I or II, Kernig sign, tripod phenomenon or neck stiffness in children > 1 year, and in children ≤ 1 year one of the previous signs or irritability during manipulation of head or legs by the paediatrician or a bulging fontanel. [6,14,16] Patients referred from other

hospitals or with a history of severe neurological disease or ventricular drain were excluded.

In a previous study on 360 children with meningeal signs, a prediction rule based on clinical signs and symptoms for the presence and absence of bacterial meningitis was derived and validated. [14] This rule can be used in practice to early determine whether or not a lumbar puncture is indicated, without missing a single case of bacterial meningitis. The following rule was defined:

$$\text{Score} = 1 \times \text{duration main problem (days)} + 2 \times \text{vomiting in history} + 7.5 \times \text{meningeal irritation} + 6.5 \times \text{cyanosis} + 4 \times \text{petechiae} + 8 \times \text{disturbed consciousness} + 0.1 \times \text{serum CRP (per 10 mg/l)}$$

Using this algorithm, a risk score could be computed for each individual patient by assigning points for each variable present. For example, a child with vomiting in history, and with meningeal irritation and petechiae at physical examination got a total score of 13.5 (2 + 7.5 + 4) points. In all 360 patients, the score ranged from 0.5 to 31 points. In those with a risk score < 9.5 points (about 35% of the patients), bacterial meningitis was always absent and a lumbar puncture could be withheld. In the remaining 227 patients (score ≥ 9.5), a lumbar puncture was indicated. In these 227 patients, the present study assessed the additional predictive value of CSF indices to the presence or absence of bacterial meningitis and their use in the decision whether or not to start empirical treatment.

Datacollection

By review of the paediatric record, demographic data and presenting signs and symptoms were collected. Data from laboratory tests of CSF, blood, stool and urine specimens were retrieved from the computer-documented hospital information system. The following CSF indices were analysed: the total CSF leukocyte count, the percentage polymorphonuclear leukocytes (PMNs), the absolute number PMNs, protein and glucose concentration and the Gram-stained smear of CSF specimen. The CSF/blood glucose ratio was computed by dividing the CSF glucose level by the serum glucose level (both samples taken at the same time) and analysed as a separate variable.

Diagnostic outcome

The diagnostic outcome was the presence or absence of bacterial meningitis. Its presence was defined as leukocytes > 5 cells/μl in CSF and a positive bacterial culture of CSF or blood. [2] Patients using antibiotics before the lumbar puncture were considered to have a pre-treated bacterial meningitis, if they had an increased CSF leukocyte count and a negative bacterial culture but were subsequently hospitalised and treated with antibiotics for at least 7 days. [9] Final diagnoses other than bacterial meningitis were based on either bacteriologic or viral cultures from CSF, blood, urine, stool and ear, nose, or throat specimens or based on a consensus diagnosis. [6] In absence of a lumbar puncture, presence or absence of bacterial meningitis was assessed by follow-up (outpatient department

visit or telephone call by one of the paediatricians (in training) within 14 days after presentation).

Analysis

The association between the CSF indices and the presence or absence of bacterial meningitis was quantified using univariate logistic regression analyses. Continuous variables were analysed without categorisation, but various cut-off levels and transformations (square root, log) were evaluated. [17] Subsequently, all CSF indices univariately associated (p value < 0.15) were included in a multivariate logistic regression model to evaluate their independent value in the prediction of bacterial meningitis. From this (overall) model, model reduction was performed by excluding predictors from the model with p-values > 0.10, since variables with a p-value ≤ 0.10 were considered to be independently related to bacterial meningitis, only. [17] Reliability (goodness of fit) of all models was estimated using the Hosmer & Lemeshow test [18], and their ability to discriminate between patients with and without bacterial meningitis using the area under the Receiver Operation Characteristic curve (ROC-area). Differences in the discriminative value between the overall and reduced models were estimated using the ROC-areas with 95% CI, taking into account the correlation between the models as they were based on the same cases. [19,20]

To reduce bias and increase statistical efficiency [21,22] missing values in the data were filled in by imputation using SOLAS (version 1.1). SOLAS uses an empirical Bayesian algorithm to impute missing data. Missing data may not be missing at random (e.g. a record of a seriously sick patient may be more complete than a less sick patient) such that the 'complete cases' would reflect a selected sample of children with meningeal signs. In order to account for uncertainties in imputed data [21,22], the imputation was repeated five times (i.e. multiple imputation) and one prediction model was estimated as described above from each of the five imputed datasets.

Next, to validate each model obtained from each dataset and to adjust for too optimistic estimates of the predictors' regression coefficients, random bootstrapping techniques were used. [17,23] In this way, the discriminative ability of each model in future but similar patients was estimated. The five adjusted regression coefficients and standard errors (i.e. from each of the five imputed datasets) were then averaged according to standard statistical techniques to obtain one final (adjusted) model. [22] This adjusted final model was then transformed into a CSF prediction rule by rounding the coefficients of the included variables to the nearest integer. A total CSF score was computed for each individual patient by assigning points for each variable present. The ROC-area of this score was estimated. Finally, the discriminative ability of the CSF prediction rule combined with the previously obtained clinical risk score [14] was evaluated.

Results

General characteristics of the 227 included patients are shown in Table 1. Bacterial meningitis was present in 44% (95% CI: 37-50%), among whom were five cases of pre-treated meningitis; 186 children were hospitalised (82%).

Table 1 General characteristics of patients with indication for lumbar puncture (n=227). (values represent absolute numbers and % in parentheses, unless stated otherwise)

Age (years)*	3.6 (3.6)
Male gender	139 (61%)
Fever	220 (97%)
Vomiting	165 (73%)
Duration main problem (days)*	2.1 (2.0)
Disturbed consciousness	82 (36%)
Meningeal irritation	221 (97%)
Petechiae	37 (16%)
Cyanosis	10 (4%)
Bacterial meningitis	99 (44%)
Hospitalisation	186 (82%)

*Mean (standard deviation)

Table 2 presents the univariate analysis of the CSF indices. Mean total CSF cell count, percentage PMNs, absolute PMN count and CSF protein concentration were significantly higher in patients with bacterial meningitis whereas CSF glucose concentration and CSF/blood glucose ratio were significantly lower. Under the assumption not to miss a single case of bacterial meningitis since this is clinically unacceptable, for none of the CSF variables a threshold value could be found that identified a meaningful number of patients without bacterial meningitis. The Gram-stained smear was negative in 29 of the 99 (29%) patients with bacterial meningitis and positive in 2 of the 128 (2%) patients without and thus did not fully discriminate either. In one of these two false-positive cases *S. epidermidis* was identified in the CSF culture, which was considered to be contamination.

Table 2 Cerebrospinal fluid laboratory findings in 227 patients with and without bacterial meningitis (values represent mean and standard deviation in parentheses, unless stated otherwise)

	BM present (n = 99)	BM absent (n = 128)	Odds Ratio (95% CI)
Total leukocyte count /µl	4,947 (6,227)	274 (1,073)	4.1 (3.0 - 5.7) †
Absolute PMN count /µl	3,523 (4,825)	193 (1,002)	3.4 (2.6 - 4.4) †
% PMNs	67 (30)	23 (31)	1.5 (1.3 - 1.6) ‡
Glucose concentration (mmol/l)	1.8 (1.3)	3.7 (1.0)	0.3 (0.2 - 0.4)
Protein concentration (g/l)	1.93 (1.62)	0.56 (0.56)	5.6 (3.3 - 9.4)
Glucose ratio CSF/blood	0.29 (0.22)	0.65 (0.21)	0.4 (0.3 - 0.5) ‡
Positive Gram-stained smear§	70	2	144.9 (33.6 - 624.5)

PMN: polymorphonuclear cells; CSF: cerebrospinal fluid; BM: bacterial meningitis; CI: confidence interval; †Odds ratio per unit ^{10}log(CSF cell count) (multiplicative), ‡Odds ratio per 10% increase (multiplicative), §percentage

Multivariate regression analysis of all CSF indices identified the absolute PMN cell count and CSF/blood glucose ratio as independent determinants of presence of

bacterial meningitis. The second column of Table 3 shows the contents of this final model before bootstrapping. The diagnostic value (ROC-area) of this CSF model was 0.93 (95% CI: 0.89-0.96). The third column shows the odds ratios and the ROC-area of this model after adjustment for overfitting (bootstrapping). Both models had a good fit, i.e. Hosmer & Lemeshow test p-value > 0.10 (data not shown).

Table 3 Odds ratios (95% confidence interval) of the independent CSF variables

Variables	Model (unadjusted)	Model (adjusted)	Risk score*
CSF absolute PMN count¶	3.0 (2.2 - 4.2)	3.0 (2.1 - 4.1)	1.0
CSF/blood glucose ratio (per 0.1 increase)¶	0.6 (0.5 - 0.8)	0.6 (0.5 - 0.8)	-0.5
ROC-area (95% CI)	0.93 (0.89 - 0.97)	0.93 (0.89 - 0.97)	0.93 (0.89 - 0.97)

CSF: cerebrospinal fluid; PMN: polymorphous cell count; ROC: receiver operating characteristic

Scoring algorithm: $1.0 \times {}^{10}\log(\text{absolute CSF PMN count}) - 0.5 \times (\text{CSF/blood glucose ratio})$

*The score per variable is obtained by rounding the regression coefficients (=ln(OR)) to the nearest fifth decimal

¶odds ratio per unit $^{10}\log$(PMN count) (multiplicative); in score coded as 0 (0–9 PMNs/μl), 1 (10-99 PMNs/μl), 2 (100-999 PMNs/μl), 3 (1,000-9,999 PMNs/μl), and 4 (>10,000 PMNs/μl).

¶in score coded as 0 (ratio <0.10), 1 (ratio 0.10-0.19), 2 (ratio 0.2-0.29), 3 (ratio 0.3-0.39), etc. up to 10 (ratio >1.0)

From the regression coefficients of the predictors in the adjusted model corresponding scores were derived (regression coefficients rounded to the nearest fifth decimal), such that a prediction rule was developed (fourth column, Table 3). A total score was computed for each patient by assigning 1 point for each increase of the $^{10}\log$ (absolute PMN count) and –0.5 point for each tenth increase of the CSF/blood glucose ratio. For instance, a patient with 1,500 cells/μl with 80% PMNs (1,200 PMNs/μl) and a CSF/blood glucose ratio of 0.2 got 2 points (3 – 1). When applied to all patients, the score ranged from –5 to +4. The ROC-area of this CSF rule was 0.93 (95% CI: 0.89 - 0.96). Table 4 shows the incidence of bacterial meningitis and the number of subjects across selected categories of the score. The CSF score identified groups with increased probability of true bacterial meningitis. No threshold value could be defined for the CSF score, however, that selected a substantial group of patients without bacterial meningitis in whom treatment could be withheld, without missing one case of bacterial meningitis.

Table 4 Distribution of patients with and without bacterial meningitis according to the CSF score

CSF score	BM+	BM-
-5 to -3.5	1 (4%)	24 (96%)
-3 to -0.5	16 (14%)	97 (86)
0 to 2.5	53 (90%)	6 (10%)
3 to 4	29 (97%)	1 (3%)
All	99 (44%)	128 (56%)

CSF: cerebrospinal fluid; BM: bacterial meningitis; +: present; -: absent

A lumbar puncture is only one step in the diagnostic process and usually performed after history taking and physical examination. Therefore, we evaluated the CSF model combined with the clinical risk score, as derived previously. [14] Figure 1 shows that combined use of both rules can very well discriminate between patients with and without bacterial meningitis. Again under the assumption not to miss any patient with bacterial meningitis, the required threshold for the CSF score varied among groups of patients with different clinical risk scores. In patients with a clinical score between 9.5 and 10.4, a threshold CSF score of < 1 identified patients without meningitis. For patients with a clinical score of 10.5 to 12.9 and 13 to 19.9, the CSF thresholds were < -2 and < -3, respectively. In patients with a very high clinical risk score (≥ 20), the CSF score could not additionally discriminate the patients with bacterial meningitis from those without. Similarly, in patients with a CSF score ≥ 1, the clinical score could not further select patients with and without bacterial meningitis. Using the thresholds (Figure 1), in 69 patients (30%, 95% CI: 24 - 36%) empirical treatment could correctly be withheld.

Figure 1 Combination of the clinical risk score with CSF score (n = 227)

CSF score	Clinical risk score			
	9.5 - 10.4	10.5 - 12.9	13 - 19.9	≥ 20
-5 to -3.5	BM- 69			BM+ 99
-3 to -2.5				
-2 to 0.5			BM- 59	
1 to 4				

	No indication for treatment
	Indication for treatment

CSF: cerebrospinal fluid; BM: bacterial meningitis; +: present; -: absent

Discussion

The absolute number of PMNs in CSF and the CSF/blood glucose ratio are independent predictors of bacterial meningitis in patients with meningeal signs. Using these early CSF indices only, bacterial meningitis cannot be predicted, without missing a case of bacterial meningitis. Combination of these two CSF indices with patient characteristics, such as the duration of the main problem, vomiting, meningeal irritation, cyanosis, petechiae, disturbed consciousness and serum CRP, however, can very well discriminate between the absence or presence of bacterial meningitis such that unnecessary treatment can be withheld. Application of this CSF rule in combination with these patient characteristics will reduce unnecessary antibiotic treatment and unnecessary side effects of this treatment (allergy, gastro-intestinal complaints, infusion problems, hospital infections, etc.) and increases clinical efficiency. Hence, empirical antibiotic treatment can correctly be withheld in 30% of the children. Of course, this reduction in treatment should be considered in view of the actual number of treatments in current practice (n = 186). The net reduction of empirical treatment as achieved by the decision rule is 28 (16%; 95% CI: 10 - 21%). This net benefit,

however, depends on the actual number of empirical treatment, and will vary among hospitals.

The combined use of the clinical risk score [14] with the CSF rule in predicting bacterial meningitis agrees with common practice, where laboratory tests usually are evaluated in view of the present clinical signs and symptoms. As illustrated in Figure 1, in patients with an intermediate clinical risk score or CSF score, both scores contribute to the assessment of the risk of bacterial meningitis; therefore the decision rule is valuable in this group of patients in particular. In patients with a very high clinical risk score (> 20), who are the most obvious cases of bacterial meningitis, the CSF score does not contribute to therapeutic decisions and empirical treatment will be started anyway; the CSF culture result, however, will guide specific antimicrobial treatment. [2,3] Similarly, patients with a very high CSF score are evident cases of bacterial meningitis and the clinical profile does not contribute much to therapeutic decisions.

The diagnostic process is a stepwise procedure, with use of diagnostic tests subsequent to patient history and physical examination. [11] Following this usual order of testing in clinical practice, we have selected patients suspected of bacterial meningitis (because of meningeal signs), who had an indication for lumbar puncture as defined by a prediction rule based on clinical symptoms. [14] In these patients, we have derived a rule to decide whether or not empirical treatment is necessary. One may question whether the decision rule including the CSF score and the clinical score together may also be applicable in a clinical setting where lumbar punctures are performed without using the clinical prediction rule. Therefore, we repeated the analyses on all patients who actually underwent a lumbar puncture (n = 256). The same CSF and clinical scoring rule were found and the same number of patients were selected for empirical treatment. This indicates that our CSF rule can both be applied in patient undergoing a lumbar puncture as selected by our clinical rule as well as in patients undergoing a lumbar puncture based on the paediatrician's decision. Nevertheless, it should be noted that in this latter clinical setting more unnecessary lumbar punctures will be performed.

That CSF indices alone cannot very well discriminative between absence or presence of bacterial meningitis, has been mentioned previously. [7,24] This underlines the diagnostic problem when evaluating a child suspected of bacterial meningitis. Given the increased risk of mortality and morbidity in a delayed diagnosis and treatment of bacterial meningitis, clinicians preferably treat each child with an increased CSF leukocyte count empirically, until the CSF culture result is available. [2,3] Although a save strategy, a large group of patients without bacterial meningitis will be unnecessarily treated with antibiotics, with unnecessary costs and risk for potential side effects of treatment. Our finding of total CSF PMN count and the CSF/blood glucose ratio to be independent predictors of bacterial meningitis has also been reported by previous studies. [7,8,10] In contrast to others [7], serum glucose was not an independent predictor in our

study, although the CSF/blood glucose ratio in our rule indirectly includes this variable. The diagnostic value of CSF C-reactive protein and lactate concentration are not evaluated in this study. Although their diagnostic value has been reported [25,26], these highly advanced tests are not available in every hospital emergency department. Since our aim was to develop a rule widely applicable in general paediatric practice, we have decided not to include these advanced tests in the study. The final CSF model also does not contain the Gram-stained CSF smear. Its addition to the CSF model with PMN count and CSF/blood glucose ratio only, significantly increased the ROC-area from 0.93 to 0.95 (95% CI: 0.92 - 0.98). Despite this ROC-area increase, however, the Gram-stain did not improve the discrimination of patients without bacterial meningitis such that more unnecessary treatments could be withheld.

To appreciate the present results some aspects need to be discussed. First, our study partly includes a time period in which bacterial meningitis caused by *Haemophilus influenzae* (HIB) was still present. Since HIB has almost been eradicated by vaccination nowadays [27], we have performed an analysis with exclusion of these meningitis cases (n = 32), as well. This exclusion, however, did not alter the results and yielded the same CSF and clinical scoring rule. Second, the CSF rule has been developed in a population of patients with meningeal signs as the main problem. It should be noted that this rule does not apply to all patient suspected of meningitis, since patients with a prominence of other symptoms of meningitis (such as convulsions, coma, etc.) are not included in our study population. [2,3,28] To our knowledge, however, this is the first study in a paediatric emergency department based on the patient's clinical presentation. Third, in some children the reference standard (lumbar puncture) for the outcome bacterial meningitis was missing. In these children absence of bacterial meningitis has been assessed using follow-up data. Although this could have introduced some diagnostic verification bias [29], we think this did not occur in our study, since bacterial meningitis is a serious and fatal disease without adequate treatment [2] and all children without a lumbar puncture were followed-up and recovered uneventfully. We may, however, have misdiagnosed some cases of viral or aseptic meningitis. Since we aimed to distinguish between the presence or absence of bacterial meningitis, this will not affect our results. Fourth, our study has been performed at a paediatric university hospital. Ninety percent of patients visiting the emergency department of this hospital, however, requires basic paediatric care. [15] Therefore, we think that the derived prediction rule is applicable both to academic and general hospitals. Finally, validation of the CSF model demonstrated that the rule is robust. Before implementation of this decision rule in clinical practice, however, a prospective validation in similar future patients is necessary and currently being performed in our hospital.

In conclusion, this study provides physicians with a rational basis for estimating the risk for bacterial meningitis in patients consulting the emergency department with meningeal signs. The decision rule is a tool in clinical practice for decisions on therapeutic interventions and therefore will optimise their use.

References

1. Bryant K, Marshall GS. Most cerebrospinal fluid cultures in children with bacterial meningitis are positive within two days. Ped Inf Dis J 1999;18:732-733.
2. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
3. Oliver LG, Harwoord-Nuss AL. Bacterial meningitis in infants and children: a review. J Emerg Med 1993;11:555-564.
4. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
5. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr (Phila) 1990;29:254-5, 258-61.
6. Oostenbrink R, Theunissen CCW, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Signs of meningeal irritation at the emergency department; how often bacterial meningitis? Ped Emerg Care, in preparation 2001.
7. Hoen B, Viel JF, Paquot C, Gerard A, Canton P. Multivariate approach to differential diagnosis of acute meningitis. Eur J Clin Microbiol Infect Dis 1995;14:267-74.
8. Spanos A, Harrell FE, Jr., Durack DT. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. JAMA 1989;262:2700-7.
9. Rodewald LE, Woodin KA, Szilagyi PG, Arvan DA, Raubertas RF, Powell KR. Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatr 1991;119:363-9.
10. Deivanayagam N, Ashok TP, Nedunchelian K, Ahamed SS, Mala N. Evaluation of CSF variables as a diagnostic test for bacterial meningitis. J Trop Pediatr 1993;39:284-7.
11. Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
12. van der Schouw YT, van Dijk R, Verbeek ALM. Problems in selecting the adequate patient population from existing data files for assessment studies of new diagnostic tests. J Clin Epidemiol 1995;48:417-422.
13. Knottnerus JA, Leffers JP. The influence of referral patterns on the characteristics of diagnostic tests. J Clin Epidemiol 1992;45:1143-1154.
14. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
15. Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, Kraayenoord S, et al. The development and applicability of a problem oriented patient classification system in a pediatric outpatient clinic. Abstract. In: The 16th Annual meeting of the European Society for Paediatric Infectious Diseases; Bled, Slovenia; 1998.
16. Vincent J, Thomas K, Mathew O. An improved clinical method for detecting meningeal irritation. Arch Dis Child 1993;68:215-8.
17. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
18. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, Inc; 1989.
19. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
20. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-843.
21. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255-1264.
22. Little RA. Regression with missing X's: A review. J Am Stat Assoc 1992;87:1227-1237.
23. Efron B. Estimating the error rate of a prediction rule: improvement on Cross-Validation. J Am Stat Ass 1983;78:316-331.
24. Carraccio C, Blotny K, Fisher MC. Cerebrospinal fluid analysis in systemically ill children without central nervous system disease. Pediatrics 1995;96:48-51.
25. Gerdes LU, Jorgensen PE, Nexo E, Wang P. C-reactive protein and bacterial meningitis: a meta-analysis. Scan J CLin Lab Invest 1998;58:383-394.

26. Bonadio WA. The cerebrospinal fluid: physiologic aspects and alterations associated with bacterial meningitis. Pediatr Infect Dis J 1992;11:423-31.
27. Conyn-van Spaendonck MA, Veldhuijzen IK, Suijkerbuijk AW, Hirasing RA. Significant decline of the number of invasive Haemophilus influenzae infections in the first 4 years after introduction of vaccination against H. influenzae type B in children [in Dutch, English summary]. Nederlands Tijdschrift voor Geneeskunde 2000;144(22):1069-73.
28. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
29. Begg CB. Biases in the assessment of diagnostic tests. Stat Med 1987;6:411-23.

A diagnostic decision rule for management of children with meningeal signs.

2.4

Rianne Oostenbrink, Karel GM Moons, Gerarda Derksen-Lubsen, Diederick E Grobbee, Henriëtte A Moll

Submitted for publication

Abstract

Use of an early applicable diagnostic decision rule, as previously derived, could improve management of children with meningeal signs, suspected of having bacterial meningitis.

Objectives: To assess the validity of this rule in an external patient population.

Design: Prospective validation study.

Setting: Emergency department of four (paediatric) hospitals in the Netherlands

Subjects: Children (0.1 to 15 years) with meningeal signs, suspected of having bacterial meningitis

Interventions: A diagnostic decision rule, including two scoring algorithms to set the indication of lumbar punctures and empirical treatment; one algorithm using symptoms, signs and serum C-reactive protein and a second one additionally using cerebrospinal fluid indices.

Outcome measures: The discriminative value of both algorithms was estimated using the area under the receiver operator characteristic curve (ROC-area), as well as the absolute numbers of correctly diagnosed patients, and compared with the results from the original population.

Results: Between November 1999 and November 2000 we included 176 children (median 2.2 years), initially presenting themselves with meningeal signs. Bacterial meningitis was diagnosed in 20 of them (11.4%). The scoring algorithms accurately predicted the frequency of bacterial meningitis. The algorithms' ROC-areas in this population were similar to those of the original population.

Conclusions: The previously derived diagnostic rule performed well in a new population of children with meningeal signs. It is a valuable tool for the clinician in making decisions on the need of a lumbar puncture or on initiating empirical treatment in these children.

Introduction

Children with meningeal signs offer the physician a diagnostic dilemma, since a large proportion of children with bacterial meningitis show meningeal signs [1,2], but many children with signs of meningeal irritation have another basis for their symptoms. [3,4] Since delayed diagnosis and treatment of bacterial meningitis

worsens its prognosis, physicians have a low threshold to perform a lumbar puncture in patients with meningeal signs and to start empirical antibiotic treatment in those with an increased cell count in cerebrospinal fluid (CSF). Hence, lumbar punctures and empirical treatment that are performed in these children may, to some extent, be regarded unnecessary in retrospect. To improve their management, a diagnostic decision rule was developed in a previous study to guide decisions on the performance of a lumbar puncture and on starting empirical antibiotic treatment for bacterial meningitis in children with meningeal signs, which showed good performance. [5,6] The question remained, however, whether this rule could be applied to other clinical settings. [7-9] The *aim of this study* was to evaluate prospectively the performance of the rule in new patients with meningeal signs at the paediatric emergency department of four hospitals.

Methods

Patients

The study was performed in the Sophia Children's Hospital Rotterdam (SCH; academic paediatric hospital), the Juliana Children's Hospital in The Hague (JCH; general paediatric hospital), and at the paediatric department of the Sint Fransiscus Hospital, Rotterdam and the Reinier de Graaf Hospital, Delft (both general hospitals; GH), The Netherlands. Children, aged from 1 month up to 15 years, who visited the emergency department with the problem 'meningeal signs', without pre-existent neurological diseases were eligible for this study. The problem 'meningeal signs', was applied to children with pain in the neck in history, or referred by the general practitioner for meningeal signs, or in whom the paediatrician has assessed meningeal irritation. [5,6,10] To ensure the enrolment of all patients with 'meningeal signs' we checked the emergency department log during the study period. Patients were included in the period of November 1999 to November 2000 (SCH and JCH during 12 months; GH 7 months).

Decision rule

The decision rule developed on 360 children suspected of having bacterial meningitis as admitted to the SCH between 1988 – 1998 [5,6] included two scoring algorithms (see Appendix for details). The first algorithm (clinical score) aimed to guide decisions on the need of a lumbar puncture and assigned the patient points for each of six characteristics: 1 point for each day of complaints before presentation, 2 points for vomiting in history; 7.5 points for meningeal irritation at examination; 8 points for disturbed consciousness; 6.5 points for cyanosis; 4 points for petechiae; and 0.5 points for serum CRP per 50 mg/l increase. The second algorithm (CSF score) aimed to guide decisions on initiating empirical treatment for bacterial meningitis and assigned the patient points for each of two cerebrospinal fluid (CSF) indices: 1 point for each ^{10}log(absolute CSF polymorphous cell count) increase and –0.5 points for CSF/blood glucose ratio per one-tenth increase. For example, a boy with complaints since half a day, who vomits, with meningeal irritation at physical examination, a serum CRP of 45 mg/l,

150 polymorphous cells in CSF/µl and a CSF/blood glucose ratio of 0.45, gets a clinical score of 10 (=0.5 + 2 + 7.5 + 0 + 0 + 0) and a CSF score of 0 (= 2 - 2). In the population the rule was derived on (further referred to as 'derivation set' [5,6]), a threshold value of a clinical score < 9.5 identified patients in whom a lumbar puncture could be omitted without missing one case of bacterial meningitis. In patients with a clinical score of 9.5 – 10.4, a CSF score of ≥ 1 identified patients in whom empirical treatment was indicated; for those with clinical scores between 10.5 – 12.9 or 13.0 - 19.9 the lower CSF thresholds for empirical treatment were ≥ -2 and ≥ -3, respectively. All patients with a clinical score ≥ 20 had an indication for empirical treatment, irrespective of the CSF score. For further information on the derivation and validation of the decision rule we refer to previous publications. [5,6]

Data collection

During the prospective application of the rule, all items of the rule and some additional general characteristics, symptoms, signs, and laboratory tests were collected. Duration of the main problem was defined as the duration of the complaint that was reason for referral (rounded to half days). Vomiting was scored positive if mentioned in patient history during the disease period. Meningeal irritation was defined as presence of Brudzinski sign I or II, Kernig sign, tripod phenomenon or neck stiffness in children older than one year and in children younger than one year as the presence of one of these signs or irritability during manipulation of head or legs or a bulging fontanel. [10] For consciousness four levels were distinghuised: alert – reaction to voice – reaction to pain – no reaction; disturbed consciousness was considered in case of reaction to pain only, or worse. Petechiae or ecchymoses were defined present if documented at presentation, not causally explained by excessive cough, crying or manipulation. Cyanosis was based on clinical judgement.

The outcome diagnosis was the presence of bacterial meningitis, defined as the presence of elevated leukocyte count (> 5 cells/µl) in cerebrospinal fluid (CSF) of a non-traumatic puncture and a positive bacterial culture of CSF or blood. [2] Elevated CSF leukocyte count with viral growth in CSF or faeces or positive viral serology was considered as a case of viral meningitis and absence of any isolated pathogen as a case of aseptic meningitis. [11] Final diagnoses other than meningitis were determined by either bacteriologic cultures of blood, urine, stool and ear, nose, or throat specimens or based on a consensus diagnosis, including a one-week outpatient follow-up. [10] To the latter aim, data on recovery of non-hospitalised patients were collected at their control visit or by telephone call within 3 - 7 days after first admission by one of the paediatricians (in training) or the research fellow.

Before applying the rule, the paediatrician was asked whether or not he or she would perform a lumbar puncture in the patient. Subsequently, the treating physician estimated the clinical score for each patient. The true decision to perform a lumbar puncture, however, was still left to the physician's opinion, as

the aim of this study was not to implement the rule but first to validate its performance in other patient populations. The same procedure was followed for the CSF score.

Analysis

The two scoring algorithms included in the decision rule were evaluated separately. First, the discriminative value of the clinical algorithm was assessed in the new population (further referred to as 'validation set') using the area under the receiver operator characteristic curve (ROC-area) and compared with results of the derivation study. [12] As in the derivation study, we also defined a lower threshold below which no case of meningitis occurred. Then, on all patients with a clinical score higher than this threshold, i.e. with an indication of lumbar puncture, the CSF scoring algorithm was validated using the ROC-area. As ROC-areas are not directly interpretable in terms of absolute patients numbers [13], we finally estimated the number of correctly diagnosed patients across categories of both scoring algorithms and compared these numbers with the derivation set.

Results

The validation population comprised 176 patients: 103 of JCH; 59 of SCH; and 14 of GH. A lumbar puncture had been performed in 108 (61%) children (Figure 1).

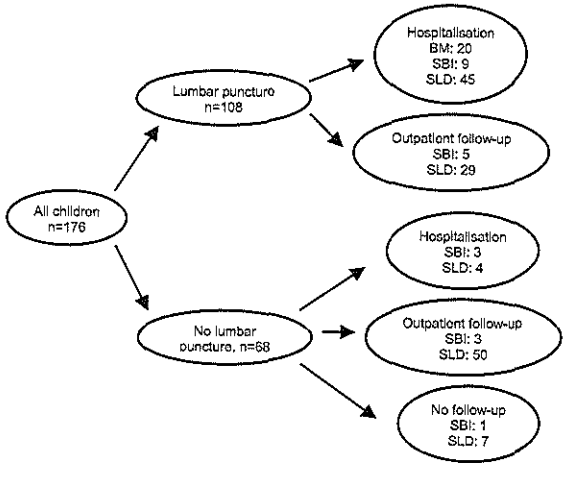

Figure 1 Flow chart of applied management to the 176 children with meningeal signs
BM: bacterial meningitis; SBI: serious bacterial infections (other than BM);
SLD: self-limiting diseases

Eighty-seven children with early discharge (with or without lumbar puncture, 34 and 53, respectively) recovered uneventfully, as documented during the outpatient department visit or telephone call. Eight children lacked follow-up. The patients' main characteristics are presented in Table 1 and compared with those of the derivation set. Patients in the validation set presented less frequently with

petechiae or a disturbed consciousness and were less frequently hospitalised than those in the derivation set. Although children were rather equally referred with meningeal signs by the general practitioner, the paediatrician confirmed presence of meningeal irritation less frequently in the validation set (56 of 111; 50%) than in the derivation set (133 of 203; 66%). The frequency of bacterial meningitis in the validation set was substantially lower than in the original population (11% and 28%, respectively).

Table 1 General characteristics of derivation and validation set.

Characteristic		Derivation set (n=360)	Validation set (n=176)
Male gender		225 (63%)	118 (67%)
Age (years) [§]		2.4 (0.8 - 5.3)	2.2 (0.5 - 6.0)
Referral	General practitioner	286 (79%)	132 (75%)
	Self referral	42 (12%)	34 (19%)
	Other	9 (3%)	9 (5%)
Neck stiffness in patient history		168 (47%)	79 (45%)
Referred with meningeal irritation by general practitioner		203 (56%)	111 (63%)
Meningeal irritation assessed by paediatrician		256 (71%)	102 (58%)
Fever in history		330 (92%)	161 (92%)
Vomiting in history		182 (51%)	89 (51%)
Duration main problem (days) [§]		1 (1 - 2)	1 (1 – 2)
Body temperature at examination (°C) [*]		39.2 (1.1)	38.9 (1.1)
Petechiae at examination		39 (11%)	24 (14%)
Disturbed consciousness		83 (23%)	14 (8%)
Cyanosis		10 (3%)	2 (1%)
Serum CRP (mg/l)[§]		54 (14-151)	18 (8-71)
Hospitalisation		218 (61%)	79 (45%)
Diagnosis	Bacterial meningitis	99 (28%)	20 (11%)
	Serious other bacterial infection[†]	36 (10%)	40 (23%)
	Viral/aseptic meningitis	44 (12%)	21 (12%)
	Other self-limiting disease[‡]	181 (50%)	95 (54%)

[§]median (25th and 75th percentiles); [*]mean (standard deviation)
[†]including septicaemia, pneumonia, urinary tract infection and bacterial gastro-enteritis
[‡]including upper respiratory tract infections, viral syndromes

The ROC-area of the clinical score was 0.86 (95% CI: 0.81 – 0.94), which was little lower than in the original data set (ROC-area 0.94; 95% CI: 0.91 – 0.96). [5] Table 2 presents the observed frequency of bacterial meningitis in the validation set in categories of the clinical score and the expected number using the probability as predicted by the logistic model underlying the clinical score. No large differences were found between the observed and predicted number of patients with bacterial meningitis within categories of the clinical score.

The validation of the CSF scoring algorithm was performed on all children with an indication of a lumbar puncture, based on their clinical score. Since bacterial meningitis was absent in all patients with a score < 8.5, we used this threshold for selecting patients in need of a lumbar puncture (n = 99; Table 2). The ROC area of the CSF score was 0.95 (95% CI: 0.89 – 1.0), which is similar to the ROC area in the

derivation set (0.93; 95% CI: 0.89 - 0.97). [6] Table 3 presents the observed frequency of bacterial meningitis in the validation set according to the CSF score and the expected number using the probability as predicted by the logistic model underlying the CSF score. In the third category of the CSF score (score –1.5 to -0.5), the expected number was higher than the observed (7 versus 2, respectively).

Table 2 Validation of the clinical score

	Clinical score				
	0 - 4.9	5.0 - 8.4	8.5 - 14.9	15.0 - 19.9	≥ 20.0
Number of patients	61	16	78	16	5
Observed prevalence of BM, n (%)	0 (0)	0 (0)	10 (12.8)	6 (37.5)	4 (80.0)
Expected prevalence of BM, n (predicted probability* in %)	0 (0.3)	0 (0.2)	9 (11.6)	9 (58.7)	4 (90.9)

BM: bacterial meningitis; n: number of patients with BM
*Predicted probability as estimated by the logistic model

We validated the threshold values of the clinical and CSF score for the indication of a lumbar puncture and for empirical treatment, as defined in the derivation set, in the new population. The lowest clinical score observed in children with bacterial meningitis in the validation population was 8.5, somewhat lower than the one observed in the derivation population. In Figure 2, the adjusted threshold values for the clinical and CSF score are presented, to set the need for a lumbar puncture or empirical treatment, such that no case of bacterial meningitis would be missed in the validation set. A clinical score threshold value of 8.5 selected 77 children (44%) with a clinical score < 8.5, in whom a lumbar puncture could be withheld, and increased the prior probability of bacterial meningitis in all 176 children with meningeal signs (20/176: 11%) to 20% (20/99) in those selected for a lumbar puncture (clinical score ≥ 8.5). Additional use of the CSF score further improved patient management by correctly withholding empirical antibiotic treatment in 48 of the 99 patients selected for lumbar puncture (48%), without missing one case of bacterial meningitis.

Table 3 Validation of the CSF score in patients with a clinical score ≥ 8.5 (n=99)

	CSF score			
	<-3	-3 to -1.0	-1.5 to -0.5	≥ 0
Number of patients*	12	25	20	16
Observed prevalence of BM, n (%)	0 (0)	1 (4.0)	2 (10.0)	13 (81.3)
Expected prevalence of BM, n (predicted probability† in %)	0 (2.6)	2 (8.7)	7 (33.3)	12 (75.3)

BM: bacterial meningitis
* n=73, since cases with missing values (n=26) are excluded
†Predicted probability computed by mean of probabilities as predicted by the logistic model

Discussion

The principle aim of diagnostic protocols is to apply them in clinical practice and to improve patient management. Clinical prediction rules may, however, not perform as well in new settings, as they had had in the settings in which they were developed. [8,14,15] Therefore, prospective validation of a rule should inform about whether the rule reflects true associations rather than the play of chance or statistical 'overfitting' and whether they can be applied appropriately in practice. In this present study, we have validated a diagnostic decision rule, as previously derived, to guide two questions in children presenting with meningeal signs, i.e. when to perform a lumbar puncture, and when to start empirical antibiotic treatment, without missing a single case of bacterial meningitis. In a new group of 176 children visiting the emergency department with meningeal signs, the scoring algorithms of this rule using symptoms and signs at presentation and early available laboratory tests from blood and cerebrospinal fluid appears to be valid.

In 26 patients (of whom three with bacterial meningitis) the CSF score could not be computed due to missing values for either the CSF cell count, or glucose concentration in CSF or serum for laboratory technical reasons. These patients were excluded from further analysis, which may explain part of the difference between the observed and expected number of cases (Table 3).

In the validation set two children with bacterial meningitis had a clinical score of 8.5, and would have been missed using a threshold value of 9.5 (as defined on the derivation set) for performing a lumbar puncture. One was a 34-days old boy, prematurely born, and thus at the borderline of the age criteria of our rule (patients aged from one month up to 15 years). He had a one-day history of complaints, meningeal irritation at physical examination, and a serum CRP of 2 mg/l. CSF contained 11,310 cells/µl (90% polymorphonuclear cells) and the CSF/blood glucose ratio was 0.49. *E. coli* was isolated from CSF. The other was a 6-month old boy, with complaints since half a day and a generalised seizure of 10 minutes. During examination, he developed a second generalised seizure. Serum CRP was 68 mg/l, and CSF contained 2,700 cells/µl (polymorphonuclear cells only); CSF/blood glucose ratio was 0.61. *S. pneumoniae* was isolated from CSF and blood. Obvious, the combination of seizures and meningeal signs is very indicative of bacterial meningitis. In a population of children with meningeal signs as the main symptom, however, seizures occur too infrequently to be included in a diagnostic prediction rule. Hence, based on these findings in the validation study, we have adjusted the former threshold values for the clinical and CSF score, such that no children with bacterial meningitis will be missed in future use of the rule.

Figure 2 Distribution of patients with and without bacterial meningitis across categories of both scores in the decision rule

CSF score	Clinical risk score				
	< 8.5	9.5 - 10.4	10.5 - 12.9	13 - 19.9	≥ 20
< -3	**BM- = 77**	**BM- = 48**			**BM- = 31**
-3 to -2.5					**BM+ = 20**
-2 to -1					
≥ -0.5					

	Neither indication for lumbar puncture nor treatment
	Indication for lumbar puncture, but no indication for treatment
	Indication for lumbar puncture and for treatment

Some comments on the use of the rule and its generalisability need to be made. First, in this validation study, the prevalence of bacterial meningitis in children with meningeal signs has reduced substantially, compared to the population the rule was derived on. This may be due to the routine *Haemophilus* type B-vaccination of infants, as introduced in the Netherlands since 1996. [16,17] Since the value of a prediction rule may be affected by differences in disease prevalence in different populations [18-20], we estimated the performance of both the clinical and CSF algorithm, after adjusting for this difference in prevalence, i.e. adjusting the intercepts of the two original logistic regression models [5,6], from which the scoring rules in the appendix were derived. These adjusted models, however, yielded similar ROC-areas as the (unadjusted) scoring rules in the appendix. In addition, the adjustment did also not improve the predictive accuracy in terms of absolute number of patients. Therefore, we think that an adjustment for differences in disease-prevalence does not necessarily have to be included in the scoring algorithms of the appendix. Second, the derivation of the rule was based on retrospectively collected data, but data were prospectively collected during validation. The rule, however, performed similar in the validation set compared to the derivation data. Therefore, we think that the rule including the symptoms and signs as we defined, is well applicable in practice. Third, since the rule aims to guide the diagnostic process before the diagnosis is known (conform practice), we selected patients by their clinical presentation, i.e. patients visiting the emergency department with meningeal signs. It should be noted that this rule does not apply to all patient suspected of having meningitis, since patients with a prominence of other symptoms of meningitis (such as coma, convulsions, etc. [1,2]) are not included in our study population. Finally, the rule was derived in an academic paediatric hospital (receiving about 90% basic paediatric care [21]) but validated in four hospitals, including three non-academic ones, with their particular patient populations. Since the rule performed well in all hospitals, we state that the rule is applicable to paediatric emergency departments in general.

In conclusion, a diagnostic decision rule for children with meningeal signs proved to perform well in a newly selected group of patients. Using this rule, patients can be classified in groups of increased probability of bacterial meningitis. This diagnostic decision rule can be used as a tool for the clinician to guide decisions on the performance of a lumbar puncture or initiating empirical treatment in children with meningeal signs in order to improve their management.

APPENDIX Contents of the diagnostic decision rule

1a Clinical scoring algorithm

Characteristic		Points assigned if characteristic present	Patient score
Duration main problem in history		1 per day (max 10)	
Vomiting in history	yes	2	
	no	0	
Meningeal irritation at physical examination	yes	7.5	
	no	0	
Cyanosis at physical examination	yes	6.5	
	no	0	
Petechiae at physical examination	yes	4	
	no	0	
Disturbed consciousness at physical examination	yes	8	
	no	0	
Serum CRP (mg/l)	< 50	0	
	50 - 99	0.5	
	100 - 149	1.0	
	150 - 199	1.5	
	≥ 200	2.0	
Total clinical risk score (sum of scores)			

1b Cerebrospinal fluid (CSF) scoring algorithm

Characteristic		Points assigned if characteristic present	Patient score
CSF polymorphous cell count (per µl)	< 10	0	
	10 - 99	1	
	100 - 999	2	
	1000 – 9999	3	
	> 10,000	4	
CSF/blood glucose ratio	< 0.1	0	
	0.1 - 0.19	-0.5	
	0.2 - 0.29	-1.0	
	0.3 - 0.39	-1.5	
	0.4 - 0.49	-2.0	
	0.5 - 0.59	-2.5	
	0.6 - 0.69	-3.0	
	0.7 - 0.79	-3.5	
	0.8 - 0.89	-4.0	
	0.9 - 0.99	-4.5	
	≥ 1.0	-5.0	
Total CSF score (sum of scores)			

References

1. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
2. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
3. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr 1990;29:254-5, 258-61.
4. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
5. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
6. Oostenbrink R, Moons KGM, Twijnstra MJ, Grobbee DE, Moll HA. Children with meningeal signs: indication for therapeutic interventions. submitted for publication.
7. Knottnerus JA. Prediction rules: statistical reproducibility and clinical similarity. Med Decis Making 1992;12:286-287.
8. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
9. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-9.
10. Oostenbrink R, Theunissen CCW, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Signs of meningeal irritation at the emergency department; how often bacterial meningitis? Ped Emerg Care, in preparation 2001.
11. Maxson S, Jacobs RF. Viral meningitis. Tips to rapidly diagnose treatable causes. Postgrad Med 1993;93:153-6, 159-60, 163-6.
12. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
13. Moons KGM, Stijnen T, Michel BC, Buller HR, Grobbee DE, Habbema JDF. Treatment thresholds in diagnostic test evaluation: an alternative approach to the comparison of areas under the receiver operating characteristic curve. Med Decis Making 1997;17:447-454.
14. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature. XXII: How to use articles about clinical decision rules. JAMA 2000;284:79-84.
15. Randolph AG, Guyatt GH, Calvin JE, Doig G, Richardson WS. Understanding articles describing clinical prediction tools. Crit Care Med 1998;26:1603-1612.
16. Adams WG, Deaver KA, L. CS, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood haemophilus influenzae type b (Hib) disease in the Hib vaccine era. JAMA 1993;269:221-226.
17. Conyn-van Spaendonck MA, Veldhuijzen IK, Suijkerbuijk AW, Hirasing RA. Significant decline of the number of invasive Haemophilus influenzae infections in the first 4 years after introduction of vaccination against H. influenzae type B in children [in Dutch, English summary]. Nederlands Tijdschrift voor Geneeskunde 2000;144(22):1069-73.
18. Poses RM, Cebul RD, Collins IM, Fager SS. The importance of disease prevalence in transporting clinical prediction rules. Ann Int Med 1986;105:586-591.
19. Wigton RS, Connor JL, Centor RM. Transportability of a decision rule for the diagnosis of streptococcal pharyngitis. Arch Int Med 1986;146:81-83.
20. Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
21. van Steensel-Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, Dekker A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics II. [in Dutch, English summary]. Tijdschr Kindergeneesk 1996;64:99-104.

Prognostic aspects of bacterial meningitis

Sequelae after bacterial meningitis

3.1

Rianne Oostenbrink, Mariëlle Maas, Karel GM Moons, Henriëtte A Moll
Submitted for publication

Abstract

In this study we evaluated retrospectively the neurological outcome of bacterial meningitis in children initially presenting with meningeal signs.

Data were collected from 103 patients, aged from one month up to 15 years, who initially visited the emergency department of a paediatric hospital in the Netherlands with meningeal signs and in whom bacterial meningitis had been diagnosed.

We found a 2% mortality in children with bacterial meningitis, and a 13% morbidity among survivors: 7% hearing impairment and 6% neurological sequelae. The worst prognosis was associated with *S. pneumoniae* and the presence of acute focal neurological symptoms. A substantial decrease in meningitis was found after the introduction of the *H. influenzae* vaccination, but the relative occurrence of sequelae remained the same. *N. meningitis* was the dominant pathogen of meningitis.

An adverse outcome was observed in 15% of children with bacterial meningitis, mainly depending on the pathogen type. Due to different pathogen occurrence frequencies, however, pathogens contributed in similar proportions to the absolute numbers of sequelae.

Introduction

Bacterial meningitis has a large impact on health care in childhood, since it still causes substantial mortality and morbidity, in spite of adequate treatment. [1] Similar to other countries [2], inclusion of the vaccination for *H. Influenzae* (HIB) in the standard vaccination programme in the Netherlands since July 1993, has lead to a substantial decrease of the incidence of meningitis. [3,4] Its effect on the mortality and morbidity after childhood bacterial meningitis, however, remains to be evaluated. Alterations of the pathogen spectrum may influence the prognosis of bacterial meningitis, since the pathogen is known to be related to the occurrence frequency of sequelae. [1,5]

In this study we evaluated the frequency, type and combinations of sequelae after bacterial meningitis in children presenting with meningeal signs in relation to pathogen type and the introduction of HIB vaccination.

Methods

This study was executed as part of large study on the diagnosis and prognosis of 367 children, aged one month to 15 years, visiting the paediatric emergency department of the Sophia Children's Hospital between 1988 - 1998 with meningeal signs. [6,7] In this study we evaluated 103 cases of bacterial meningitis. We collected clinical characteristics and results from laboratory tests at presentation, during hospitalisation and from follow-up visits in the first year after diagnosis. Children with severe pre-existent neurological diseases were excluded. Bacterial meningitis was defined as bacterial growth in cerebrospinal fluid (CSF) or blood with > 5 leukocytes/µl in CSF. [5,7] If antibiotics were used before performing a lumbar puncture, patients with an increased CSF leukocyte count and a negative bacterial culture were considered to have pre-treated bacterial meningitis if they were subsequently hospitalised and treated with antibiotics for at least seven days. [7,8] Presence or absence of neurological sequelae was determined based on neurological examination as documented in the patient record during follow-up visits. Hearing function was assessed during follow-up using conventional behavioural pure tone or brainstem electric response audiometry. The following sequelae of bacterial meningitis persistent after 6 months after diagnosis were distinguished: *1) Hearing loss:* unilateral or bilateral retrocochlar or cochlear hearing loss ≥ 30 decibels (severe loss: bilateral loss ≥ 70 decibels), 2) *Locomotor deficits* assessed by neurologist, 3) *Abducens or oculomotorius nerve palsy*, 4) *Epilepsy:* indication for anti-epileptic drugs after a first seizure or repeated seizures without fever after hospitalisation and 5) *Retardation:* delay >6 months in psychomotor and mental development. [1]

Frequencies of sequelae and death after bacterial meningitis were computed with 95% confidence intervals (95% CI). In order to evaluate the effect of vaccination to *H. influenzae*, an analysis was performed for the pathogen types separately, and on the periods from 1988 up to June 1993 and from July 1993 up to 1998, separately.

Results

Results were based on 103 children with bacterial meningitis: 51 boys (50%), median age 2.5 years (interquartile range 1.0 - 5.1 years). *N. meningitidis* (NM) was identified in 51 (50%; 95% CI: 40 - 59%), *S. pneumoniae* (SP) and *H. influenzae* (HIB) in 10 (10%; 95% CI: 5 - 17%) and 34 (33%; 95% CI: 24 - 42%), respectively. Other pathogen types (n = 8, 8%; 95% CI: 3 - 15%) included six pre-treated cases of bacterial meningitis, one with *Streptococcus sanguis* and one with *Streptococcus* group B. Acute focal neurological symptoms (abducens nerve palsy, limb paresis, pathologic Babinsky sign, fixed head position) were present in 12 children (12%), and seizures in 14 (14%): six before hospital admission only, six upon presentation and in two occurring within the first 24 hours in hospital. The median duration of hospitalisation was 12 days (interquartile range 10 - 15 days) and 46

children (45%) were admitted to the intensive care unit. The empirical antibiotic treatment consisted of a third generation cephalosporin in all patients (either or not combined with amoxicillin), except for four patients receiving amoxicillin with chloramphenicol. Dexamethason treatment was not given to any patient. Two children died during the acute phase of bacterial meningitis (one from acute neurological complications, one from multi-organ failure). The median duration of follow-up of survivors as available from the patient records was 6.7 months (interquartile range 3.1 - 12.2 months). In 13 patients persistent neurological sequelae were assessed during follow-up. Sequelae included deafness in one child (1%), mild hearing loss in six (6%), mental retardation in five (5%), persistent palsy of the abducens nerve in three (3%), locomotor deficits in three (3%) and epilepsy in one (1%). A description of the type of sequelae in individual patients is presented in Table 1.

Table 1 Frequency of neurological and audiological sequelae among survivors of bacterial meningitis (n=101)

Description of sequelae	Number of patients (%; 95% CI)
Deafness	1 (1%; 0 - 5%)
Mild hearing loss	5 (5%; 2 - 11%)
Mild mental retardation	2 (2%; 0 - 7%)
Palsy of nervus abducens	2 (2%; 0 - 7%)
Mild hearing loss and mild mental retardation	1 (1%; 0 - 5%)
Severe mental retardation and locomotor disorders with either epilepsy or palsy of nervus abducens	2 (2%; 0 - 7%)

In Table 2 the occurrence of mortality and morbidity of bacterial meningitis is presented for the pathogens separately. *S. pneumoniae* was related to the highest mortality and morbidity. In the period from January 1988 up to June 1993, 78 cases of bacterial meningitis occurred (NM: 31; SP: 7; HIB: 32; other: 8), from June 1993 up to December 1998 only 25 cases (NM: 20; SP: 3, HIB: 2). The frequencies of sequelae for these periods were 13% (95 CI: 6 - 22%) and 20% (95% CI: 7 - 41%), respectively. Although *N. meningitidis* had the lowest mortality and morbidity rate, it substantially contributed to the total morbidity and mortality in absolute numbers of patients, due to its frequent occurrence.

Table 2 Mortality and morbidity after bacterial meningitis related to the pathogen.

Pathogen	Mortality N (%)[§¶]	Hearing loss N (%)[‡]	Neurological sequelae; N (%)[‡]	Total sequelae N (%; 95% CI)[‡]
N. meningitidis (n = 51)	1 (2%)	1 (2%)	2 (4%)	3 (6%; 1 – 17%)
S. pneumoniae (n = 10)	1 (10%)	2 (22%)	3 (33%)	5 (56%; 21–86%)
H. influenzae (n = 34)	0	3 (9%)	1 (3%)	4 (12%; 3–28%)
Other (n = 8)	0	1 (11%)	1 (11%)	1 (11%; 0–48%)
All (n = 103)	2 (2%; 0 – 7%)	7 (7%; 3 – 14%)	6 (6%; 2 – 13%)	13 (13%; 6 – 19%)

[§]percentage among all

[‡]percentage among survivors

[¶]death causes: acute neurological complications and multi-organ failure.

In children with focal neurological symptoms or seizures in the acute phase (n = 26), four had neurological sequelae in follow-up and four hearing loss (n = 8; 31%; 95% CI: 14 - 51%). No differences in frequencies of sequelae were found between those with acute focal neurological symptoms and those with seizures. In children without focal neurological symptoms or seizures in the acute phase (n = 77) two children died during hospitalisation (2.6%; 95% CI: 0 - 9%), two had neurological sequelae in follow-up and three hearing loss (n = 5; 7%; 95% CI: 2 - 15%).

The median duration of complaints before the presentation was 1.0 day (interquartile range: 0.5 - 3.0) in patients with neurological sequelae or hearing loss and 1.0 days (interquartile range: 1.0 and 3.0) in those without. Duration of fever before presentation was also similar in patients with and without sequelae: 1.5 days (interquartile range: 0.5 - 4.0) and 1.5 (interquartile range: 1.0 - 3.0), respectively.

Discussion

In children with bacterial meningitis who initially presented themselves with meningeal signs, we found 2% mortality and 13% sequelae among survivors, including in 7% hearing impairment and 6% neurological sequelae. Neurological sequelae often occurred combined with each other, whereas hearing impairment was mainly present as isolated sequelae. Patients with focal neurological symptoms or seizures in the acute phase tended to have sequelae in follow-up more often than those without. *S. pneumoniae* was related to the highest occurrence frequency of sequelae. In absolute numbers, however, *N. meningitidis* contributed to a similar number of sequelae. Therefore, follow-up strategies of children with bacterial meningitis should include all cases, and not children with known risk factors only.

A substantial decrease in meningitis was found in our hospital after the introduction of the HIB-vaccination (25 versus 78 patients, both in a 5.5 years period). The relative frequency of sequelae, however, remained similar. Since in this study patients were treated similarly, we think that the incidence of sequelae is not influenced by changes in treatment over time.

Although this study is based on small numbers, most findings in this study agree with previous reports. [1,9-12] We could not confirm an association between the duration of complaints or fever and mortality and morbidity. In literature controversial results are present on this association. [10,13,14] The mortality rate in this study is somewhat lower compared to others. This may result from our inclusion criteria, i.e. patients initially presenting themselves with meningeal signs. Subsequently, other presentations such as the predominance of seizures or coma, which are known to be related to a worse outcome, are not included. [5,10] The overall occurrence of hearing impairment in our study is also lower compared to others. This may be the effect of the decrease in HIB-meningitis,

which is relatively more frequently related to audiological than neurological sequelae. [1] Although neurological sequelae are known to occur concomitantly in patients after bacterial meningitis, most reports on occurrence of sequelae after meningitis report occurrence rates per type of sequelae. [1,15,16] Quantification of outcome after meningitis in terms of health related quality-of-life, as is necessary in cost-effectiveness analyses, requires specific descriptions of combinations of sequelae and their frequency of occurrence in patients. Although based on small numbers, the results of Table 1 may be of value for this aim. In this study, minor sequelae such as behaviour problems and mild learning or attention disorders were not addressed. Information on these mild sequelae is much less precisely documented routinely in the patients' record, in contrast to the neurological examination and hearing test results. As we used retrospectively collected data, these mild sequelae are more likely to be missed.

In conclusion, we found a 2% mortality rate in children with bacterial meningitis, initially presenting with meningeal signs, and a 13% morbidity rate among survivors. The worst prognosis seems to be associated with *S. Pneumoniae* and the presence of acute focal neurological symptoms. A substantial decrease in meningitis was found after the HIB-vaccination, but the relative occurrence of sequelae remained the same. *N. Meningitis* is the dominant pathogen since the introduction of HIB-vaccination and substantially contributed to the absolute number of patients with sequelae. Therefore, follow-up strategies of children with bacterial meningitis should include all cases, and not children with known risk factors only.

References

1. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993;12:389-94.
2. Adams WG, Deaver KA, L. CS, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood haemophilus influenzae type b (Hib) disease in the Hib vaccine era. JAMA 1993;269:221-226.
3. van Alphen L, Spanjaard L, van de Ende A, Dankert J. Absence of Haemophilus influenzae type b meningitis in the Netherlands in twice vaccinated children [in Dutch, English summary]. Ned Tijdschr Geneeskd 1995;139:880-884.
4. Conyn-van Spaendonck MA, Veldhuijzen IK, Suijkerbuijk AW, Hirasing RA. Significant decline of the number of invasive Haemophilus influenzae infections in the first 4 years after introduction of vaccination against H. influenzae type B in children [in Dutch, English summary]. Nederlands Tijdschrift voor Geneeskunde 2000;144(22):1069-73.
5. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
6. Oostenbrink R, Theunissen CCW, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Signs of meningeal irritation at the emergency department; how often bacterial meningitis? Ped Emerg Care, in preparation 2001.
7. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
8. Rodewald LE, Woodin KA, Szilagyi PG, Arvan DA, Raubertas RF, Powell KR. Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatr 1991;119:363-9.
9. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990;323:1651-7.

10. Kaplan SL. Clinical presentations, diagnosis, and prognostic factors of bacterial meningitis. Infectious Disease Clinics of North America 1999;13:579-593.
11. Grimwood K, Nolan TM, Bond L, Anderson VA, Catroppa C, Keir EH. Risk factors for adverse outcomes of bacterial meningitis. J Paediatr Child Health 1996;32:457-462.
12. Valmari P, Makela M, Kataja M, Peltola H. Multivariate prognostication in bacterial meningitis of childhood. Scand J Infect Dis 1987;19:29-34.
13. Kilpi T, Anttila M, Kallio MJ, Peltola H. Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. Pediatr Infect Dis J 1993;12:184-8.
14. Kaaresen PI, Flaegstad T. Prognostic factors in childhood bacterial meningitis. Acta Paediatr 1995;84:873-8.
15. Kornelisse RF, Westerbeek CM, Spoor AB, van der Heijde B, Spanjaard L, Neijens HJ, et al. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis 1995;21:1390-7.
16. Sell SH. Long term sequelae of bacterial meningitis in children. Pediatr Infect Dis 1983;2:90-3.

Early prediction of neurological sequelae after bacterial meningitis

3.2

Rianne Oostenbrink, Karel GM Moons, Gerarda Derksen-Lubsen, Diederick E Grobbee, Henriëtte A Moll

Submitted for publication

Abstract

In this study, we determined independent predictors of the occurrence of permanent neurological sequelae or death after the onset of childhood bacterial meningitis.

Data were used from a large study on children (1 month up to 15 years), initially presenting themselves with meningeal irritation. A nested case-control study was performed on children with (n = 23) and without (n = 70) permanent neurological sequelae (hearing impairment, locomotor dysfunction, mental retardation or epilepsy) or death after bacterial meningitis. Predictors obtained from clinical evaluation and laboratory tests at presentation and during the clinical course were identified by multivariate logistic regression analysis and Receiver Operating Characteristic (ROC) curve analyses.

The study population comprised 23 cases and 70 controls: 52% boys, median age 2.8 years. Independent predictors for an adverse outcome after bacterial meningitis were male gender, atypical convulsions in history, low body temperature at admission and the pathogen *S. pneumoniae*. The area under the ROC-curve of this rule was 0.87 (95% CI: 0.78 - 0.96), which was not improved by adding other characteristics. A scoring formula including these independent predictors could classify patients into categories with increased risk for an adverse outcome.

Permanent neurological sequelae or death after bacterial meningitis in childhood can be predicted based on clinical characteristics available early in the clinical course. The pathogen type is the main prognostic determinant of childhood bacterial meningitis.

Introduction

In spite of optimal intensive care facilities and antibiotic treatment, childhood bacterial meningitis still causes mortality and persistent neurological sequelae in about 5% and 10 - 20%, respectively. [1] Early prediction of an adverse outcome may help to determine which children require more intensive or longer follow-up. Furthermore, early prediction may provide the physician with a rationale for parental counselling about the prognosis of their child in an early phase of the disease. Prognostic outcome of individual patients can be estimated by the use of prediction rules that calculate the probability of occurrence of an adverse outcome as a function of (various) prognostic factors. [2] Although many studies have been performed on prognostic characteristics of children with bacterial meningitis [3-14], their conclusions are different and sometimes contradicting. In addition, only few studies evaluated the independent value of predictors using multivariate analysis. Finally, most studies on prognosis include a substantial number of patients with meningitis caused by *Haemophilus influenzae* (HIB), which pathogen has nearly been eradicated since the introduction of routine immunisation of infants. [15]

The *aim of this study* was to determine independent predictors of neurological sequelae or death after childhood bacterial meningitis. With these predictors a prediction rule was derived for early classification of increased risk for neurological sequelae or death.

Methods

Patients

The present study was executed as part of a large study on the diagnosis and prognosis of bacterial meningitis in children (aged from 1 month till 15 years) presenting with meningeal signs, who initially visited the emergency department of the Sophia Children's Hospital in Rotterdam or Juliana Children's Hospital in The Hague, The Netherlands, between 1988 and 1998. [16] From this population a cohort of all children who suffered from bacterial meningitis, was selected (n = 170) , which formed the basis for the present nested case-control study. Bacterial meningitis was defined as presence of leukocytes > 5 cells/µl in cerebrospinal fluid (CSF) after a non-traumatic puncture, with a positive bacterial culture of CSF or blood. [16,17] If antibiotics were used before performing a lumbar puncture, patients with an increased CSF leukocyte count and a negative bacterial culture were considered to have (pre-treated) bacterial meningitis, if they were subsequently hospitalised and treated with antibiotics for at least 7 days. [18] Meningitis cases caused by *H. influenzae* and patients with pre-existent neurological diseases were excluded from the study.

For the present study, cases were defined as patients with neurological sequelae persisting for more than 6 months or who died after bacterial meningitis. The

following neurological sequelae were distinguished: 1) deafness (bilateral hearing loss > 70 dB), 2) mild hearing loss (hearing loss unilateral or bilateral > 30 dB), 3) severe mental retardation with locomotor deficits 4) epilepsy (repeated seizures without fever or indication for anti-epileptic treatment after first afebrile seizure), 5) mild locomotor deficits as documented by the neurologist, 6) mild mental retardation and 7) a combination of these latter three. Patients were classified to one of the seven described sequelae, 'death' or 'complete health' by two independent paediatricians, using the available information from the patient record, radiological imaging and functional tests (EEG, hearing tests). Discordant classifications by the two paediatricians were judged by an independent third, in order to reach a final consensus on the prognostic outcome classification. Within the total cohort of 170 patients, 23 cases with neurological sequelae or death occurred. Seventy healthy recoveries (controls) were sampled from the remainder of the cohort (case control ratio 1:3; sample fraction 0.48).

Potential predictors

By review of the patient record and the computer documented hospital information system three categories of potential prognostic factors were obtained: 1) data from patient history and physical examination obtained at admission, such as demographic data and presenting signs and symptoms; 2) data from laboratory tests of CSF, blood, stool and urine specimens available at admission and 3) clinical findings and laboratory data obtained during the hospital stay. In order to reduce the amount of potential predictors to be evaluated in this study, we only selected those that were previously reported to be prognostic determinants in childhood bacterial meningitis in the literature. [19] Since we were interested in prognostic predictors of childhood bacterial meningitis after introduction of the HIB only, studies among adults and on HIB-meningitis were excluded from this literature search.

Data analyses

The association between the presence and absence of neurological sequelae or death and each potential prognostic determinant was quantified using univariate logistic regression analyses. Subsequently, predictors that were univariately associated with the outcome (odds ratio with a p-value < 0.15) were included in a multivariate logistic regression model to evaluate their independent value in the prediction of outcome. [20] The multivariate analyses followed the order in which data are obtained in practice. [21] Model reduction was performed by excluding predictors from the model with p-values > 0.10, such that a reduced model was derived, including independent predictors of neurological sequelae or death. Reliability (goodness of fit) of the all models was estimated using the Hosmer & Lemeshow test [22], and their prognostic ability to discriminate between patients with and without adverse outcome using the area under the Receiver Operation Characteristic curve (ROC-area). Difference in prognostic ability between models was estimated by difference in ROC-area with 95% confidence intervals (95% CI), taking into account the correlation between models as they were based on the same cases. [23,24]

To reduce bias and increase statistical efficiency and to account for uncertainties in imputed data, multiple imputation was used for missing values in the data. [25,26] To estimate the prognostic ability of the final model in future but similar patients, the model was validated by random bootstrapping techniques. [20,27] The final model was then transformed into a scoring rule by dividing the regression coefficients of the included predictors by the smallest one and rounding them subsequently to the nearest integer. A total risk score was computed for each individual patient by assigning points for each predictor present. Next, patients were classified according to their risk score and the absolute numbers of mortality and morbidity among categories of risk scores were evaluated.

Results

The general characteristics of all 93 children presenting with meningeal signs are presented in Table 1. The number of cases with neurological sequelae or death in the total cohort (n = 170) was 23: a prevalence of 14% (95% CI: 8 - 19%). Of the 23 cases, two died (8.7%), six were deaf (26.1%), eight children had mild hearing loss (34.7%), four had severe retardation (17.4%) and three had epilepsy, mild locomotor deficits or mild mental retardation (13.0%).

Table 1 General characteristics (n = 93)

Characteristic	Number (%) *
Age (years) †	2.8 (0.9 - 5.8)
Male gender	48 (52%)
Admission to intensive care unit	50 (54%)
Pathogen type	
S. pneumoniae	16 (17%)
N. meningitidis	64 (69%)
Other ‡	13 (14%)
Duration follow-up (years) †	0.6 (0.02 - 3.3)
Outcome	
Complete recovery	70
Deafness	6
Mild hearing loss	8
Epilepsy, mild locomotor deficits and/or mild mental retardation	3
Severe mental retardation and tetraplegia	4
Dead	2

*Values represent absolute numbers with % between parentheses; otherwise if stated.
†Median (range)
‡Other include group B *Streptococcus* (n = 2), *Salmonella* (n = 1), *Streptococcus sanguis* (n = 1) and pre-treated bacterial meningitis (n = 9)

Table 2 presents the results of our literature search from 1984 till 1999 on potential prognostic determinants of childhood bacterial meningitis predictors (excluding HIB-meningitis). Not all prognostic determinants were included in all studies, and the results were partially contradicting. The studies differed in their selection of the study population (defined by e.g. age, pathogen type or disease severity) and in the definition of the final outcome.

Table 2 Overview of prognostic predictors after childhood bacterial meningitis from literature (1984 - 1999).

Characteristic	Associated with adverse outcome	Not associated with adverse outcome	Independent prognostic predictors in present study
Male gender	3, 4	5, 6, 7, 8	Yes
Young age	5, 9*. 10	3, 6, 7, 8, 13	No
Seizures before presentation	5, 6, 8, 9*	4, 7, 10 ,14	Yes
Longer duration of complaints	3, 5, 6, 9	7, 8, 11, 13	No
Low body temperature	6, 14	4, 9*	Yes
Coma/disturbed consciousness	7, 9*, 13	4, 5, 6, 10	No
Shock	7, 9, 10		No
Focal neurological deficits	3, 5, 9	8, 13	No
Petechiae	3	9*	No
Meningeal signs/irritability	3, 4	7	No
Absence of meningeal signs	9		No
Decreased serum sodium	5	6	No
Low peripheral blood WBC		4	No
High peripheral blood WBC	3, 13		No
Low blood thrombocyte count	3	6	No
Low CSF glucose	3, 7, 8	5, 6, 10, 13	No
High CSF protein		4, 6, 7, 8, 13	No
Low CSF WBC	3, 6, 7	4, 5, 8, 10, 13	No
Low glucose ratio CSF/blood		7, 13	No
Pathogen type	4	3, 5, 8	Yes
Fever pattern in clinical course	14	5, 12	No
Duration of meningeal signs	14		Yes
Seizures > 72 hrs	5		No

WBC: white blood cell count; CSF: cerebrospinal fluid
Numbers refer to studies as numbered in the reference list.
Studies concern all pathogens (except for ref. 7 and 13: *S. pneumoniae* cases only), on children from one month up to fifteen years (except for ref. 7: < 18 yrs; ref. 5 and 14: three months up to fifteen yrs; ref 4 and 11: children without age specification), with outcome including death and neurological sequelae (except for ref. 7, 9 (if marked with *), 8, 12 and 13: sequelae only; ref. 4: hearing loss only).

In Table 3 the univariate significant correlates with neurological sequelae or death as found in this present study are presented ($p < 0.15$). Significant predictors from patient history were gender and the occurrence of atypical convulsions before admission (i.e. duration > 15 minutes, non-generalised jerks, incomplete recovery, or multiple convulsions within 24 hours). If age was dichotomised, the odds ratio for an adverse outcome in children younger than one year was 2.5 ($p = 0.09$) with reference to those older than one year. Duration of the disease or fever duration before admission were not related. At physical examination, significant correlates were body temperature, the presence of petechiae and focal neurological signs. Disturbed consciousness (reaction on pain only, or no reaction) was not related. From laboratory tests available at admission, only the protein concentration in cerebrospinal fluid (CSF) was associated with the outcome. Blood leukocyte or thrombocyte count, the CSF total polymorphonuclear cell count (PMN) or CSF/blood glucose ratio were not correlated. Significant correlates among data that come available after admission were pathogen type and insufficient respiration during clinical course,

convulsions two days after admission, meningeal signs still present after three days of admission and time to the first afebrile day. Repeated laboratory tests, such as leukocyte count or absolute polymorphonuclear leukocyte count in blood or serum CRP concentration at the third or fifth day were not correlated with the outcome.

Table 3 Univariate correlates ($p < 0.15$) with presence or absence of neurological sequelae or death

Variable	Number of subjects*	Sequelae present (n = 23)	Sequelae absent (n = 70)	Odds ratio	p-value
Patient history					
Male gender	93	74%	44%	3.5	0.02
Age (years) †	93	3.5 (4.2)	4.3 (3.9)	0.9	0.40
Atypical convulsions	93	30%	7%	5.7	0.01
Physical examination					
Body temperature †	92	38.2 (1.4)	39.2 (1.0)	0.5	0.01
Petechiae/ecchymoses	93	26%	49%	0.4	0.05
Focal neurological signs	93	35%	14%	3.2	0.03
Initial laboratory tests					
CSF protein (g/l) †	81	2.5 (1.6)	1.9 (1.7)	1.2	0.03
Pathogen	93				0.01
S. pneumoniae		43%	9%	9.1	
N. meningitidis		48%	76%	1.1	
Other		9%	15%	RC	
Clinical course					
Mechanical ventilation	93	35%	4%	11.9	0.01
Anti-epileptica > 2 days	91	35%	1%	36.8	0.01
Meningeal signs > 3 days	80	30%	9%	4.7	0.01
Time to first afebrile day (days)†	74	2.6 (1.9)	3.3 (1.9)	0.8	0.14

CSF: cerebrospinal fluid; RC: reference category; values represent percentages, otherwise if stated

* number of subjects for whom the variable was obtained

† mean and standard deviation between parentheses

After stepwise multivariate analysis of univariate correlates according to the sequence they are obtained clinical practice, the independent predictors for an adverse outcome were male gender, presence of atypical convulsions in history, a lower body temperature at physical examination and the pathogen *S. pneumoniae*. The odds ratios and regression coefficients of these independent predictors after bootstrapping are presented in Table 4. Pathogen type was categorised in three groups (i.e. *S. pneumoniae* (SP), *N. meningitidis* (NM) and others) and was included in the model as two indicator variables with the category 'other' as the reference. The ROC-area of this model was 0.87 (95% CI: 0.78 - 0.96).

Table 4 Independent predictors of neurological sequelae or death after bacterial meningitis

	Odds ratio (95% CI) *	Regression coefficient *†	Contribution to score ‡
Male gender	4.4 (0.9 - 20.7)	1.48	2
Atypical convulsions	9.7 (1.0 - 98.5)	2.27	3
Body temperature (°C)§	0.5 (0.2 - 0.9)	-0.75	-1
Pathogen SP	22.6 (1.3 - 393.8)	3.12	4
NM	4.4 (0.5 - 41.7)	1.48	2
ROC-area (95% CI)	0.87 (0.78 - 0.96)		

SP: *Streptococcus pneumoniae*, NM: *Neisseria meningitidis*

* Odds ratios and regression coefficients adjusted for overoptimism by bootstrapping

† Regression coefficient = ln(OR)

‡ Risk score computed by dividing the regression coefficient by the smallest one (i.e. body temperature; 0.75) and rounded to nearest integer.

§ Odds ratio per unit of °C (multiplicative), in total score –1 point is 'added' to the total score for each degree above 35.0 °C.

Based on the regression coefficients (third column in Table 4), a risk score was derived (fourth column in Table 4). By assigning points for each variable present, a total score was computed for each individual patient using the following formula:

$$\text{Score} = 4 + 2 \times \text{male gender} + 3 \times \text{convulsions} - 1 \times (\text{body temperature} - 35) + 4 \times \text{SP} + 2 \times \text{NM}$$

In our population, the score ranged from 0.5 to 11.5 and the ROC-area of this score was 0.87 (95% CI: 0.78 - 0.96). To obtain an estimate of the absolute incidence of sequelae across categories of the score in the total cohort, all control subjects were given a weight which was the inverse of the sampling fraction (weight = 2.1). [28] Hence, a new dataset was created which included all 23 cases and the weighted control group resembling the entire cohort (n = 170). Table 5 shows the incidence of neurological sequelae or death for the cohort and the number of subjects across selected categories of the score. Reading the table in a horizontal way, one can derive the predictive value for an adverse outcome per score category. For example, in none of the children with a score < 2.5 (15% of all subjects), neurological sequelae or death occurred (predictive value = 0%). In those with a score > 5.5, sequelae or death occurred in 44% (15/34). The sensitivity and specificity at different score thresholds can be derived by reading Table 5 vertically. E.g. a threshold score < 2.5 predicted 17% of all healthy recoveries (i.e. specificity of 17%), without missing one case with sequelae or death (i.e. sensitivity of 100%). Using a threshold score > 5.5, the sensitivity was 65% with 13% false positives (specificity 87%).

Table 5 Number of patients (%) with and without neurological sequelae or death in the original cohort across categories of the risk score.

Risk score	N*	Patients with sequelae	Healthy recoveries
< 2.5	25 (15%)	0	25 (17%)
2.5 to 4.5	78 (46%)	2 (9%)	76 (52%)
5.0 to 5.5	33 (19%)	6 (26%)	27 (18%)
> 5.5	34 (20%)	15 (65%)	19 (13%)
Total	170 (100%)	23 (100%)	147 (100%)

*N = number of subjects per score category

Table 6 presents the frequency of the type of sequelae among categories of the risk score. The most severe sequelae and death occurred in patients with the highest predicted risk group. The rule, however, could not clearly differentiate between the different types of sequelae.

Table 6 Risk stratification per type of sequelae

Score	Healthy*	Deaf*	MHL*	Mild deficits*	Severe retardation*	Dead*
< 2.5	25					
2.5 to 4.5	76	2				
5.0 to 5.5	27	1	4	1		
> 5.5	19	3	4	2	4	2
Total	147	6	8	3	4	2

MHL: mild hearing loss; Mild deficits: epilepsy, mild mental retardation or locomotor deficits

*Values represent absolute numbers of patients per risk score category.

Discussion

We identified independent predictors of death or neurological sequelae after bacterial meningitis in childhood. A prediction rule based on male gender, atypical convulsions in history, body temperature at admission and the pathogen type could classify patients with an increased risk of sequelae or death. Early assessment of the prognosis by this rule may help the physician in parental counselling and defining the duration of follow-up in case of a predicted fair prognosis. In addition, the prediction rule allows for classification of patients with a similar risk of sequelae, as a function of various prognostic factors. For instance, a male subject without convulsions, with a body temperature of 39 °C and *N. meningitidis* meningitis receives a score of 5 (= 5 + 2 + 0 + -4 + 2; Table 4), corresponding with a 18% risk for sequelae (6/33; Table 5), whereas a similar patient, but with convulsions and *S. pneumoniae* meningitis receives a score of 10 (= 5 + 2 + 3 + -4 + 4), corresponding with a higher risk of 44% (15/33). Unfortunately, the type of sequelae could not be predicted by the rule. This probably results from the fact that the model was derived to predict a dichotomous outcome, including all types of sequelae and death together. Model derivation to predict an ordinal outcome, i.e. for different sequelae types separately, may lead to a better discrimination of types of sequelae. [29] Due to the limited number of patients with sequelae, however, this was not possible in the present study.

The outcome of our prediction model combined neurological sequelae and death such that specific determinants of sequelae after survival of bacterial meningitis may not have been identified in this study. We therefore performed a sub-analysis on survivors after bacterial meningitis only. This analysis yielded the same predictors, although determinants available later in the clinical course, such as the duration of meningeal signs for three days or more (OR = 4.1, p-value = 0.09), seemed to be of additional importance. This modified prediction rule, however, neither improved the discrimination of patients with and without

sequelae (ROC-area = 0.87), nor the prediction of the type of sequelae, compared to the model (Table 4) derived on the outcome including death.

We recognise that the classification of patients with increased risk of death and neurological sequelae by the rule is not optimal, since in the highest risk category complete recovery still occurs in 56%. Differentiating between an 18% and 44% risk on sequelae may be of limited value in clinical practice. In a few patients, however, the risk of sequelae can be ruled out by the prediction rule. Although all children with bacterial meningitis require careful follow-up by hearing tests and neurological examinations, in these children with a very low risk on sequelae, follow-up can be shorter if initial hearing tests or neurological examination are normal.

Validation of the model by bootstrapping techniques demonstrated that the prediction rule is robust. Before implementation of the model in clinical practice, however, the actual performance of this scoring rule should be proven by using this rule in a new group of children with bacterial meningitis. [27,30] A future study is planned to validate this scoring rule in similar children with bacterial meningitis, initially presenting with meningeal signs.

We observed substantial differences in the results of previous studies on prognostic characteristics of children with bacterial meningitis (Table 2). This may result from the differences in study population (defined by e.g. age, pathogen type or disease severity), from the potential predictors included in the analysis, and from different statistical methods (uni- or multivariate, or stratified analysis). Since the number of patients with sequelae in the study population is often limited, the power of a particular study to select important predictors is rather limited. In order to overcome this problem in our study, we combined the information available from the literature with our study results. As shown in the final column of Table 2, our results concord with previous studies. The fact that we did not find an association between age and outcome, in contrast to others [2,5,9,10], may be the result of the small age range in our study population (50% younger than 2.8 years). Another explanation may be that clinical signs correlated with age are included in our model, and therefore age itself does not contribute additional to these variables. Similar to previous reports [14], we did not find independent associations of repeated laboratory tests, such as blood leukocyte count or serum CRP at 3 or 5 days after admission with the prognosis. Although in practice these laboratory tests are repeatedly performed during the convalescent period, they do not have prognostic value. In this study we identified the pathogen type as one of the most important predictors for the prognosis after bacterial meningitis in childhood. The vaccination of HIB and subsequent decrease of meningitis caused by this pathogen, will lead to a relatively higher proportion of *S. pneumoniae* and thus to a subsequent higher risk of mortality and morbidity after meningitis.

To appreciate the results of this study, some topics need to be further discussed. First, in this study, cases of HIB were excluded because of the decreasing

importance of this pathogen after the introduction or routine vaccination in infants. Most previous studies on prognosis included cases of HIB. Since the various clinical signs and symptoms may be related to a particular pathogen type, other studies with mixed pathogens may have revealed other associations. Second, this study was based on patients with bacterial meningitis who initially presented with meningeal signs. Cases of bacterial meningitis with a predominance of coma or convulsions, which may be associated with higher frequencies of morbidity and mortality [6-8], were not included. This inclusion criterion may explain the relative low base-line risk of sequelae and mortality (14%) as found in this study. Third, in this study we did not include sequelae such as amputations and scarring, which may occur in patients with meningococcal septicaemia with concomitant meningitis. These patients, however, present themselves with a predominance of septicaemia and petechiae, but not with meningeal signs. In addition, these sequelae have a different cause and therefore are related to other prognostic factors. [31] Fourth, the present study followed a nested case-control design for efficiency reasons. Hence, the baseline risk of a neurological sequelae or death (i.e. the intercept of the model) could not be directly estimated in contrast to the odds ratios (regression coefficients) of the predictors which are correct estimates. [22] Therefore, we reported in Table 4 a transformed scoring rule which does not use the intercept (as it is equal for each subject anyway), but still enables classification of subjects according to their absolute risk of sequelae, based on differences in their risk profile (risk score). Moreover, the scoring rule is easier to apply in practice. The number of points assigned to each predictor, if present, indicates its relative importance on the prognosis. Finally, minor sequelae, such as behaviour problems and mild learning or attention disorders were not included in the outcome in this study. This is because information about mild or subjective sequelae is much less precisely documented routinely in the patient record, in contrast to the neurological examination and hearing test results. The children in our study (median age = 2.8 years) are much younger than school-going age and therefore small deficits may not have been detected till the child started at school. [5]

In conclusion, permanent neurological sequelae or death after bacterial meningitis in childhood can be predicted using clinical characteristics available early in the clinical course. The pathogen type is the most important prognostic determinant of bacterial meningitis. Additional independent predictors of an adverse outcome are male gender, atypical convulsion in history, and body temperature at physical examination. Clinical characteristics or laboratory tests from the reconvalescent period do not improve the prediction of sequelae.

References

1. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993;12:389-94.
2. Aronin SI, Peduzzi P, Quagliarello J. Community Acquired Bacterial Meningitis: Risk Stratification for Adverse Clinical Outcome and Effect of Antibiotic Timing. Ann Intern Med 1998;129:862-869.
3. Valmari P, Makela M, Kataja M, Peltola H. Multivariate prognostication in bacterial meningitis of childhood. Scand J Infect Dis 1987;19:29-34.
4. Woolley AL, Kirk KA, Neumann AM, Mc Willams SM, Freind D, Wiatrak BJ. Risk Factors for Hearing Loss From Meningitis in Children. Arch Otolaryngol Head Neck Surg 1999;125:509-514.
5. Grimwood K, Nolan TM, Bond L, Anderson VA, Catroppa C, Keir EH. Risk factors for adverse outcomes of bacterial meningitis. J Paediatr Child Health 1996;32:457-462.
6. Kaaresen PI, Flaegstad T. Prognostic factors in childhood bacterial meningitis. Acta Paediatr 1995;84:873-8.
7. Kornelisse RF, Westerbeek CM, Spoor AB, van der Heijde B, Spanjaard L, Neijens HJ, et al. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis 1995;21:1390-7.
8. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990;323:1651-7.
9. Akpede GO, Akuhwa RT, Ogiji EO, Ambe JP. Risk factors for an adverse outcome in bacterial meningitis in the tropics: a reappraisal with focus on the significance and risk of seizures. Ann Trop Paediatr 1999;19:151–159.
10. Madagame ET, Havens PL, Bresnahan JM, Babel KL, Splaingard ML. Survival and functional outcome of children requiring mechanical ventilation during therapy for acute bacterial meningitis. Crit Care Med 1995;23:1279-1283.
11. Radetsky M. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. Pediatric Infectious Disease Journal 1992;11:694-8; discussion 698-701.
12. Lin TY, Nelson JD, McCracken GH, Jr. Fever during treatment for bacterial meningitis. Pediatr Infect Dis 1984;3:319-22.
13. Pikis A, Kavaliotis J, Tsikoulas J, Andrianopoulos P, Venzon D, Manios S. Long-term sequelae of pneumococcal meningitis in children. Clincial Pediatrics 1996;35:72-78.
14. Anttila M. Clinical criteria for estimating recovery from childhood bacterial meningitis. Acta paediatr 1994;83:63-67.
15. Dawson KG, Emerson JC, Burns JL. Fifteen years of experience with bacterial meningitis. Ped Infect Dis J 1999;18:816-822.
16. Oostenbrink R, Theunissen CCW, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Signs of meningeal irritation at the emergency department; how often bacterial meningitis? Ped Emerg Care, in preparation 2001.
17. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
18. Rodewald LE, Woodin KA, Szilagyi PG, Arvan DA, Raubertas RF, Powell KR. Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatr 1991;119:363-9.
19. Steyerberg EW, Eijkemans MJC, Habbema J, D, F. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. J Clin Epidemiol 1999;10:935-942.
20. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
21. Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
22. Hosmer DW, Lemeshow S, editors. Applied logistic regression. New York: John Wiley & Sons, Inc; 1989.
23. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.

24.Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-843.
25.Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255-1264.
26.Little RA. Regression with missing X's: A review. J Am Stat Assoc 1992;87:1227-1237.
27.Efron B. Estimating the error rate of a prediction rule: improvement on Cross-Validation. J Am Stat Ass 1983;78:316-331.
28.Mietinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol 1974;99:325-333.
29.Harrell FE, Jr., Margolis PA, Gove S, Mason KE, Mulholland EK, Lehmann D, et al. Development of a clinical prediction model for an ordinal outcome: the World Health Organization Multicentre Study of Clinical Signs and Etiological agents of Pneumonia, Sepsis and Meningitis in Young Infants. WHO/ARI Young Infant Multicentre Study Group. Stat Med 1998;17:909-44.
30.Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-9.
31.Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome for meningococcemia: a review and recent experience. Pediatr Infect Dis J 1996;15:967-979.

The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis – a head-to-head comparison

3.3

Rianne Oostenbrink, Marie-Louise Essink-Bot, Henriëtte A Moll
Submitted for publication

Abstract

This study evaluated the preference scores ('utilities') for permanent sequelae after childhood bacterial meningitis, obtained with two different instruments: the EQ-5D and Health Utilities Index (HUI).

Seven standardised case descriptions of patients with permanent sequelae after bacterial meningitis were classified on the EQ-5D and HUI classification system, respectively, by a panel of 28 paediatricians. Preference scores for each classification were calculated using the EQ-5D and HUI standard scoring algorithms.

HUI Mark 3 preference scores were substantially lower than the EQ-5D for all case descriptions (mean difference 0.11; 95% CI: 0.08 - 0.14). Mean Kendall W for agreement of the ranking order between EQ-5D and HUI Mark 3 was 0.90. For both methods, the procedure as a whole was sufficiently reliable. The EQ-5D and HUI resulted in different absolute preference scores, in particular for states associated with 'deafness' and 'mental retardation'.

In studies focussed on 'sensation' (hearing, vision, speech) and / or 'cognition', the HUI may be preferable to EQ-5D. Furthermore, sensitivity analysis to preference scores is recommended.

Introduction

The call for evidence-based medicine requires quantification of health outcomes of diagnostic and therapeutic interventions in (cost-)effectiveness analysis. Health outcomes are commonly defined by two components, i.e. duration of life and health-related quality-of-life (or, in short, health status). The assessment of duration of life is technically straightforward. To take health status into account in effectiveness analysis, composite health outcome measures such as *quality-adjusted-life-years* (QALYs) have been developed, combining the outcomes in terms of duration of life and health status using 'time' as the common denominator. In QALYs, years lived in an optimal health state count as 1.0, and years not-lived due to mortality as 0. Years lived with a specified disability are combined with a preference score ('utility'), reflecting the relative severity of the disabled health state. [1,2]

Currently two widely applied instruments are available to obtain such preference scores: the EQ-5D, developed by the EuroQol Group, and the Health Utilities Index (HUI), developed at the McMaster University in Hamilton, Canada. [3-5] Both provide 1) a patient questionnaire that classifies health status of patients through a multi-dimensional classification system, resulting in composite standardised health state descriptions and 2) a scoring algorithm based on external valuations to obtain a preference score (utility) associated with each particular health state description. [1,2,6] The scoring algorithms for both EQ-5D and HUI are based on valuations of subsets of health states by the general public.

In a current study on children suspected for bacterial meningitis at the emergency department of a large paediatric hospital in the Netherlands, a diagnostic prediction rule for bacterial meningitis has been developed in order to reduce the amount of diagnostic procedures. [7] The cost-effectiveness of this diagnostic prediction rule from a societal perspective is being evaluated using decision tree analysis. Bacterial meningitis with adequate treatment still carries a mortality risk of 3 - 4% and a risk of 9 - 14% for neurological sequelae (about two thirds hearing impairment). These percentages are even higher in cases of delayed treatment. [8,9] The sequelae vary from complete deafness, localised neurological disabilities such as paresis or epilepsy, to severe mental retardation and tetraplegia. [10,11] To include the distal consequences of the diagnostic prediction rule, in terms of an increase or a decrease of adverse outcomes in the decision tree, preference scores for permanent disabling sequelae after bacterial meningitis were needed. Both the EQ-5D and the HUI seemed potentially useful for this aim and their particular strengths or weaknesses did not convince us in advance to prefer one above the other in deriving these preference scores. [12,13] Although the short EQ-5D patient questionnaire is known to be completed easily, the HUI-15Q appears to generate only little more effort (about 5 - 10 minutes completion time), and may result into a more comprehensive description of health status. [6] The effect of differences in the dimensional contents of the EQ-5D and the HUI on the resulting preference scores for health states at interest is not known.

We therefore conducted an empirical study including expert evaluation of representative narrative health-state descriptions by using both the EQ-5D and the HUI with the following aims: 1) empirical comparison of EQ-5D and HUI preference scores, and 2) obtaining preference scores for health states associated with neurological sequelae after bacterial meningitis.

Methods

Health-status measures

The EQ-5D includes a 5-dimensional classification system, with three ordered levels of severity for each dimension (Appendix 1). The patient questionnaire consists of 5 questions that lead to a direct classification with regard to these dimensions. In total, 243 different health-state descriptions are possible. The 5-

item classification data can be converted to a preference score (utility) by a scoring algorithm. The standard scoring algorithm (the so-called York A1 tariff) was derived from data of the York 'Measurement and Valuation of Health' study, in which 42 composite EQ-5D health states were empirically valued by 2,997 persons using time-trade-off (TTO) as the valuation method, and subsequent linear regression modelling after a transformation of the TTO valuations. The scoring formula yields preference scores ranging from -0.594 (the worst imaginable health state) to 1.0. Anchor points are 'Healthy' (valued as '1.0') and 'Dead' (valued as '0'). [3]

The Health Utilities Index Mark 2 version (HUI-2) consists of a descriptive system with six dimensions, i.e. sensation, mobility, emotion, cognition, self-care and pain with four to five levels for each attribute. The fertility dimension is optional. HUI-2 was originally developed for assessing the quality-of-life in childhood cancer. [5] The 6-dimensional HUI-2 classification allows for 24,000 different health-state descriptions. A more recently developed system, complementary to the Mark 2 version, is the Mark 3 version (HUI-3), consisting of eight attributes with five to six ordered levels for each attribute (Appendix 2). HUI-3 allows for 972,000 different health states. [4,14] The patient (or parent) HUI-15Q questionnaire consists of 15 questions. Completion of this questionnaire leads to classification of the patient (child) on both the HUI-2 and the HUI-3, that can be directly converted into a preference score by a scoring algorithm. Both HUI-2 and HUI-3 scoring algorithms are based on standard gamble and visual analogue scale scores obtained from a random sample of parents or children older than 16 years from the general population. For HUI-2, one scoring algorithm has been derived, with anchor points 'Healthy' (preference score '1.0') and 'Dead' (preference score '0'), allowing for negative valuation of health states worse than 'Dead' (minimum value -0.03). For the HUI-3, two algorithms are provided: the first (further referred to as HUI-3A) with anchor points 'Healthy' (preference score '1.0') and the health state having the lowest level on each of the 8 attributes (named 'Pits', preference score '0'), with 'Dead' valued in between (0.22); the second (further referred to as HUI-3B) with anchor points 'Healthy (preference score '1.0') and 'Dead' (preference score '0'), allowing for negative valuation of health states worse than 'Dead' with a minimum value of -0.36. [4,5]

Case descriptions

Descriptions of the health states in narrative style were focussed on seven types of permanent sequelae after bacterial meningitis, selected on the basis of frequency, severity, and the availability of diagnostic criteria (i.e., excluding relatively 'vague' sequelae such as mild learning problems). The case descriptions were associated with: 1) deafness; 2) mild hearing loss; 3) epilepsy; 4) mild mental retardation; 5) severe mental retardation combined with tetraplegia, 6) paresis of the leg, and 7) mild mental retardation combined with epilepsy and paresis of the leg. An additional description of a 'normal' child was provided as a reference case. All descriptions had a similar structure, and contained (in about 200 words) information on the domains mobility, self-care,

daily activities (school, hobbies, social activities), emotional state, and pain or other symptoms for a 6-year old child, based on literature and expert opinions.[10,11,15,16] All case descriptions were judged on their consistency of structure and information on all domains, and followed by a detailed notification of their accuracy by experts (ear-nose and throat-physician, neurologist, one physician in a rehabilitation centre and one in a centre for mentally and/or physically handicapped children). An example of one case description is given in Figure 1.

> A child, aged 6, suffers from total deafness after bacterial meningitis two years before. Despite a hearing-aid, his hearing function is minimal. He attends a special school for hearing-disabled children. At this school, he performs well. His vocabulary is adequate. Additionally, he has learned how to express himself through sign language, that he can use in conversations with relatives. He can write his name, read and write simple words, count up to 20 and perform easy computations. Because he attends a special school, most of his school-mates live far from home, but he has some friends in the neighbourhood. He has troubles with playing games with his friends, because he does not hear them well and does not understand what they are talking about. He plays in the local football team weekly. He does not always understand the instructions given by the trainer, but then he imitates his team-mates. Apart from his hearing disability, he does not have other physical symptoms. Walking and running go without problems. He can wash and dress himself properly, knows how to tie his shoelaces and how to button up his shirt. In general he is a cheerful child. Sometimes, when he is understood wrongly by strangers because of his deafness, he feels angry.

Figure 1 Case description (example)

Respondents

A convenience sample of 36 general paediatricians with several years of working experience was asked to participate in the expert panel. The paediatricians were working in one of the 7 academic teaching hospitals of the Netherlands, or in a general hospital from the adherence area of the Sophia children's University Hospital in Rotterdam. The paediatricians were asked to use the case descriptions to generally imagine a child with the specified sequelae as described in each case description and to complete the EQ-5D and the HUI-15Q questionnaires for each case description. Utility estimates were derived from their completed questionnaires using the standard population-based scoring algorithms for both the EQ-5D and HUI. General information like age, gender and years of practical experience from the panel members was collected. Panellists were invited to comment on the items of the patient questionnaires.

Analysis

The primary comparison involved the preference scores generated by the EQ-5D and HUI. Additionally we evaluated some aspects of feasibility of the patient questionnaires and the reliability of the preference scores.

Feasibility of the patient questionnaires We assessed the missing value rates and used the written comments of the respondents on vagueness and ambiguities in the item phrasings.

Descriptive precision We assessed the number of different health states used by experts to classify each case description for the three classification systems and the percentage included in the modus.
Preference scores The preference scores for the health state classifications were computed using the standard EQ-5D, HUI-2 and HUI-3 (both types) algorithms respectively. [3-5] Mean preference scores with their standard deviations (SD) for all case descriptions were computed and displayed graphically. Differences and similarities between the mean preference scores per case description were interpreted quantitatively by F-test. Significant differences (p-value < 0.05) were interpreted qualitatively on the basis of the dimensional contents of the case descriptions in relation to the contents of the classification systems.
Ranking order of case descriptions The case descriptions were ranked by their preference score per respondent and the level of agreement per respondent for the ranking order as assessed by the EQ-5D, HUI-2 and HUI-3 was determined (Kendall's coefficients for concordance *W*). In addition, the mean rank was computed for each case description. We evaluated to what extent differences in ranking order could be explained by the contents of the classification systems.
Profile analysis Using MANOVA, a profile analysis (comparing EQ-5D, HUI-2, HUI-3A and HUI-3B) was performed, to test whether 1) the four different preference scores were equal for each of the seven health states ('coincident profiles'), 2) the four different preference scores differed by a constant level at each of the seven health states ('parallel profiles'), and 3) the seven case descriptions all obtained the same average preference score ('flatness'). [17] Since profile analysis requires equal units of measurement, method specific z-scores were used instead of the raw preference scores.
Measurement error of preference scores We analysed the relative contribution of different sources of variance (measures, respondents, health states) at interval level using Generalisability Theory. G-theory is a specific application of analysis of variance. [18] The G-study was performed twice, i.e. each with EQ-5D, HUI-2 and one of the HUI-3 variants. The relative contribution (variance components) of the different factors in this study (facets), i.e. 'health states' (H; 7 levels), 'methods' (M; EQ-5D, HUI-2, HUI-3, so 3 levels) and 'respondents' (R; $n = 28$), their first-order interaction terms (H×M, H×R, M×R) and one second order interaction (H×M×R), including (by definition) all the unexplained error variance, were estimated separately. Since this G-study requires complete data, missing values in the HUI-15Q and the EQ-5D questionnaires were imputed by the modal answer for that question per case description among the other respondents.
Reliability of preference scores G-theory was also used to estimate reliability coefficients for the separate classification methods. The variance component computed in a G–study for health states can be interpreted as a reliability coefficient among participants in their valuation of the different health states.
All analysis were conducted with SPSS, release 8.0 [19], except for the G-study which was conducted in SAS, version 6.11. [20]

Results

Twenty-eight paediatricians were willing to co-operate: 16 male and 12 female with mean age 45.8 years (SD = 6.5). They had average 13.8 year (SD = 6.4) of practical experience.

Feasibility of patient questionnaires For EQ-5D and HUI questionnaires two and nine answers, respectively, were missing, all concerning the questions about pain/discomfort. These missing answers led to two missing preference scores for EQ-5D (1% on a total number of 7×28=196), and five (3%) for both the HUI-2 and HUI-3. The respondents most frequently reported problems on items combining two issues in some questions or their response categories ('double-barrelled' items [18]), e.g. the use of 'discomfort' and 'pain' in the same question although their meaning is not equivalent. In particular, the non-consistent use of double-barrelled items through all response categories in the HUI-15Q led to problems for the respondents. For example, the first response category of question 7 in HUI-15Q contains 'happiness and interest in life', whereas the other answering categories include 'happiness' only.

Table 1 Number of health states per case description for EQ-5D classification and HUI-3 classification

	Case description	No. of unique health state classifications	Modal health state classification	Frequency (%) of the modal health state classification
EQ-5D*				
1	Deafness	7	11211	11 (39.3%)
2	Mild hearing loss	6	11211	14 (50%)
3	Epilepsy	6	11212	10 (35.7%)
4	MR	8	12212	7 (25%)
5	SMR and tetraplegia	7	33322	10 (35.7%)
6	Leg paresis	6	22211	22 (78.6%)
7	Epilepsy, MR and leg paresis	6	22212	15 (53.6%)
HUI-3†				
1	Deafness	23	15313211 / 15414211 / 16313111 / 16414311	2 (7.1%)‡
2	Mild hearing loss	21	13111111 / 13212111	3 (10.7%)‡
3	Epilepsy	19	11123211	4 (14.3%)
4	MR	26	11343311	2 (7.1%)
5	SMR and tetraplegia	16	66565266	5 (17.9%)
6	Leg paresis	14	11113124	8 (28.6%)
7	Epilepsy, MR and leg paresis	24	11244334	3 (10.7%)

MR = mild mental retardation, SMR = severe mental retardation

*number of possible unique classifications: 243

†number of possible unique classifications: 972,000

‡all modal classifications are provided if no unique modus present, e.g. four health state classifications each used by 2 experts

Descriptive precision The number of different classifications used by the experts to classify each case description for EQ-5D and HUI-3, respectively and the percentage included in the modus is shown in Table 1. For presentational reasons HUI-2 data are not shown in the Table. The HUI-3 led to unique classifications per respondent for almost each health state description. The modus included maximally 79% of the respondents for the EQ-5D, 67% for the HUI-2 and 29% for the HUI-3. With respect to the number of total possible classifications for each method, the EQ-5D used about 1/35 and the HUI-3 1/50,000 of the possible classifications (243 and 972,000 in total, respectively) for each case description.

Table 2 Mean index-scores (standard deviation) per case description for EQ-5D, HUI-2, and HUI-3

Case description	EQ-5D	HUI-2	HUI-3A[§]	HUI-3B[¶]
1 Deafness	0.81 (0.15)	0.79 (0.06)	0.47 (0.10)	0.28 (0.14)
2 Mild hearing loss	0.91 (0.08)	0.84 (0.07)	0.74 (0.11)	0.65 (0.14)
3 Epilepsy	0.83 (0.08)	0.88 (0.06)	0.78 (0.11)	0.70 (0.14)
4 Mild mental retardation (MR)	0.62 (0.11)	0.55 (0.08)	0.44 (0.14)	0.24 (0.18)
5 Severe retardation and tetraplegia	-0.15 (0.13)	0.12 (0.03)	0.02 (0.02)	-0.33 (0.02)
6 Leg paresis	0.67 (0.12)	0.80 (0.10)	0.64 (0.10)	0.51 (0.14)
7 Epilepsy, MR and leg paresis	0.47 (0.25)	0.46 (0.07)	0.28 (0.10)	0.02 (0.14)

[§]HUI-3A = index scores of HUI Mark 3 computed by the algorithm with anchor points 'Pits' and 'Healthy'

[¶]HUI-3B = index scores of HUI Mark 3 computed by the algorithm with anchor points 'Dead' and 'Healthy'

Preference scores In Table 2 and Figure 2 mean preference scores for each case description are presented for the three methods (EQ-5D, HUI-2 and HUI-3). For the HUI-3, the preference scores resulting from both scoring algorithms are presented. HUI-3B preference scores were all significantly lower than EQ-5D, HUI-2 and HUI-3A preference scores ($p < 0.05$). Because of this systematical difference, we focussed the comparison of the preference scores on the latter three. The HUI-3A preference scores were significantly lower than HUI-2 preference scores for all case descriptions. HUI-3A preference scores were also significantly lower than the EQ-5D preference scores, except for 'paresis of the leg', which was scored almost equally by HUI-3A and EQ-5D and except for 'severe mental retardation with tetraplegia' which was scored significantly lower by EQ-5D than by HUI-3A. The largest difference between EQ-5D and HUI-3A was found for 'deafness'. Comparing the preference scores as generated by HUI-2 and EQ-5D resulted in no differences for the case description 'deafness' and 'mild mental retardation with epilepsy and leg paresis'. The HUI-2 preference scores for 'mild hearing loss' and 'mild mental retardation' were significantly lower and the others significantly higher than those generated by EQ-5D.

Ranking order of case descriptions The HUI-2 and HUI-3 (A and B) resulted in identical ranking orders. An inverse ranking order was present for 'Epilepsy' and 'Mild hearing loss' by EQ-5D, occurring as first and second in ranking on the HUI-scales. Similarly, the EQ-5D inverted the ranking order of 'Paresis of a leg' and

'Severe deafness', ranked 3rd and 4th on the HUI-scales. Since all HUI-scales (HUI-2, HUI-3 A, and B) resulted in the same ranking order, the level of agreement in ranking order per respondent was determined for EQ-5D with HUI-3 only. The mean Kendall's coefficient for concordance *W* of all respondents was 0.90 (SD: 0.057).

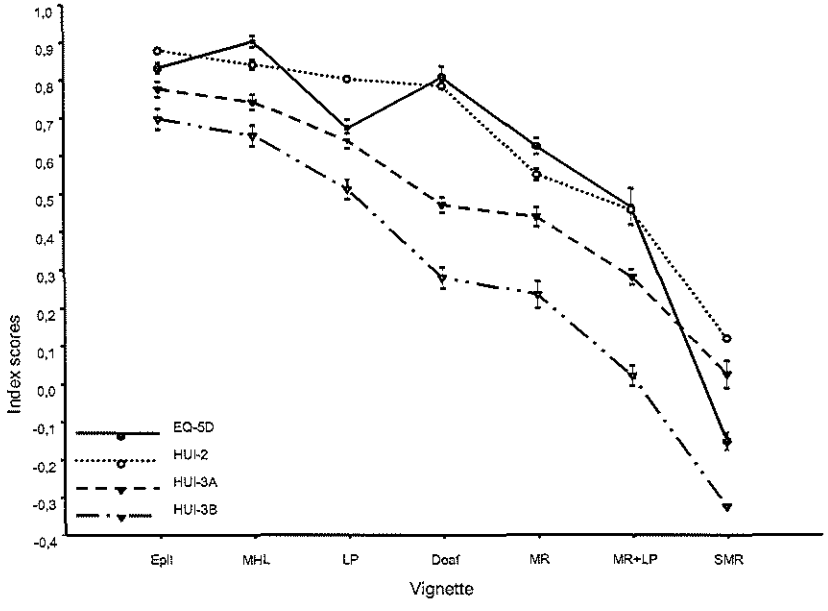

Figure 2 Mean index scores with 95% confidence intervals per health state description for each health state measure method. Case descriptions on x-axis are sequenced according to the ranking order by HUI-3.

Profile analysis The comparability of the preference scores of all four health state measures for each case description was evaluated by profile analysis in more detail. The assumptions of 'coincidence', 'parallelism' and 'flatness' were all rejected ($p < 0.001$). Thus the value of preference scores differed among the four methods (absence of 'coincidence') and differences in preference scores of the four methods were not constant over the seven case descriptions (absence of 'parallelism'). The latter is also visualised by one line crossing another in Figure 2. Absence of 'flatness' indicates that there was a substantial difference in the average preference scores obtained for the seven case descriptions. In particular, there was a reliable difference between the four measures in the preference scores obtained for the case descriptions 'Deafness', 'Epilepsy', 'Severe mental retardation and tetraplegia' and 'Leg paresis'.

G-studies Table 3 shows the results of the G-studies. First, the G-study was conducted on raw preference scores. In the G-study including EQ-5D, HUI-2 and HUI-3A, the largest proportion of variance could be attributed to 'health states' (79%), leaving 7% for the first order interaction 'health states × methods' (meaning that *some* health states are valued differently by *some* methods), 5% error variance, 4% for 'methods' as main effect and very low percentages for the other facets. In the G-study on EQ-5D, HUI-2 and HUI-3B, the facet 'method' took 20% of variance, as expected since the HUI-3B scores were so much deviant from the others (line of HUI-3B much lower than the others in Figure 4), leaving 65% for 'health states', 5% for the first order interaction 'health states × methods', 6% error and small percentages for the other variance components. In an additional analysis we investigated whether the *relative* differences between EQ-5D, HUI-2 and HUI-3 were similar. Therefore, the absolute difference between the methods was eliminated by transforming individual values for the health state descriptions to method-specific z-values, yielding by definition zero variance for the facet 'method'. The result of this analysis on EQ-5D, HUI-2 and HUI-3A was similar to the one including HUI-3B. The percentage of variance uniquely attributable to the health states increased to 84%, and the first order interaction 'health states × method' was 5%.

Table 3 Variance components (percentages) of health states (7) × respondents (28) × methods (3)

	Variance components (%)		
Source of variation	Raw index scores		Transformed z-scores*
	EQ-5D/HUI-2/HUI-3A	EQ-5D/HUI-2/HUI-3B	
Respondent (R)	1	1	1
Health State (H)	79	65	84
Method (M)	4	20	0
R×H	2	1	2
R×M	2	2	2
H×M	7	5	5
Residual (R×H×M)	5	6	6

*analysis on transformed z-scores yielded similar results for EQ-5D, HUI-2 and each of the HUI-3 variants (A and B); transformed z-score for 'Method' per definition zero.

Reliability of preference scores The results of the G-study for each method separately are shown in Table 4. The variance components for the health states can be regarded as (standard) reliability coefficients. The HUI-2 showed the highest reliability (0.94), but the reliability of the other methods (0.86-0.87) was sufficiently high.

Table 4 Variance (percentages) of absolute index scores per health state measure method.

Source	EQ-5D	HUI-2	HUI-3A (pits=0, healthy=1)	HUI-3B (death=0, healthy=1)
Respondent (R)	3	1	3	3
Health State (H)	86	94	87	87
R×H	11	5	10	10

Discussion

In this study we compared three methods (EQ-5D and two versions of the Health Utilities Index) for the classification and valuation of health states, primarily regarding the preference scores they generated for the seven case descriptions, and additionally regarding aspects of feasibility and reliability. Such an empirical head-to-head comparison may help in decisions about which instrument is preferable to use in particular disease contexts. Furthermore, this study offers preference scores for health states potentially helpful for investigating the sequelae after bacterial meningitis.

Feasibility of health state classification The number of missing classifications was similar for all methods. The panellists frequently commented on the use of 'double-barrelled' items in questions (mostly *'pain/discomfort'*), which is generally considered as 'wrong' in devising questionnaire items [18], and this may hopefully be taken into account if the original authors of EQ-5D and the HUI decide about developing an improved version of the patients questionnaires.

Descriptive precision As expected from the larger numbers of attributes and levels, the HUI-3 classification resulted in many more different health state classifications per case description than the EQ-5D. This illustrates that the HUI classification is more detailed than the EQ-5D, and therefore gives more opportunity to represent variability in functioning. At the descriptive level, the HUI-3 can be more precise than the rather crude EQ-5D.

Preference scores Variations in preference scores observed for the same health states may have different sources. The first source may be the health concept of a particular classification system (e.g. one concept may cover aspects that are ignored by another concept). The EQ-5D and HUI-2 and HUI-3 were developed with a similar application in mind, i.e. for use to classify patients in various illness groups with the opportunity to provide every health-state description with a preference score, but their health concepts are different. The HUI focuses on 'disability' as defined by the WHO [21], representing difficulty in performing activities due to functional limitations. The EQ-5D additionally focuses on aspects of 'handicap' incorporating the consequences of the disability on the social activities. [6] Furthermore, the dimensional content of the three measures is different. EQ-5D does not contain 'cognition' in contrast to HUI-3, which may explain the large differences between the HUI-3 and EQ-5D found for the three health states with mental retardation. This illustrates one of the disadvantages of the EQ-5D for populations characterised (in part) by cognitive dysfunction (e.g. dementia, intellectual disability, etc). [22] The EQ-5D also does not include a specific dimension for 'sensation', so that the effect of hearing impairment on health-related quality-of-life can only be covered by its effect on functional domains, such as 'usual activities' or 'anxiety/discomfort'. These latter domains, however, are not well correlated with hearing function. [13] The fact that the preference scores for 'Mild hearing loss' and 'Deafness' as generated by the EQ-

5D in our study were higher (closer to the value for optimal health) than for 'Epilepsy' and 'Paresis', respectively, is probably caused by the lack of a sensory domain, subsequently resulting in an inverse ranking order compared to both HUI methods. [3-5] The difference between HUI-2 and HUI-3 for 'deafness' can be explained by the fact that HUI-2 has just one dimension 'sensation' while in HUI-3 this dimension is split into three separate dimensions, i.e. hearing, vision and speech. All four measures result in a different pattern of low and high preference scores, as illustrated by the profile analysis results.

The second possible source of variation in preference scores from different measures is the scoring attitude towards the fixed endpoints of the scales (anchor points) and the position and handling of 'dead' by the classification method. The differences in preference scores between HUI-3A (anchor points 'Pits' and 'Healthy') and HUI-3B (anchor points 'Death' and 'Healthy') are largely attributed to the difference in anchor points.

Another source of differences in preference scores may be the elicitation valuation method used for valuing health states in the empirical study. Standard gamble (HUI) and time-trade-off (EQ-5D), however, yield almost identical values in the same experimental setting. [12-23] Therefore in the results of the present study this source of differences was considered negligible.

The final source of variation in preference scores may be the method of analysis for estimation the prediction model of the classification system (linear regression after several transformations for EQ-5D, multiplicative modelling for HUI-2 and HUI-3. [3-5] Since this is part of the development of the measurement method, and since we aimed at a comparison of the methods 'off-the-shelf', this source of differences was not explored in the present study.

Error components of preference scores Most of the variance of the preference scores was attributable to the health state descriptions themselves, i.e. 79% and 65% in case of evaluating EQ-5D, HUI-2 and HUI-3A or HUI-3B, respectively. Partly, this was to be expected, since the case descriptions as used in this study were more or less covering the whole range between complete health and dead. Obviously, a G-study on very similar health states would result in a smaller variance component for the health states. The general effect of the facet 'method' was relatively small. The first order interaction H×M, however, was substantial (5 - 7%). This should be interpreted as that *some* health states obtain a different preference score for *some* of the methods. This interaction between the health state measures and the health states is also illustrated by the absence of 'parallelism' in the profile analysis, as described before. This is further evidence for the hypothesis that differences in dimensional contents cause the main differences in preference scores generated by the different methods. [6]

Reliability of classification and preference scores The reliability of the whole procedure of derivation of the preference scores was similar for all methods

(> 0.85). It should be noted, however, that the respondents were all paediatricians and that the reliability of the classification may be lower in a less homogenous population of respondents.

The fact that experts (paediatricians) served as respondents for the classification of the patient case descriptions in the current study may impress as peculiar and deserves further attention. First, it is important to distinguish, in a general sense, classification from valuation. Preference scores as generated by the standard EQ-5D and HUI methodology are derived following a two-step procedure essentially involving two different groups of respondents. The first step is classification of patients' health status by completion of patient questionnaires. The second step involves the linking of the result to a preference score using a scoring algorithm based on valuations of composite health state descriptions from the general public. Preference scores thus derived are regarded to reflect preferences from the societal viewpoint, and hence applicable in cost-effectiveness studies conducted from this viewpoint. [24] Application of utilities in decision analysis at the individual patient level is quite another issue; in such a case, both description and valuation should be elicited from the individual patient himself. Note that the panel members in the current study did not take part in the estimation of the utilities associated with the case descriptions. The utility estimates were derived using the standard population-based scoring algorithms for bot the EQ-5D and HUI. However, also in the generation of 'societal' preference scores, the *classification* of patients should come preferably from the patients, or parents in the case of young children, themselves. In the current study, the comparison of the preference scores generated by the three measures will not be affected by the use of experts instead of parents, since this potential bias [25-26] is consistently present across the three methods. But we also had a positive argument for choosing experts for the classification step. The EQ-5D and HUI patient questionnaires both are in the current standard format not applicable to young children, since they contain questions about school, reading and self-care. [1,6] Children at risk for meningitis in general are much younger than school-going age, and use of the questionnaires in this population requires either years of follow-up or extrapolation of the child's functioning to the age of at least 6 years. Experts (paediatricians) could, because of their professional experience, be asked to imagine what a child aged six with permanent sequelae after meningitis at age one or two would be like.

From the literature, there are a few examples of utility assessment for adverse outcomes associated with meningitis. [27-28] The results of these studies are only to a very limited extent comparable to the results of the present study, due to differences in the subjects who performed the valuation task, descriptions of the states that were valued, and valuation methods.

Given the availability of two standard instruments for utility estimations, the situation would have been easy if both measures resulted in the same preference scores estimates. With regard to the practicality of the classification

questionnaires, and the agreement and reliability of the measures, we did not find decisive differences between the measures. The relative performance of the measure is related to the dimensional contents of the methods, which may be the best foundation for a choice. Although this intuitively may be thought upon on beforehand, it is now supported by empirical evidence. In this study we needed preference scores for health states associated with neurological sequelae after bacterial meningitis. Since hearing impairment and cognitive disabilities are the most frequent sequelae for this disease [8], we decided to prefer the preference scores obtained by the HUI-3. Finally, since the estimation of preference scores depends on the classification system that has been used and are not so absolute as thought, the sensitivity to differences in the preference scores estimates included must be an integral part of any study using such values.

References

1. Pal DK. Quality of life assessment in children: a review of conceptual and methodological issues in multidimensional health status measures. J Epidemiol Community Health 1996;50:391-6.
2. Jenney ME. Theoretical issues pertinent to measurement of quality of life. Med Pediatr Oncol 1998;Suppl:41-5.
3. Dolan P. Modeling valuations for the EuroQol health states. Med Care 1997;35:1095-1108.
4. Furlong W, Feeny D, Torrance GW, Goldsmith CH, DePauw S, Zhu Z, et al. Multiplicative multi-attribute utility function for the health utilities index Mark 3 (HUI3) system: a technical report.; 1998.
5. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702-22.
6. Feeny DH, Furlong WJ, Barr RD. Multiattribute approach to the assessment of health-related quality of life: Health Utilities Index. Med Pediatr Oncol 1998;Suppl:54-9.
7. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
8. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993;12:389-94.
9. Lebel MH, McCracken GH, Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989;83:161-167.
10. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
11. Fortnum HM. Hearing impairment after bacterial meningitis: a review. Arch Dis Child 1992;67:1128-33.
12. Brazier J, Deverill M, Green C, Harper R, Booth A. A review of the use of health status measures in economic evaluation: Health Technol Assess; 1999. Report No.: 9.
13. Belanger A, Berthelot JM, Guimond E, Houle C. A head-to-head comparison of two generic health status measures in the household population: McMaster Health Utilities Index (Mark 3) and the EQ-5D: Statistics Canada; Health Analysis and Modelling Group; 2000 April.
14. Feeny DH, Furlong WJ, Torrance GW. The health utilities index: an update. Qol Newsletter 1999(22):8-9.
15. Hanai T. Quality of life in children with epilepsy. Epilepsia 1996;37(Suppl 3):28-32.
16. Aicardi J. Diseases of the Nervous System in Childhood. London: Mack Keith Press; 1998.
17. Tabachnick BG, Fidell LS. Using Multivariate Statistics. 3rd ed. New York: Harper Collins College Publishers; 1996.
18. Streiner DL, Norman GR. Health measurement scales. A practical guide to their development and use. Second edition. New York: Oxford University Press; 1995.
19. SPSS Inc. SPSS for Windows: Base System User's Guide, release 8.0. 8.0 ed. Chicago, Ill: SPSS Inc.; 1998.

20. SAS Institute Inc. SAS/STAT user's Guide, version 6. Fourth edition ed. Cary, NC, USA: SAS Institute Inc.; 1989.
21. World Health Organization. International classification of Impairments, Disabilities, and Handicaps. Geneva; 1980.
22. Krabbe PFM, Stouthard MEA, Essink- Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol 1999;52:293-301.
23. Krabbe PFM, Essink-Bot ML, Bonsel GJ. The comparability and reliability of five health-state valuation methods. Soc Sci Med 1997;45:1641-1652.
24. Gold MR, Siegel JE, Russel LG, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
25. Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, Rosenbaum PL, et al. Differences in preferences or neonatal outcomes among health care professionals, parents, and adolescents. JAMA 1999;281:1991-1997.
26. Sprangers MAG, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol 1992;45:743-760.
27. Bennet JE, Sumner W, Downs SM, Jaffe DM. Parents' utilities for outcomes of occult bacteremia. Arch Pediatr Adolesc Med 2000;154:43-48.
28. Kramer MS, Etezadi-Amoli J, Ciampi A, Tange SM, Drummond KN, Mills EL, et al. Parents' versus physicians' values for clinical outcomes in young febrile children. Pediatrics 1994;93:697-702.

Appendix 1 EQ-5D

Attribute	Level	Description
Mobility	1	No problems walking about
	2	Some problems walking about
	3	Confined to bed
Self-care	1	No problems with self-care
	2	Some problems washing or dressing self
	3	Unable to wash or dress self
Usual Activities	1	No problems with performing usual activities (e.g. work, study, housework, family or leisure activities)
	2	Some problems with performing usual activities
	3	Unable to perform usual activities.
Pain / Discomfort	1	No pain or discomfort
	2	Moderate pain or discomfort
	3	Extreme pain or discomfort
Anxiety / Depression	1	Not anxious or depressed
	2	Moderately anxious or depressed
	3	Extremely anxious or depressed

Appendix 2 Health utilities Index, version Mark 3.

Attribute	Level	Description
Vision	1	Able to see well enough to read ordinary newsprint and recognise a friend on the other side of the street, without glasses or contact lenses
	2	Able to see well enough to read ordinary newsprint and recognise a friend on the other side of the street, but with glasses
	3	Able to see well enough to read ordinary newsprint with or without glasses but unable to recognise a friend on the other side of the street, even with glasses
	4	Able to see well enough to recognise a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses
	5	Unable to read ordinary newsprint and unable to recognise a friend on the other side of the street, even with glasses
	6	Unable to see at all
Hearing	1	Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
	2	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people
	3	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid and able to hear what is said in a group conversation with at least three other people
	4	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid
	5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid
	6	Unable to hear at all

Appendix 2 Health utilities Index, version Mark 3 (cont'd)

Speech	1	Able to be understood completely when speaking with strangers or friends.
	2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well
	3	Able to be understood partially when speaking with strangers or people who know me well
	4	Unable to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well
	5	Unable to be understood when speaking to other people (or unable to speak at all)
Dexterity	1	Full use of two hands and ten fingers.
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person
	3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person)
	4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools
	5	Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools)
	6	Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools)
Ambu-lation	1	Able to walk around the neighbourhood without difficulty, and without walking equipment
	2	Able to walk around the neighbourhood with difficulty; but does not require walking equipment or the help of another person
	3	Able to walk around the neighbourhood with walking equipment, but without the help of another person
	4	Able to walk around the neighbourhood with walking equipment, and requires a wheelchair to get around the neighbourhood
	5	Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood
	6	Cannot walk at all
Emotion	1	Happy and interested in life
	2	Somewhat happy
	3	Somewhat unhappy
	4	Very unhappy
	5	So unhappy that life is not worthwhile
Cognition	1	Able to remember most thighs, think clearly and solve day to day problems
	2	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems
	3	Somewhat forgetful, but able to think clearly and solve day to day problems
	4	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems
	5	Very forgetful, and have great difficulty when trying to think or solve day to day problems
	6	Unable to remember anything at all, and unable to think or solve day to day problems
Pain	1	Free of pain and discomfort
	2	Mild to moderate pain that prevents no activities
	3	Moderate pain that prevents a few activities
	4	Moderate to severe pain that prevents some activities
	5	Severe pain that prevents most activities

4 Economic evaluation in paediatrics

Cost reduction by introducing a diagnostic decision rule in children with meningeal signs

4.1

Rianne Oostenbrink, Jan B Oostenbrink, Karel GM Moons, Gerarda Derksen-Lubsen, Diederick E Grobbee, W Ken Redekop, Henriëtte A Moll

Submitted for publication

Abstract

Background: Decision rules may provide the physician a rationale to decide on the use of diagnostic and therapeutic procedures and improve the quality and cost-effectiveness of medical care. Recently, we developed a diagnostic rule to decide when to perform a lumbar puncture and to initiate empirical antibiotic treatment in a child with meningeal signs. In this study we estimated cost savings of the rule compared to current practice.

Methods: Data were used of 360 children visiting the emergency department of the Sophia Children's Hospital with meningeal signs between 1988 and 1998, who followed routine care. Costs of diagnostic and therapeutic procedures were estimated using financial accounts of an academic and a general paediatric hospital. The number of performed procedures actually performed and as expected when using the decision rule and total costs (i.e. unit costs × consumer frequency) were estimated and compared.

Results: The population of children with meningeal signs comprised 99 with bacterial meningitis (27%), 36 with another serious bacterial infection (10%) and 225 with a self-limiting disease (63%). Application of the rule would have led to a net reduction of 30 lumbar punctures and 33 hospitalisations for empirical treatment with the same diagnostic accuracy as current practice. The rule would save € 292 per patient (relative reduction 10%); € 33 by diagnostic procedures and € 259 by therapeutic interventions. Cost savings were mainly achieved in children with self-limiting diseases. Cost savings were most sensitive to inpatient nursery costs and the a priori probability of bacterial meningitis in the population.

Conclusion: A diagnostic decision rule for children with meningeal signs has the potential to improve the appropriate use of medial resources, to be cost-effective and to early ascertain the absence of bacterial meningitis.

Introduction

The critical evaluation of diagnostic tests and therapeutic strategies has lead to the development of decision rules. These rules may provide physicians a more rational basis for decisions on the use of diagnostic and therapeutic procedures and may improve quality and the cost-effectiveness of medical care.

In previous reports, we assessed the value of diagnostic and therapeutic procedures in management of children with bacterial meningitis visiting the emergency department with meningeal signs. [1,2] Since delayed diagnosis and treatment of bacterial meningitis worsens its prognosis, physicians have a low threshold to perform a lumbar puncture in patients with meningeal signs. Moreover, patients with an increased cell count in cerebrospinal fluid (CSF) will immediately get empirical antibiotic treatment for bacterial meningitis until the CSF bacterial culture result is available (after 48 - 72 hours). [3,4] Although a safe strategy, this results in a large group of patients without bacterial meningitis that unnecessarily undergoes a lumbar puncture and is treated with antibiotics. In order to safely reduce the number of lumbar punctures and empirical treatments in patients without true bacterial meningitis, a diagnostic decision rule for the indication of a lumbar puncture and empirical treatment for bacterial meningitis has been developed. [1,2] This rule has yet only been evaluated on its diagnostic accuracy.

The *aim of the present study* was to estimate possible cost savings that could be achieved by a rule predicting bacterial meningitis in children with meningeal signs compared to current practice. To extrapolate these results to other clinical settings, we also investigated key-parameters that mainly determined the cost savings after introduction of the diagnostic decision rule.

Methods

Patients

This study used data from a large ongoing diagnostic study in children with meningeal signs, which has been described previously. [1,2] In brief, 360 children (aged from 1 month up to 15 years) visiting the emergency department of the Sophia Children's Hospital, Rotterdam, The Netherlands, with meningeal signs between 1988 and 1998 were included. Demographic data, presenting signs and symptoms on admission as recorded in the standardised paediatric patient record, and clinical findings during hospitalisation or outpatient follow-up were documented. In addition, data from all other diagnostic procedures such as laboratory tests of cerebrospinal fluid (CSF), blood, stool and urine specimens and radiographic tests at admission and during hospitalisation, were retrieved from the computer-documented hospital information system.

Decision rule

The developed diagnostic decision rule included two scoring algorithms: one using characteristics from patient history (duration of the complaints and presence of vomiting), physical examination (presence of meningeal signs, petechiae, disturbed consciousness and cyanosis) and serum C-reactive protein (CRP), to guide decisions on the need of a lumbar puncture, and a second one, using cerebrospinal fluid (CSF) indices (CSF/blood glucose ratio and the absolute polymorphonuclear cell count), to decide upon initiating empirical treatment. [1,2] Total scores can be computed by assigning points for each factor present in the individual patient and may guide decisions on the performance of a lumbar puncture or the use of empirical treatment in practice as presented in Appendix 1.

For example a boy with complaints since half a day, who vomits, with meningeal irritation at physical examination, a serum CRP of 45 mg/l, 150 polymorphonuclear cells in CSF/μl and a CSF/blood glucose ratio of 0.45, gets a clinical score of 10 (= 0.5 + 2 + 7.5 + 0 + 0 + 0) and a CSF score of 0 (= 2 - 2). In all patients with a clinical score < 9.5 points bacterial meningitis was absent, such that a lumbar puncture and empirical treatment could safely be withheld in these patients. In patients with a clinical score of 9.5 – 10.4, a CSF score of ≥1 identified patients in whom empirical treatment was indicated; for those with clinical scores between 10.5 – 12.9 or 13.0 - 19.9 the lower CSF thresholds for empirical treatment were ≥ -2 and ≥ -3, respectively, without missing a single case of bacterial meningitis. All patients with a clinical score ≥ 20 had an indication for empirical treatment, irrespective of the CSF score. For further information on the derivation and validation of the decision rule we refer to previous publications. [1,2]

Resource use

During the diagnostic phase the following resources were distinguished: emergency department visit, lumbar puncture procedure, laboratory tests (including haematology, blood chemistry, urinalysis, CSF cytology and biochemical analysis and microbiology of blood and urine and CSF), and chest radiography. Resources during the therapeutic course included hospitalisation (days on a intensive care unit, isolation or paediatric ward), consultations by the paediatric specialist, laboratory and radiographic tests additional to those performed during the diagnostic phase, and prescription of medication use either in hospital or during outpatient treatment (such as antibiotics, anti-epileptics, procedure of intravenous treatment). The actual resource use was based on the frequencies of resources in current practice as documented in the database. To estimate the expected resource use after applying the diagnostic decision rule, we simulated the consequences of all possible scenarios that could follow from applying the decision rule. In Figure 1 the eleven possible scenarios are outlined, with the expected number of patients per scenario when applying the rule on the database of children with meningeal signs. Three groups of diagnoses were distinguished, according to their need of therapeutic interventions: 1) patients with bacterial meningitis (BM), 2) patients with serious bacterial infections other

than meningitis (SBI; i.e. septicaemia, pneumonia, urinary tract infection or bacterial gastro-enteritis) and 3) patients with viral or aseptic meningitis or with other self-limiting diseases (SLD; i.e. upper respiratory tract infections, non-specified viral infections, myalgia). To estimate the resource use of each scenario, various assumptions were made. We assumed that some diagnostic tests not part of the decision rule or not indicated by the decision thresholds, would be performed in some patients anyway for differential diagnosis or for therapeutic purposes. [5] Similarly, we assumed that hospitalisation could be indicated in a patient by disease severity also. To determine patients that were actually hospitalised for illness severity or for empirical treatment in case of suspicion of bacterial meningitis, we checked the patients' discharge letters. Hospitalised patients who did not actually undergo a lumbar puncture or those who continued treatment even after the results of CSF cultures were considered negative, were assumed to be hospitalised even though the decision rule would indicate otherwise. Finally, since the decision rule aimed not to miss any patient with bacterial meningitis, we assumed that all patients were correctly treated after applying the decision rule and had a similar risk of mortality and morbidity as in current practice. These assumptions had the following consequences:

1. The diagnostic decision rule would not change actual resource use of the diagnostic and treatment course in patients with true bacterial meningitis. Diagnostic tests actually performed, but not part of the decision rule would still be performed in these patients (e.g. for therapeutic purposes).
2. In patients with true SBI the decision rule would not lead to another diagnostic strategy as actually applied except for the use of lumbar punctures.
3. In SBI patients actually hospitalised for other reasons than for presumed bacterial meningitis (scenario 4 and 8) the hospitalisation frequency and the use of therapeutic interventions would remain unchanged.
4. In SLD patients, diagnostic tests of the diagnostic decision rule would be required only to rule out bacterial meningitis. Since other tests may still be required to rule out the presence of other severe bacterial infections, some additional diagnostic tests might be used anyway. We assumed this would occur in a same number of patients with SLD as those with SBI.
5. In SLD patients actually hospitalised for other reasons than for presumed bacterial meningitis (scenario 5 and 9), the hospitalisation frequency and the use of therapeutic interventions would not change.

Unit costs

Average unit prices of diagnostic tests and therapeutic interventions were estimated in Euro (€ 1 = $ 0.946, January 2001) using financial accounts of the Sophia Children's Hospital, Rotterdam of 1996 and time-estimates of procedures by experts. Unit costs of an emergency department visit included personnel costs of the paediatrician, a resident (45 minutes per visit each) and nurse (15 min). Unit costs of a lumbar puncture included costs of a paediatrician (15 min), nurses (2 nurses, summed time 45 min) and material costs. Unit costs of laboratory tests were calculated by dividing the annual laboratory costs by the weighted number

of annual tests. Costs of radiographic tests included the time spent by the radiologist, materials and radiographic equipment. Costs of medication were based on actual purchase prices enlarged with an allowance for chemists' costs. Inpatient nursing costs were based on mean costs of the Sophia Children's hospital (academic hospital) and the Juliana Children's Hospital, The Hague (a large general paediatric hospital). Unit costs of inpatient nursing days included costs of a paediatrician and residents, and nursery, material and hotel costs. All unit costs were enlarged with the costs of general equipment, buildings and overhead expenses by using direct allocation. [6]

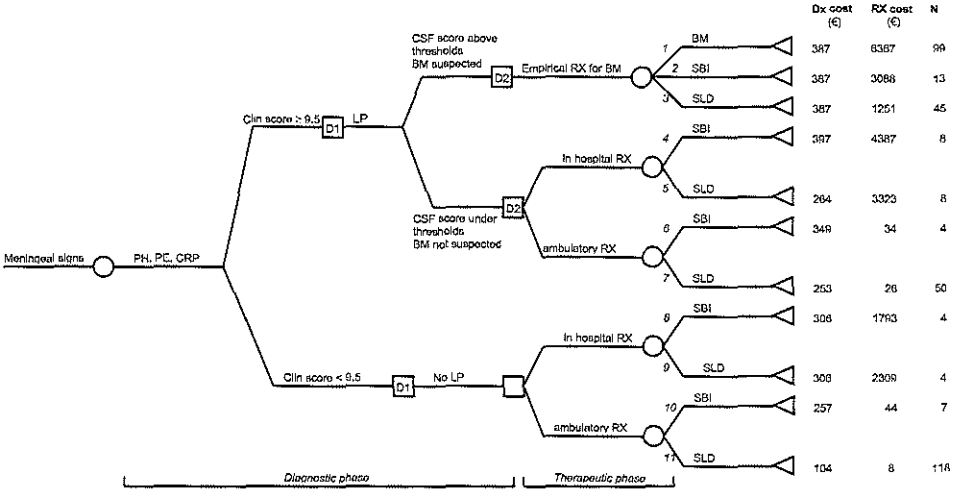

Figure 1 Clinical scenarios expected following the application of the decision rule
Costs estimated in Euros (€ 1 = $ 0.946)
Number of patients per scenario is the expected number of patients per scenario when applying the rule on the database of 360 children with meningeal signs. BM: bacterial meningitis; SBI: serious other bacterial infection; SLD: self-limiting disease; DX: diagnostic procedures; RX: treatment; PH: patient history; PE: physical examination; D1: decision using the clinical scoring algorithm; D2: decision using the CSF formula.

Analysis

Total costs were estimated in Euro per patient by multiplying the unit costs per resource with the diagnostic and therapeutic resource use as actually performed and as expected when applying the decision rule (given the above assumptions on resource use). In a cost-minimisation analysis the possible cost savings by the introduction of the diagnostic decision rule compared to current practice were estimated. Since costs of treatment (hospitalisation in particular) were much higher than costs of diagnostic tests, we compared the cost savings achieved in the diagnostic and therapeutic phase separately. The impact of changes in base-case estimates of unit costs and frequencies of diagnoses and our assumptions on resource use was evaluated by sensitivity analysis. Inpatient nursing costs were varied by 20%, which is a plausible variation of inpatient nursing costs between an academic hospital and a general hospital. [7] The frequency of bacterial

meningitis was reduced by 50%, with a proportional increase of the other two diagnostic categories (SBI and SLD). The impact of the previous assumptions on resource use was assessed by an analysis under the assumption that all diagnostic tests and interventions other than indicated by the decision rule (e.g. for a differential diagnosis or for therapeutic purposes), indeed were saved in all patients. Therefore, in this analysis we included costs of determining serum CRP and glucose, CSF cell count, glucose and bacterial cultures, and costs of treatment as indicated in patients by the rule, only. Finally, we estimated the possible cost reduction by the rule, using data from a general paediatric hospital with a lower frequency of bacterial meningitis and lower inpatient nursing costs.

Results

General characteristics of the 360 included children are presented in Table 1. Bacterial meningitis was diagnosed in 99 children (28%). A lumbar puncture had actually been performed in 256 children (71%) and 217 children hospitalised (60%). Table 2 presents the unit costs in Euro of the main diagnostic tests and therapeutic interventions, as used in the cost analysis. The unit cost of a lumbar puncture was estimated to be € 49. Inpatient nursing costs varied from € 343 per day on a paediatric ward to € 480 per day on an isolation ward and to € 832 per day on an intensive care unit.

Table 1 General patient characteristics

Characteristic	Number (%)
Male gender	225 (62.5%)
Age (years)*	2.4 (0.8-5.3)
Referral pattern	
General practitioner	286 (79%)
Self referral	42 (12%)
Other specialist	9 (3%)
Fever in history	330 (92%)
Body temperature at examination (°C)$	39.2 (1)
Pain in the neck in history	168 (47%)
Referred with meningeal signs	203 (56%)
Meningeal irritation assessed by the paediatrician	256 (71%)
Diagnosis	
Bacterial meningitis	99 (28%)
Viral/aseptic meningitis	44 (12%)
Pneumonia	28 (8%)
Other bacterial infections†	8 (2%)
Self limiting diseases‡	181 (50%)
Lumbar puncture performed	256 (71%)
Hospitalisation	217 (60%)

*Median (25^{th} – 75^{th} percentile)
$Mean (standard deviation)
†Other bacterial infections included septicaemia, urinary tract infections, gastro-enteritis
‡Self-limiting diseases are upper respiratory tract infections or non-specified viral infection

In patients with SBI and SLD 26 and 132 lumbar punctures had actually been performed, respectively. After using the decision rule this would be 25 (Figure 1,

sum of patients in scenario 2, 4 and 6) and 103 (Figure 1, sum of patients in scenario 3, 5 and 7), respectively. Twenty-five SBI patients and 93 SLD patients had actually been hospitalised; this would be 25 (Figure 1, sum of scenario's 2, 4 and 8) and 55 (Figure 1, sum of scenario's 3, 5 and 9), respectively when using the decision rule. The actual hospitalisation rate in SLD patients decreased from 41% to 24% by the diagnostic decision rule (40% reduction). By multiplying the estimated resource use per patient in each scenario with fixed unit costs, the mean costs per patient in each scenario were calculated (Figure 1). In particular, large differences in therapeutic costs were found between the scenarios, due to relative high inpatient nursing costs.

Table 2 Unit costs of resources in diagnostic and therapeutic strategy

Type of resource	Unit cost (€*)
Visits	
Emergency department	90
Inpatient nursing consultation to paediatric specialist	46
Outpatient consultation to paediatric specialist	13
Laboratory tests	
Haematology†	10
Serum CRP	2
Acid-base balance	4
Serum glucose	2
Lumbar puncture‡	49
Bacteriologic cultures§	20
Virology§	35
Chest radiography	35
Antibiotic treatment (per day)¶	
3rd generation cefalosporine	13
Amoxicillin	1
Benzylpenicillin	4
Inpatient nursing costs (per day)	
Intensive care unit	832
Isolation ward	480
Paediatric ward	343

* € 1 = $ 0.946 (January 2001)
†Including hemoglobin, and leukocyte, thrombocyte and differential count
‡Including the costs of the puncture and cerebrospinal fluid cytology and chemistry
§Specimens of blood, urine, cerebrospinal fluid or faeces
¶Price of daily dose for a child aged 2.5 years with a weight of 15 kg

Total costs and costs per diagnostic group as actually observed and as expected by the decision rule are presented in Table 3. The decision rule would reduce total costs by € 292 per patient (10%); € 33 in the diagnostic phase (11% of total reduction) and € 259 in the therapeutic course (89%). The largest cost reduction would be achieved in patients with SLD (33% reduction of total costs), as shown by the ratio of cost reduction per diagnosis category. The proportional contribution to the total costs shows that BM patients accounted for 62% of the total costs in current practice (Table 3). Since we assumed that the decision rule would not lead to a change in costs in BM patients, the maximum reduction in costs could be 38% of total costs. The decision rule would achieve 10% reduction of total costs of this maximum.

Table 3 Mean costs in Euro (€ 1 = $ 0.946) per patient per diagnosis group

	Number of patients	Costs current practice	Proportional contribution to costs of current practice	Costs decision rule	Cost savings	Proportional cost savings*
Diagnostic phase						
BM	99	387	0.36†	387	0	0
SBI	36	353	0.12	351	2	0.01
SLD	225	252	0.53	199	53	0.21
Total	360	299	1.00	266	33	0.11
Therapeutic course						
BM	99	6,367	0.65	6,367	0	0
SBI	36	2,650	0.10	2,460	190	0.07
SLD	225	1,057	0.25	673	384	0.36
Total	360	2,677	1.00	2,418	259	0.10
Total (diagnostic and therapeutic)						
BM	99	6,754	0.62	6,754	0	0
SBI	36	3,003	0.10	2,811	192	0.06
SLD	225	1,309	0.28	872	437	0.33
Total	360	2,976	1.00	2,684	292	0.10

BM: bacterial meningitis; SBI: serious bacterial infection; SLD: self-limiting disease.
* Computed by cost savings/ costs current strategy
† E.g. computed by number BM patients × costs/number all patients × costs:
(99 × 387)/(360 × 299)

Table 4 presents the results of the sensitivity analysis compared to the base-case analysis (Table 3) with a mean saving of € 292 per patient (relative reduction of 10%). A 20% decrease or increase of inpatient nursing costs would save € 243 and € 341, respectively (a relative cost saving of 10% in both cases, similar to the base-case analysis). A 50% decline in the frequency of bacterial meningitis saved € 347, increasing the relative cost saving from 10% (base-case analysis) to 15%. Under the assumption that all diagnostic tests and therapeutic interventions other than those indicated by the diagnostic decision rule indeed would not be performed anymore, € 824 would be saved (relative reduction 32%). Using the rule in a general paediatric hospital with a relative lower frequency of bacterial meningitis and lower inpatient nursing costs, would result in a similar absolute cost saving compared to the base-case analysis (€ 283), but in higher relative cost savings (14%).

Discussion

In this study we estimated the possible cost reduction following the introduction of a diagnostic decision rule predicting the absence of bacterial meningitis in children with meningeal signs. Ruling out bacterial meningitis early in the diagnostic phase prevents unnecessary lumbar punctures and hospitalisations for empirical antibiotic treatment. The use of a diagnostic decision rule to guide the decisions when to perform a lumbar puncture and when to start empirical antibiotic treatment, will reduce total costs by 10% compared to current practice.

Savings of therapeutic costs mainly contribute to the total cost reduction (89%); diagnostic cost savings only with 11%. The cost reduction is inversely related to the frequency of bacterial meningitis in the population, since cost savings are attained particularly by reducing the resource use in patients with self limiting diseases. The absolute cost reduction is linearly related to inpatient nursing costs.

Table 4 Sensitivity analysis: mean costs per patient in Euro (€ 1 = $ 0.946)

	Current strategy	Decision rule	Cost-savings	Relative cost-savings
Base-case analysis	2,976	2,684	292	10%
Effect of inpatient nursing costs				
80% of base-case estimate	2,475	2,232	243	10%
120% of base-case estimate	3,477	3,135	341	10%
BM frequency 14% (50% decline of BM prevalence)	2,268	1,921	347	15%
Analysis without assumptions about impact of patients' clinical presentation on resource use	2,976	2,152	824	32%
Analysis using data of a general children's hospital*	1,994	1,711	283	14%

BM: bacterial meningitis

* Input data derived from Juliana Children's Hospital, The Hague, 1998: 17% BM, 9% SBI and 74% SLD among children with meningeal signs; inpatient nursery costs 80% of base-case input

The cost reduction in this study is the difference in (diagnostic and therapeutic) resource use between current practice in the Sophia Children's Hospital and as estimated after using the diagnostic decision rule. In order to extrapolate these results to other hospitals, main influencing factors on cost savings, according to the sensitivity analysis should be taken into account. The cost savings mainly depend on the inpatient nursing costs, the frequency of SLD patients among patients with meningeal signs and their hospitalisation rate. Under the assumption that a 40% reduction in hospitalisations for empirical treatment will be achieved in patients with SLD by the diagnostic decision rule (as was achieved in our analysis), a crude calculation of the cost savings per year can be computed by:

Number of patients with meningeal signs per year × % SLD patients × hospitalisation rate × 0.4 × length of hospital stay for empirical treatment × daily inpatient nursing costs

It should be noted that additional cost savings due to the reduction in diagnostic tests and empirical antibiotic use and those costs savings in patients with serious bacterial infections, etc. are not included in this crude estimate.

To appreciate the results of this study some topics need to be discussed. First, in our base-case estimate of costs of patient management following the use of our diagnostic decision rule, we took into account that patient management by the physician is influenced by the patients' clinical presentation. Neglecting this impact would grossly overestimate the cost-reduction: € 824 cost saving (32%) versus € 292 (10%) in the base-case analysis (Table 4). The assumptions on future

resource use per scenario, however, are based on current practice and are not evaluated further in this study. Evidence whether all these tests are indeed necessary to set a differential diagnosis after bacterial meningitis has been ruled out or for therapeutic management is lacking. Second, we distinguished three patient groups according to their true diagnosis, disease severity and necessity of treatment. The group of self-limiting diseases also included the aseptic and viral meningitis cases, since treatment of these patients is mainly symptomatic. [8] This assumption may need modification in future if antiviral treatment for enteroviral meningitis becomes available. Third, in this cost-minimisation study, our point of view was a similar effectiveness of the decision rule compared to current practice in terms of mortality and morbidity. In particular, the thresholds in Appendix 1 have been chosen in such a way, that applying our rule would miss no case of bacterial meningitis. One could, however, choose higher thresholds in the decision rule than those presented in Appendix 1 for the indication of a lumbar puncture or empirical treatment. These modified thresholds will change the initial diagnostic and treatment costs but will misdiagnose some cases of bacterial meningitis cases, as well. The extra diagnostic cost savings realised by varying these thresholds should be evaluated in view of the increased mortality and morbidity following misclassification of bacterial meningitis cases, incorporating the long-term costs and quality-adjusted-life-years lived in a particular health state associated with neurological sequelae after bacterial meningitis. [9] Such a cost-utility analysis, however, was beyond the scope of this study. Finally, cost savings by the rule were mainly determined by inpatient nursing costs and hardly affected by cost savings in the diagnostic phase. Therefore, it seems that using more diagnostic tests in order to prevent unnecessary hospitalisations results in a larger cost-effectiveness. More diagnostic tests, however, may lead to more false-positive diagnoses of bacterial meningitis, resulting in an increase of unnecessary treatments and, therefore, in a decrease in cost-effectiveness. [10,11] For this reason, we believe that the economic evaluation of any diagnostic rule should include the consequences of the rule on both the diagnostic and therapeutic management.

In conclusion, a diagnostic decision rule for children with meningeal signs at the emergency department will safely achieve a substantial cost reduction of diagnostic and therapeutic procedures. The largest cost reduction will be achieved in the therapeutic course. The amount of cost reduction in a particular setting mainly depends on the frequency of bacterial meningitis in the patient population to whom the rule is applied, the costs of inpatient nursing days and the frequency in which diagnostic and therapeutic procedures are actually used in the hospital. The relative contribution of these main determinants of cost savings may help to define key parameters in future economic studies of paediatric care.

Appendix 1 Diagnostic decision rule

Scoring algorithm of the clinical score

Characteristic		Points assigned if characteristic present	Patient score
Duration main problem in history		1 per day (max 10)	
Vomiting in history	yes	2	
	no	0	
Meningeal irritation at physical examination	yes	7.5	
	no	0	
Cyanosis at physical examination	yes	6.5	
	no	0	
Petechiae at physical examination	yes	4	
	no	0	
Disturbed consciousness at physical examination	yes	8	
	no	0	
Serum CRP (mg/l)	< 50	0	
	50 - 99	0.5	
	100 - 149	1.0	
	150 - 199	1.5	
	≥ 200	2.0	
Total clinical risk score (sum of scores)			

Scoring algorithm of the cerebrospinal fluid (CSF) score

Characteristic		Points assigned if characteristic present	Patient score
CSF polymorphonuclear cell count (per μl)	< 10	0	
	10 - 99	1	
	100 - 999	2	
	1000 - 9999	3	
	≥ 10,000	4	
CSF/blood glucose ratio	< 0.1	0	
	0.1 - 0.19	-0.5	
	0.2 - 0.29	-1.0	
	0.3 - 0.39	-1.5	
	0.4 - 0.49	-2.0	
	0.5 - 0.59	-2.5	
	0.6 - 0.69	-3.0	
	0.7 - 0.79	-3.5	
	0.8 - 0.89	-4.0	
	0.9 - 0.99	-4.5	
	≥ 1.0	-5.0	
Total CSF score (sum of scores)			

CSF score	Clinical risk score				
	< 9.5	9.5 - 10.4	10.5 - 12.9	13 - 19.9	≥ 20
<-3					
-3 to -2.5					
-2 to 0.5					
≥ 1					

	Neither indication for lumbar puncture nor for treatment
	Indication for lumbar puncture, but not for treatment
	Indication for lumbar puncture and for treatment

References

1. Oostenbrink R, Moons KGM, Twijnstra MJ, Grobbee DE, Moll HA. Children with meningeal signs: indication for therapeutic interventions. submitted 2001.
2. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
3. Bryant K, Marshall GS. Most cerebrospinal fluid cultures in children with bacterial meningitis are positive within two days. Ped Inf Dis J 1999;18:732-733.
4. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
5. Asch DA, Patton JP, Hershey JC. Knowing for the sake of knowing: The value of prognostic information. Med Decis Making 1990;10:47-57.
6. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. second edition. Oxford: Oxford University Press, 1997.
7. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Manual for cost evaluation, methods, guidelineprices for economic evaluation in health care. [in Dutch]. Amstelveen, The Netherlands: College voor zorgverzekeringen, 2000.
8. Rotbart HA. Enteroviral infections of the central nervous system. Clin Infect Dis 1995;20:971-81.
9. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980;302:1109-1117.
10. Pauker SG, Kassirer JP. Therapeutic decision making: a cost-benefit analysis. N Eng J Med 1975;293:229-234.
11. Kassirer JP. Our stubborn quest for diagnostic certainty. A cause of excessive testing. N Engl J Med 1989;320:1489-1491.

Cost-utility analysis of patient care in children with meningeal signs

4.2

Rianne Oostenbrink, Jan B Oostenbrink, Karel GM Moons, Gerarda Derksen-Lubsen, Marie-Louise Essink-Bot, Diederick E Grobbee, W Ken Redekop, Henriëtte A Moll

Submitted for publication

Abstract

Objectives: We designed a model to determine the consequences for the society of adequate diagnosis and treatment in patients with meningeal signs in terms of quality-adjusted life-years (QALYs) and costs.
Study design: Data were used from 360 children with meningeal signs (0.1 - 15 years), visiting the paediatric emergency department of the Sophia Children's Hospital Rotterdam, The Netherlands (1988 – 1998). Model inputs included probabilities of meningitis and adverse outcome, preference scores for years lived with long-term sequelae, and costs of tests and treatments. We estimated costs and effects of diagnostic and therapeutic interventions in children suspected of bacterial meningitis, we defined key determinants of the model outcomes, and evaluated alternative diagnostic strategies and two vaccination programmes in a cost-utility analysis.
Results: The population comprised 99 children with bacterial meningitis (adverse outcome in 10), 36 with serious other bacterial infections and 225 with self-limiting diseases. Key determinants of costs and health effects were the risk of bacterial meningitis or sequelae, costs of treatment and long-term morbidity. Minimising lumbar punctures and empirical treatments by use of a diagnostic decision rule, without missing a single case of meningitis, was a dominant strategy to actual practice. Vaccination strategies of *S. pneumoniae* and *N. meningitidis* resulted in our model in incremental cost-utility ratios of 401,965 €/QALY and 22,635 €/QALY, respectively.
Conclusions: Costs of long-term morbidity of bacterial meningitis largely outweigh diagnostic and treatment costs. Modelling interventions in children at risk of bacterial meningitis should include long-term consequences in terms of costs and QALYs.

Introduction

The presence of bacterial meningitis is suspected in a child with meningeal signs. Because of the severity of this illness, physicians have a low threshold to perform diagnostic tests and to start treatment. In about 60% of children with meningeal signs, however, no bacterial meningitis, but other (often self-limiting) diseases are diagnosed. [1,2] In spite of adequate diagnosis and treatment, bacterial meningitis is still associated with a 5% mortality and 10 - 15% morbidity. [3] The prognosis has not changed much by improvements in therapy. [4] Prevention of meningitis seems to be more promising. *Haemophilus influenzae* (HIB) vaccination has reduced the incidence of bacterial meningitis in young children considerably. [5-8] Research on *S. pneumoniae* and *N. meningitidis* vaccination is in progress. [9,10] The largest benefit of such interventions is probably to be found in the reduction of mortality and the long-term morbidity of bacterial meningitis and associated costs.

This study built on our earlier work in which we developed a diagnostic decision rule for the diagnosis and treatment of children with meningeal signs. [11,12] This decision rule aimed to reduce diagnostic and therapeutic procedures in children suspected of having bacterial meningitis, using predictors from clinical evaluation and early available laboratory tests of blood and cerebrospinal fluid for the absence or presence of bacterial meningitis. In the current study we modelled the consequences of adequate diagnosis and treatment in patients with meningeal signs in terms of quality-of-life and costs. The model takes into account the entire path of diagnosis, treatment and management of long-term sequelae from a societal perspective. By using this model, we could assess the impact of the decision rule on the costs of diagnosis and treatment of patients with meningeal signs and the consequences of misdiagnosis. Furthermore, by taking into account the long-term consequences of bacterial meningitis, we estimated the effect of vaccination programmes on total costs of care.

Methods

Diagnostic decision rule

In a large diagnostic study on children presenting with meningeal signs, a diagnostic decision rule was developed, to predict the presence or absence of bacterial meningitis. [11,12] This decision rule included two scoring algorithms: one to guide decisions on the need of a lumbar puncture, using characteristics from patient history (duration of the complaints and presence of vomiting), physical examination (presence of meningeal signs, petechiae, disturbed consciousness and cyanosis) and serum C-reactive protein (CRP), and a second one, to decide upon initiating empirical treatment, using cerebrospinal fluid (CSF) indices (CSF/blood glucose ratio and the absolute polymorphonuclear cell count). Hence, this decision rule allowed for classifying patients in groups of increased probability of bacterial meningitis at several steps in the diagnostic path, i.e. after

clinical evaluation and after performing a lumbar puncture. In its use, threshold values were introduced for the scores in order to reduce the number of lumbar punctures and empirical treatments in such a way that no single case of bacterial meningitis was misdiagnosed. For details on the rule we refer to previous publications. [1,12]

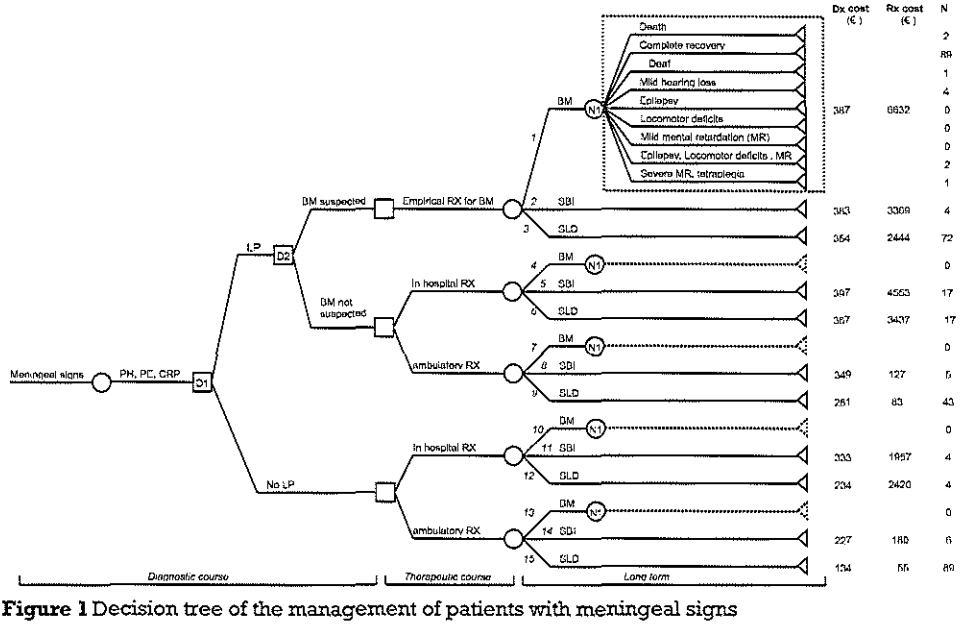

Figure 1 Decision tree of the management of patients with meningeal signs
PH: patient history; PE: physical examination; CRP: serum C-reactive protein; LP: lumbar puncture; BM: bacterial meningitis; SBI: other serious bacterial infection; SLD: self-limiting disease; DX: diagnostic; RX: treatment; N: number of patients per branch as observed in the data; D1: decision node 1; D2: decision node 2. Dashed lines indicate that similar outcomes occurs as after probability node 1 (N1); Numbers in italic refer to branch numbers as cited in text

Model design for cost-effectiveness analysis

We designed a decision tree, including the main possible diagnostic and therapeutic strategies in children presenting with meningeal signs (Figure 1). In the diagnostic course, physicians first need to decide whether or not a lumbar puncture is indicated as guided by the first part of our rule, using patient history, physical examination and serum CRP (D1 in Figure 1). Subsequently, based on the additional CSF analysis results, empirical antibiotic treatment may be started because of suspected bacterial meningitis, or other treatment because of suspected other diagnoses (D2). Accordingly, after node 2, patients with bacterial meningitis are correctly diagnosed and treated (branch 1 in Figure 1) or initially misdiagnosed and therefore, receive delayed treatment (branch 4, 7, 10 or 13). Any patient with bacterial meningitis may recover uneventfully, die or survive with long-term neurological sequelae, in frequencies related to adequate or delayed treatment. [3,13,14] Patients with meningeal signs, suffering from other

diagnoses than bacterial meningitis (BM) were divided into two distinctive categories, according to their need for therapeutic interventions: one with serious bacterial diseases (other than BM) and one with self-limiting diseases. Patients without bacterial meningitis could be diagnosed and treated (in hospital or ambulatory) correctly from presentation onwards, either or not undergoing a lumbar puncture, or empirically treated for suspected BM for three days on average (at that moment bacterial culture results are available [15]; branch 2 and 3 in Figure 1). In the model were included 1) the proportion of patients in each branch 2) costs of diagnosis and treatment per branch, 3) probabilities of mortality and sequelae after bacterial meningitis, 4) quality-adjusted life-years for patients' years lived in a particular health state with (and without) sequelae, and 5) costs of long-term sequelae. The time-horizon of the model was 15 years. Costs and life-years were discounted by 4% per year. [16] Discounting is based on the idea that a person prefers to enjoy benefits at the present rather than in the future (time-preference). [17] Hence, future costs and effects are valued lower than those that occur in the near future.

The proportion of patients in each branch was based on empirical data of the 360 children with meningeal signs (aged from 1 month up to 15 years) visiting the paediatric emergency department of the Sophia Children's hospital, Rotterdam, The Netherlands between 1988 and 1998 with meningeal signs as the reason for encounter.

The costs of diagnosis and treatment per branch were estimated by multiplying the resource use of each patient (using the empirical data) with the estimated average unit prices of diagnostic tests and therapeutic interventions. [18] Resource use included the emergency department visit, diagnostic tests performed at admission (laboratory and radiographic tests) or during clinical course, and in-hospital or ambulatory treatment (nursing days, attendance by paediatrician, and prescription of medication use). [19] Unit cost calculations in Euro (€ 1= $ 0.946; January 2001) were based on the financial accounts of the Sophia Children's Hospital, Rotterdam of 1996.

Probabilities of neurological sequelae after proper and delayed treated bacterial meningitis were derived from literature data. [3,13,14]

Preference scores for long-term health outcomes. Apart from perfect health and death, we distinguished in the model permanent health states associated with deafness, mild hearing loss, epilepsy, mild mental retardation, mild locomotor deficits, a combination of epilepsy, mild mental retardation and locomotor deficits and severe mental retardation with tetraplegia following bacterial meningitis. Health states associated with particular sequelae were valued by preference scores to express the relative severity of the sub-optimal health state with reference to perfect health (value 1.0) or death (value 0). These preference scores were derived from a study, in which vignettes describing these health states were classified by 28 paediatricians using a quality-of-life questionnaire (Health Utilities Index Mark 3; HUI-3). [20] Years lived in a particular health state were adjusted for quality-of-life in the model (QALYs) using these preference scores. Treatment of 'false-positives' (i.e. treating non-bacterial meningitis patients as if they had bacterial meningitis) was assumed not to have any long-lasting effect in

terms of mortality or morbidity compared to correct treatment.
Long-term costs of sequelae included inpatient and outpatient institutional care, special school attendance, medical supports (such as wheelchair, crutches, hearing aid), and supportive treatment by paediatrician, neurologist, physiotherapist, ergo-therapist. Cost-estimations were obtained from literature [21,22] and expert interviews. Costs of institutional care were derived from the financial account of a health care centre for mentally and physically disabled children and one for hearing disabled children in The Netherlands.

Analysis
First, the costs and effects of the diagnostic and therapeutic course were estimated for the 360 observed patients. Calculations of costs and quality-adjusted-life-years (QALYs) were performed using values for the inputs in the model as presented in Figure 1 and Table 2 (base-case values). Subsequently, we assessed in a sensitivity analysis the main determinants of the model's outcome by varying base-case values of model inputs over plausible ranges. Costs of procedures (of diagnostic and therapeutic course and in the long term) and probabilities of sequelae were varied by 20% of the base-case values. Sensitivity analysis of the preference scores included values obtained by parents valuing health states of children with bacteraemia [23], instead of those derived from questionnaire responses of paediatricians as used in the base-case analysis. The discount rate was varied from 0% to 8% and the time-horizon from 10 to 20 years. Then, costs and benefits of different management strategies of children with meningeal signs were estimated. Finally, as an example of the use of our model, we performed a cost-utility analysis on the effect of reducing the incidence of bacterial meningitis by introducing new vaccination strategies. Model outcomes were expressed in mean costs and QALYs per patient. Comparative results of two strategies were expressed in incremental cost-utility ratios with the cost difference as the numerator and the difference in quality-adjusted life-years as the denominator.

Results

Table 1 presents the general characteristics of the 360 children, initially presenting themselves with meningeal signs at the emergency department. Bacterial meningitis was diagnosed in 99 patients (28%), of whom two (2%) died, five (5%) were hearing disabled, one (1%) had severe retardation and tetraplegia, and two (2%) suffered from mild mental retardation, epilepsy, or locomotor deficits.

Table 1 General patient characteristics (n = 360)

Characteristic	Number (%)
Male gender	225 (62.5%)
Age (years)*	2.4 (0.8 - 5.3)
Outcome	
Bacterial meningitis	99 (28%)
Other bacterial infections†	36(10%)
Self limiting diseases‡	225 (62%)
Lumbar puncture performed	256 (71%)
Hospitalisation	217 (60%)
Intensive care hospitalisation	53 (15%)

*Mean (standard deviation)
†Other bacterial infections included septicaemia, urinary tract infections, pneumonia and bacterial gastro-enteritis
‡Self-limiting diseases included viral/aseptic meningitis (n = 45), upper respiratory tract infections (n = 94) and non-specified viral infections (n = 86)

Figure 1 presents the costs of the diagnostic and therapeutic course and the number of patients following a particular diagnostic and therapeutic strategy, as actually observed. Table 2 presents the estimated probabilities, preference scores and long-term costs associated with each possible outcome: perfect health, death and morbidity, as applied in the model. Application of the model on actual practice of the 360 children with meningeal signs resulted in mean total costs of € 8,393 per patient. Sixty-five percent of total costs were associated with long-term sequelae and 31% with therapy. Costs of the diagnostic course contributed to 4% of total costs, only. The mean QALYs without discounting was 14.5 on a time-horizon of 15 years. This means that the original time-horizon of 15 years was reduced by 0.5 QALYs due to mortality and morbidity. Discounting of the years lived in future compared to those lived in present further reduced the number of QALYs to 11.2.

Table 2 Model inputs for permanent sequelae and death after bacterial meningitis (BM)

Outcome	Probability after correct treatment of BM ¶	Probability after delayed treatment of BM †	Preference scores*	Long-term costs (€)
Death	4.5%	26.0%	0.0	0
Perfect health after survival	84.4%	22.1%	1.0	0
Deaf	5.1%	35.0%	0.47	12,000
Mild hearing loss	5.4%	NA	0.74	5,000
Epilepsy	0.5%	3.9%	0.78	1,500
Mild mental retardation (MR)	1.5%	11.7%	0.44	9,000
Mild locomotor deficits	0.5%	3.9%	0.68	9,000
Mild MR, epilepsy and locomotor deficits	1.0%	7.8%	0.28	13,000
Severe MR and tetraplegia	2.0%	15.6%	0.03	30,000

NA: not available
¶ Baraff et al. 1993 [3]
† Lebel et al. 1989 [13]
* estimated by Health Utilities Index Mark 3

Sensitivity analysis

The model outcomes were particularly sensitive to variations in the prior risk of bacterial meningitis in all patients with meningeal signs (i.e. the prevalence of bacterial meningitis in the population), the risk of sequelae after bacterial meningitis, costs of treatment and long-term follow-up, the time-horizon and to variation in the discount rate. In a comparison of management strategies (see below), however, variation of the latter two (time-horizon and discount rate) affected both strategies, such that the difference in costs or QALYs hardly changed. A 20% increase or decrease of the prior risk of bacterial meningitis in patients with meningeal signs, increased or decreased costs with 17%, respectively. Similarly, it decreased and increased the QALYs by 1%, respectively. A 20% increase or decrease of the risk of sequelae resulted in a 12% change of total costs and a 1% inverse change of total QALYs. A 20% variation in cost of treatment and long-term follow-up influenced total costs by 13% and 20%, respectively. The model was not sensitive to variation in diagnostic costs or to the use of other preference scores of long-term health outcomes.

Evaluation of different diagnostic strategies

The impact of different (diagnostic and therapeutic) management strategies that could be applied to children with meningeal signs on costs and QALYs is presented in Figure 2. Strategy 2 in the figure reflects actual practice in the study period, i.e. the application of a lumbar puncture and empirical treatment as observed in the actual practice. Strategy 3 reflects the results after using the above-described diagnostic decision rule, i.e. such that lumbar punctures and empirical treatment are minimised, without missing one case of bacterial meningitis. For comparison, we considered three additional hypothetical management strategies. Strategy 1 in the figure presents the results when every child with meningeal signs would undergo a lumbar puncture and empirical treatment until bacterial cultures are conclusive. Strategy 4 implies empirical treatment to be initiated in patients with a 5% probability of bacterial meningitis or higher only, as predicted by the decision rule. Following this strategy, 13% of children with bacterial meningitis would be misdiagnosed and treated with delay. In strategy 5 empirical treatment is never unnecessarily applied in patients without bacterial meningitis, resulting in misdiagnosis and delayed treatment in 56% of the children with bacterial meningitis. Total costs and QALYs and costs of the diagnostic and therapeutic course and in the long term, separately were computed for these five strategies, which range from very conservative to very reluctant management. Strategy 3 led to the lowest total costs (€ 8,094) and highest QALYs (11.19). More conservative strategies (strategy 1 and 2) were related to higher costs (increase of € 1,243 and € 299, respectively), but achieved a same number of QALYs. Less conservative strategies (strategy 4 and 5) were related to higher costs (increase of € 845 and € 11,069, respectively) and a reduction of QALYs (0.08 and 0.86 QALYs, respectively) due to increased mortality and morbidity after misdiagnosed and delayed treated bacterial meningitis.

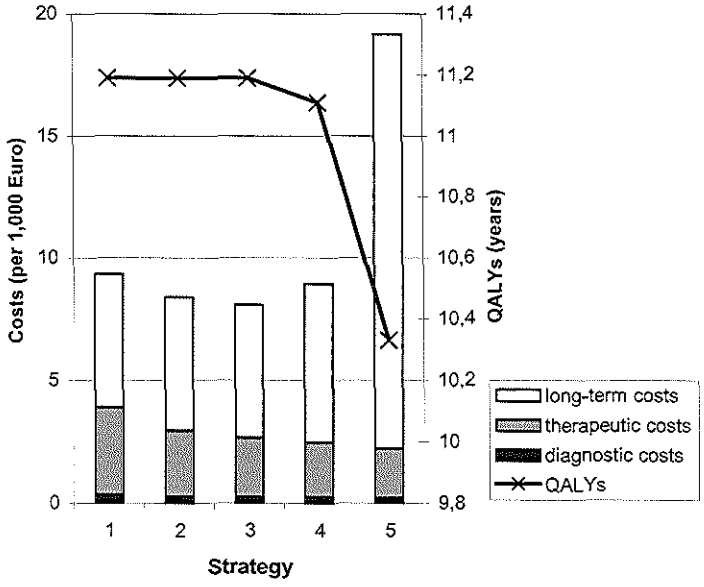

Figure 2 Costs of different management strategies in children with meningeal signs
1 Lumbar puncture and empirical treatment in all
2 Lumbar punctures and empirical treatment as observed in data
3 Minimal use of lumbar punctures and empirical treatment, without missing one case of bacterial meningitis
4 No empirical treatment in patients with a predicted risk of bacterial meningitis < 5%.
5 No empirical treatment in any patient without bacterial meningitis

Effect of new vaccination strategies

In this section we will illustrate how the model can be used in evaluating the potential long-term effects of *S. pneumonia* (SP) or *N. Meningitidis* (NM) vaccination. The results are summarised in Table 3. In the Netherlands nearly 450 cases of bacterial meningitis (BM) annually occur in children < 15 years. [24] Assuming that 'meningeal signs' is the main presenting symptom in 50% of patients with BM [2,25] and that BM is present in 20% of patients with meningeal signs, as observed in our study after the use of routine HIB-vaccination of infants [11], about 1,125 children annually visit the emergency department with meningeal signs in the Netherlands. By using our decision model described above, total costs and QALYs in these 1,125 patients with meningeal signs, of whom 225 having true bacterial meningitis (20%), would be € 7,342,875 and 12,701 QALYs, respectively (Table 3; base-case).

To estimate effects of SP-vaccination, we estimated that routine SP-vaccination (including 3 doses) in the Netherlands would cost € 9,591,701, annually (195,749 infants), and could achieve a 51% reduction of SP-meningitis (data obtained from the Dutch National Institute of Public Health [26]). Assuming a similar pathogen

distribution in children with meningeal signs as observed in our data (77% NM, 12% SP and 11% other pathogens), SP-vaccination with a 51% effectiveness would prevent 14 patients with SP-meningitis in this population each year (225 × 0.12 × 0.51). Mean model outcomes then were € 6,996,375 and 12,724 QALYs (Table 3). Taking into account the costs of vaccination (€ 9,591,701), SP-vaccination led to a net cost increase of 9,245,201 and a QALY increase of 23 years: incremental cost-utility ratio 401,965 €/QALY.

To estimate the effects of NM-vaccination, we assumed that routine NM-vaccination (including 4 doses) would cost € 6,068,219, annually, and achieved a 64% reduction of NM-meningitis. [26] NM-vaccination would then prevent 111 patients with NM-meningitis in the population each year (225 × 0.77 × 0.64). Using our model this resulted in € 4,581,000 and 12,859 QALYs (Table 3). Taking into account the costs of vaccination, the incremental cost-utility ratio was 22,635 €/QALY.

Table 3 Effects of new vaccination strategies

	Costs (€)	Incremental costs (€)*	QALYs	Incremental QALYs*
Base-case (1125 children with meningeal signs, 20% BM)	7,342,875		12,701	
SP vaccination effects				
Model outcome	6,996,375		12,724	
Costs of vaccination	9,591,701			
Total	16,588,076	9,245,201		23
NM vaccination effects				
Model outcome	4,581,000			
Costs of vaccination	6,068,219		12,859	
Total	10,919,219	3,576,344		158

*Costs and QALYs incremental to the base case costs and QALYs

Discussion

To determine the impact of adequate management of children with meningeal signs in terms of survival, quality-of-life and total costs of care, we have designed a model incorporating the entire management path including diagnosis, treatment and management of long-term prognosis. The total costs are mainly determined by the costs associated with long-term morbidity after bacterial meningitis. The model is most sensitive to the prior probability (prevalence) of bacterial meningitis in patients with meningeal signs, the risk of neurological sequelae after meningitis, and the costs associated with long-term neurological sequelae. This model allows to assess the impact of different management strategies on total costs and QALYs. More conservative use of diagnostic and therapeutic interventions increases total costs only slightly. These strategies, however, do not improve the outcome and increase the patient burden by unnecessarily undergoing a lumbar puncture and hospitalisation. Less conservative approaches, that may lead to delayed diagnosis and treatment of bacterial meningitis, have a large impact on costs and QALYs associated with long-term sequelae, These costs largely overrule the small savings in the diagnostic and therapeutic course.

In diagnostic and therapeutic management of a patient with meningeal signs, the physician implicitly considers the trade-offs to administer or to withhold therapy, or to order additional tests. [27] If the consequences of missing a diagnosis are serious, as is the case in children suspected of bacterial meningitis, physicians have a low threshold to perform additional tests. [28,29] Diagnostic tests aim to discriminate between diagnoses. As a consequence, they will influence choices on therapeutic strategies and outcome. [30,31] This study has explicitly shown from a cost perspective that it is not worth running the risk of missing one case of bacterial meningitis by reducing diagnostic tests. Furthermore, we showed that a change in diagnostic strategies particularly influences the therapeutic strategy and prognostic outcome and their associated costs and QALYs. This underlines the importance of including these long-term effects in the evaluation of diagnostic strategies. Previous studies evaluating the costs and outcome following different diagnostic strategies of children at risk of bacterial meningitis [32,33], have not incorporated the long-term consequences in terms of QALYs and costs, both.

Key determinants of the model outcome are the prior probability of bacterial meningitis, the risk of sequelae after bacterial meningitis, and the costs of treatment and long-term follow-up. Although uncertainties may exist in estimates of the latter, we think that variation in their estimates will not lead to materially different conclusions. The risk of sequelae after meningitis could be derived with adequate certainty from literature data. [3,13,14] Since the risk of mortality and morbidity is related to pathogen type [3], this aspect should be taken into account when applying the model to populations with very different pathogen distributions. The sensitivity of the model to the prior probability of bacterial meningitis allowed us to use the model for evaluation the impact of new vaccination strategies on the outcome, as will be discussed below. The fact that the model was mainly sensitive to long-term costs and less to diagnostic and therapeutic costs (which may vary among hospitals), increases the generalisability of the model. The frequency of health states associated with low preference scores in patients with meningeal signs was relatively low. As a consequence, the model outcome in terms of QALYs was hardly sensitive to small variations of model inputs.

Guidelines for economic evaluations recommend to use a time-horizon that allows inclusion of all relevant costs and effects. [16] Instead of using the life expectancy of the study population, we restricted the time-horizon in the current study to 15 years. The main reason for this was the uncertainty around the long-term costs and preference scores. Costs and quality-of-life not only depend on the severity of sequelae, but also on other situation-specific factors. [34,35] For instance, whether a child lives in institutional care or at home highly depends on the care-givers' social and financial capacity and on facilities available in the situation the patient lives in. This increases the uncertainty of costs and quality-of-life estimates. We do not think, however, that the inclusion of a longer time-horizon would substantially have affected the outcomes of the model. First, the model aims at incremental analyses comparing two different management strategies. Hence, differences in

costs and effects are important rather than the absolute values of one strategy. Secondly, due to discounting, the effect of future costs and QALYs is limited compared to the effect of these variables in more recent years.

To illustrate further applications of the model, we estimated the long-term effect of the introduction of *S. pneumoniae* (SP) and *N. meningitidis* (NM) vaccination. It should be noted that this example concerns children initially presenting with meningeal signs, only, and does not include all patients with meningitis. Furthermore, our simplified example does not consider all consequences of vaccination thoroughly. First, the risk of an adverse outcome was assumed to remain stable in the model, although SP is known to carry a higher risk of sequelae than NM. [3] Second, we did not consider the reduction of other invasive infections by vaccination, such as pneumonia and otitis due to SP [22] or meningococcal septicaemia and their subsequent mortality or morbidity. Consequently, overall cost savings and gain in QALYs are underestimated. Third, side effects of vaccination and associated costs were not included. Finally, in contrast to the costs of the vaccination program, that are occurring in the present, the benefits of vaccination (reduction of long-term morbidity and related costs) will occur in future. Since the model included a discount rate of costs and benefits in future, the beneficial effects of vaccination are valued relatively less than their present costs. Estimation of effects of vaccination programmes in a model without discounting the benefits resulted in lower cost-utility ratios of 271,918 €/QALY and 18,724 €/QALY for pneumococcal and meningococcal vaccination, respectively (a 32% and 17% decrease of the cost-utility ratios, respectively). Although discounting costs is generally accepted by the investment argument, it is questionable to discount the future benefits of preventive measures. [36] Our model, however, shows how to assess the cost-effectiveness of vaccination programmes including the long-term consequences on survival, morbidity and associated quality-of-life following from bacterial meningitis. According to our model, vaccination against SP and NM would gain QALYs in future at certain costs in present. Of course, it remains to be discussed whether the gain in QALYs is worth the additional costs. Some authors have proposed criteria when to recommend a technology to be introduced. Strong evidence for adoption would exist for technologies with incremental cost-utility ratios of 20,000 €/QALY or less, and a moderate evidence for those with incremental cost-utility ratios of 100,000 €/QALY or less. [37] Decisions on whether or not to introduce a new technology, however, may be influenced by other considerations than the economic aspects, such as ethical or political reasons, or personal preferences, as well.

In conclusion, costs of long-term morbidity of bacterial meningitis largely outweigh the costs of initial diagnosis and treatment of children suspected of bacterial meningitis. In a model for accurate evaluation of preventive, diagnostic or therapeutic interventions in children at risk of bacterial meningitis, these long-term costs and QALYs should be considered.

References

1. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
2. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures [see comments]. Clin Pediatr (Phila) 1990;29:254-5, 258-61.
3. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993;12:389-94.
4. McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. JAMA 1997;278:925-31.
5. Adams WG, Deaver KA, L. CS, et al. Decline of childhood haemophilus influenzae type b (Hib) disease in the Hib vaccine era. JAMA 1993;269:221-226.
6. van Alphen L, Spanjaard L, van de En Avd, Dankert J. Absence of *H. Influenzae* type b (Hib) meningitis in the Netherlands in twice vaccinated children. [in Dutch, English summary] Ned Tijdschr Geneeskd 1995;139:880-884.
7. Conyn-van Spaendonck MA, Veldhuijzen IK, Suijkerbuijk AW, Hirasing RA. Significant decline of the number of invasive Haemophilus influenzae infections in the first 4 years after introduction of vaccination against H. influenzae type B in children [in Dutch, English summary]. Nederlands Tijdschrift voor Geneeskunde 2000;144(22):1069-73.
8. Dawson KG, Emerson JC, Burns JL. Fifteen years of experience with bacterial meningitis. Ped Infect Dis J 1999;18:816-822.
9. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatric Infectious Disease Journal 2000;19(3):187-95.
10. Borrow R, Richmond P, Kaczmarski EB, et al. Meningococcal serogroup C-specific IgG antibody responses and serum bactericidal titres in children following vaccination with a meningococcal A/C polysaccharide vaccine. FEMS Immunology & Medical Microbiology 2000;28(1):79-85.
11. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
12. Oostenbrink R, Moons KGM, Twijnstra MJ, Grobbee DE, Moll HA. Children with meningeal signs: indication for therapeutic interventions. submitted for publication.
13. Lebel MH, McCracken GH, Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989;83:161-167.
14. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990;323:1651-7.
15. Anttila M. Clinical criteria for estimating recovery from childhood bacterial meningitis. Acta paediatr 1994;83:63-67.
16. Riteco JA, de Heij LJM, van Luijn JCF, Wolff I. Dutch guidelines for pharmacoeconomic research. Amstelveen [in Dutch]. The Netherlands: College voor zorgverzekeringen, 1999.
17. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. Jama 1996;276(15):1253-8.
18. Oostenbrink R, Oostenbrink JB, Moons KGM, et al. Cost reduction by introduction of a diagnostic decision rule in children with meningeal signs. submitted for publication 2001.
19. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. second edition. 2nd ed. Oxford: Oxford University Press, 1997.
20. Oostenbrink R, Moll HA, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis - a head -to-head comparison. Submitted 2001.
21. Fendrick AM, Lee JH, LaBarge C, Glick HA. Clinical and economic impact of a combination Haemophilus influenzae and Hepatitis B vaccine: estimating cost-effectiveness using decision analysis. Archives of Pediatrics & Adolescent Medicine 1999;153(2):126-36.
22. Lieu TA, Ray GT, Black SB, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. Jama 2000;283(11):1460-8.
23. Bennet JE, Sumner W, Downs SM, Jaffe DM. Parents' utilities for outcomes of occult bacteremia. Arch Pediatr Adolesc Med 2000;154:43-48.

24. Anonymous. Bacterial meningitis in the Netherlands. Annual report 1999. Amsterdam, The Netherlands: Netherlands reference laboratory for bacterial meningitis, Academic Medical Center and National Institute of Public Health and the Environment, 2000.
25. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
26. Bos JM, Rumke HC, Welte R, Postma MJ, Zwanepol E, Jager JC. Cost-effectiveness of vaccination of peumococcal and meningococcal infections in children [in Dutch]. Bilthoven, The Netherlands: National Institute of Public Health and the Environment, 2000.
27. Sox HC, Jr. Probability theory in the use of diagnostic tests. An introduction to critical study of the literature. Annals of Internal Medicine 1986;104(1):60-6.
28. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. Jama 1997;277(6):488-94.
29. DeKay ML, Asch DA. Is the defensive use of diagnostic tests good for patients, or bad? Med Decis Making 1998;18:19-28.
30. Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
31. Sassi F, McKee M, Roberts JA. Economic evaluation of diagnostic technology. Int J Technology Assessment in Health Care 1997;13:613-630.
32. Lieu TA, Schwartz JS, Jaffe DM, Fleisher GR. Strategies for diagnosis and treatment of children at risk for occult bacteremia: clinical effectiveness and cost-effectiveness [see comments]. J Pediatr 1991;118:21-9.
33. Downs SM, McNutt RA, Margolis PA. Management of infants at risk for occult bacteremia: a decision analysis. J Pediatr 1991;118:11-20.
34. Rosenbaum P. Measuring the quality of life for disabled children. Balliere's Clin Paediatr 1996;4:527-542.
35. Jenney ME. Theoretical issues pertinent to measurement of quality of life. Med Pediatr Oncol 1998;Suppl:41-5.
36. Weinstein MC. Economic assessments of medical practices and technologies. Med Decis Making 1981;1:309-330.
37. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J 1992;146:473-481.

3 Diagnostic research in paediatrics

Diagnostic research in paediatrics: prospects and problems

5.1

Rianne Oostenbrink, Karel GM Moons, Sacha E Bleeker, Henriëtte A Moll, Diederick E Grobbee

Submitted for publication

Abstract

Diagnostic practice is a sequential process starting with a patient with a particular set of signs and symptoms. In diagnostic research, the issue is to determine the added value of a diagnostic test to the information already available. Electronic patient files including data from routine patient care receive increased attention in medical science, and are supposed to facilitate scientific research and evaluation of routine care. Various problems arise, however, using routine care databases in diagnostic research. First; most databases do not label patients by their symptoms or signs but by their final diagnosis. Second; in routine care the diagnostic work-up of a patient is by definition determined by previous diagnostic (test) results. Therefore, routinely documented data are subject to so-called work-up bias. Third; the reference test is in practice always interpreted with knowledge of the preceding test information, such that in scientific studies the diagnostic value of a test under evaluation is commonly overestimated. Fourth; routinely documented databases are likely to contain missing data. In this paper we will elaborate on these four problems in diagnostic research using routine care data and discuss whether and how they can be overcome.

Introduction

Diagnostic practice is a sequential, stepwise process starting with a patient with a particular set of signs and symptoms. In order to ascertain or rule out a diagnosis, the physician decides upon additional tests based on his findings in previous steps, to increase or decrease the probability of a particular disease (target disease). Hence, to serve practice, diagnostic research should follow the sequential process of making a diagnosis in practice and quantify the added value of a diagnostic test to information already available. [1,2] Although this is recognised by various authors [2,11], most prevailing diagnostic research still focus on the value of a single test (so-called test research) in patients selected on the presence or absence of the disease. But, as we will discuss below and as mentioned by others [12], test research does not cohere with clinical practice. The fact that test research is the most prevailing kind of diagnostic research is probably because, in contrast to therapeutic research, a general methodological framework for diagnostic research hardly exists. The limited literature on methodology mainly describes test research. [10,13-16]

The use of electronic patient files and the construction of large databases including data from routine patient care is of growing interest in medical science. In theory, such databases may include all patient data that are relevant to ascertain a diagnosis in routine practice in hospital or by the general practitioner. Hence, the data allow to quantify the value of diagnostic tests additional to other (previously) obtained diagnostic information, which is the relevant knowledge for clinical practice. It has been argued, however, that diagnostic research using data from routine care may not provide valid results. [3,5,8] In this paper we consider the advantages and disadvantages of routine care data for diagnostic research. We first put forward the nature of diagnosis in practice and the preferred design for evaluating diagnostic tests. Subsequently, we will summarise the potential problems that may occur when using routine care data and discuss how these problems may be handled. This will all be illustrated by a clinical study on diagnostic procedures in children suspected of having bacterial meningitis at a paediatric emergency department.

Clinical example

At the emergency department of the Sophia Children's Hospital, Rotterdam, The Netherlands, we performed a study on children visiting the emergency department because of meningeal signs. [17,19] These children pose a diagnostic dilemma for the physician, because they are at risk of bacterial meningitis (target disease [16]), but may have self-limiting diseases in 50 - 60% as well. [18,20,21] The question is in which of these children a lumbar puncture should be performed and empirical antibiotic treatment should be started, such that not a single case of bacterial meningitis will be missed. Therefore, a prediction rule for bacterial meningitis was derived and validated in children presenting with meningeal signs at the emergency department. The rule included independent predictors of bacterial meningitis, obtained from patient history, physical examination and laboratory tests of blood and cerebrospinal fluid as performed in routine care. For further details, we refer to previous publications. [17,19]

Diagnostic practice and the nature of diagnostic research

In practice, a diagnosis starts with a patient with a clinical problem (symptoms or signs) and suspected of having a particular disease, the so-called target disease [2,7,22] In our example this would be children with meningeal signs, suspected of having bacterial meningitis. As shown in Figure 1, the physician commonly applies a phased work-up starting with patient history and physical examination. Subsequent steps in general may be additional laboratory tests of e.g. blood or urine, imaging or other invasive tests such as in our example a lumbar puncture. After each phase the physician will consider the available diagnostic information to implicitly estimate the probability of the presence of the target disease ($p(D+|ph, pe)$ or $p(D+|ph, pe, t1)$ in Figure 1). [2,11] In patients with a very low

probability of the target disease, the physician may refrain from further diagnostic testing for that disease, and if necessary, search (or test) for the presence of alternative diseases or even discharge the patient. In patients with a high target disease probability, treatment will be initiated. As long as uncertainty remains, further diagnostic tests are applied until a treatment decision (including no treatment) can safely be made. In this sense, to set a diagnosis is to know that more information would not change the decision to act as if the patient has the disease; to rule out a disease is to know that more information would not change the decision to act as if the patient did not have the disease. [23-25]

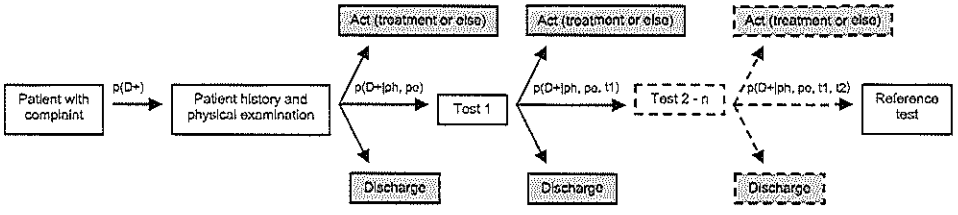

Figure 1 Illustration of a typical diagnostic process in clinical practice
PH: patient history; PE: physical examination; t1: result of test 1; t2 - n: result of test 2 up to test n; Dashed elements not necessarily occur in all patients
p(D+): probability of disease; p(D+ | ph, pe): probability of disease given the information from ph and pe

Diagnostic research is pragmatic research, meaning that it should reflect the (sequential) process of diagnostic practice. In the conventional outlook of diagnostic research (i.e. 'test research'), however, the test result appears to be the central source of information. Commonly this test result is expressed as a function of presence or absence of the illness in terms such as sensitivity and specificity. [2,6,7,10,11,25] In practice, however, as illustrated in Figure 1, every test is evaluated with reference to preceding information and a diagnosis is set by considering all information combined. Setting a diagnosis is of multivariate concern per se. Furthermore, in most diagnostic research patients are selected on the known presence or absence of a particular disease (i.e. that they had undergone the reference test). For example, studies on the diagnosis of meningitis selected patients with (by lumbar puncture) proven presence or absence of bacterial meningitis and compared the frequency of symptoms of those with and without bacterial meningitis. [26,27] Such study design and analysis, however, does not inform about the probability of the presence or absence of a disease in patients with a particular set of symptoms or signs. [25] Patient selection on the presence or absence of a diagnosis leads to inclusion of selected patient groups and will overestimate the true value of the evaluated tests. [2-5,8,9,12] Also, studies on the value of a particular diagnostic test (e.g. routine blood values) only include those patients that had undergone that test. [28] But, in practice, a physician

refers patients selectively for additional diagnostic tests, based on previous findings (Figure 1). Thus, selection on whether a patient underwent a particular test or not, is influenced by the physicians work-up, which will, again, leads to biased estimates of the sensitivity and specificity of that particular test. [3,5,8,29,30].

To serve clinical practice, diagnostic research should quantify which findings contribute to the estimation of the probability of the presence or absence of the disease. [2,31,32] The motive of such research is efficiency. From this, it follows that every finding that may contribute to probability estimation should be considered. To this aim routinely documented data may be used, since they in principle comprise all patient data that may be relevant to ascertain a diagnosis in practice. Furthermore, as routinely documented data include the entire diagnostic and therapeutic process, they allow for the stepwise analysis of tests in the sequence as they occurred in routine practice, and to estimate their added value. [2,33]

Problems of using routine data

Selection of the proper patient population

As discussed above, in diagnostic research patients should be selected on the symptoms or signs by which they come to the physician's attention. [2,5,8,9,11,31,32] In our example, we selected children presenting themselves with meningeal signs. The aim was to determine the independent (added) value of diagnostic tests (including patient history and physical examination items) in the discrimination between presence or absence of bacterial meningitis. This selection included the complete spectrum of differential diagnoses of patients with meningeal signs conform practice. [18] Of course this population did not reflect all patients with meningitis, since meningitis may be present without meningeal signs [34,35], but that was the purpose of the study. To enhance the applicability of diagnostic study results in future patients, they should be selected on a same, clearly defined, patient profile, by which they may visit the physician. [22,36,37]

The selection of patients on symptoms or signs is often not feasible in studies using existing databases, since most patient classification systems in hospitals are based on the final diagnosis. The presence of a *problem-oriented* patient classification system, however, allows to perform (retrospective) diagnostic studies with patients selected on their clinical profile. Such a classification system has been used in the Sophia Children's Hospital, Rotterdam since 1988. In this system, presenting problems are classified first by organ system and subsequently by a sign or symptom, an abnormal laboratory result or a presumed diagnosis. The main reason for consulting the outpatient or emergency department is prospectively coded for each patient by one of the paediatricians. [38,39] Using this coding system, we could identify all children with 'meningeal signs' as the main reason for encounter. To include such a problem oriented coding system in the hospital registration may be recommended to other hospitals interested in diagnostic research.

Verification bias

Ideally, in diagnostic research all patients suspected of a particular disease have the same diagnostic work-up, i.e. undergo the same diagnostic phases, including the reference test for the outcome diagnosis. As reference tests sometimes convey a (mortality) risk, are invasive or expensive, the results from such a test are not always routinely available in all patients. This is particularly likely in patients with a low probability of the target disease based on previous information. [3,5,6,40-42] For research purposes, the clinical course over time or a combination of test results (so-called 'consensus diagnosis') is often used to define the final diagnosis in such patients without a reference test result. [32,40,43] Such an approach is not uncommon in diagnostic studies. [44,45] Of course, such an assessment of the final diagnosis is not as 'established' as perhaps preferred for research and the true diagnosis may even be missed. This misclassification in the diagnostic outcome categories may result in a biased value of tests under study (verification or work-up bias). In case of a disease that is fatal or rapidly progressing without treatment, however, it seems reasonable to consider the target disease to be absent if the patient that did not undergo the reference test recovers without treatment. Target diseases with a subclinical or self-limiting course, however, are easily subject to misclassification, leading to work-up bias. [3,12,42] In our example, the outcome diagnosis was the presence or absence of bacterial meningitis, which is a rapidly progressing disease without treatment. [46] In patients without a lumbar puncture, bacterial meningitis was ruled out based on an uneventful clinical course without treatment. An alternative outcome definition would have been the presence or absence of meningitis (including bacterial, viral en aseptic, defined by bacteriologic and viral cultures from cerebrospinal fluid). Since viral meningitis, if untreated, may recover uneventfully [47], this alternative would have increased misclassification and biased the results.

Blinding

If the reference test is interpreted using information from preceding tests, this may overestimate the diagnostic value of the preceding test, also referred to as 'incorporation bias', 'test review bias', or 'diagnostic review bias'. [6,9,18,32,48] Blinding the interpreter of the reference test from the test under study prevents this incorporation bias. In practice, however, each test is always considered with knowledge of other information. Hence, in diagnostic studies using routinely documented data such blinding is commonly not guaranteed. But, a reference test yielding merely objective results, i.e. not based on subjective interpretation (as is the case with imaging tests), nor influenced by preceding information, does suffer less from this potential bias. In such instances, the reference test result as found in the routine care data can be used validly. In our example [17,19], the reference test included an increased cell count in cerebrospinal fluid (CSF) and a positive culture from CSF of blood, which is rather objective and not influenced by subjective interpretation.

Missing data and analysis

Missing data are more likely in routinely documented data than in prospectively collected data. Standard data analytical techniques exclude subjects with a missing value on a variable. [49,50] Consequently, the data-analysis in diagnostic research commonly includes cases without missing data only. In case of a high frequency of missing data or if many variables are considered, this may grossly reduce the number of patients to be included in the analysis and therefore the power of the study. Furthermore, this 'complete case' analysis may yield biased results, since the cases excluded because of missing data may systematically differ from the complete cases. [49-52] A patient with a very severe condition, for example, is probably referred for more sophisticated diagnostic tests, before full completion of patient history and physical examination. On the other hand, in a patient presenting with a disease of very low severity, additional test information may be incomplete, as the physician ruled out a serious disease early in the diagnostic process and did not consider additional tests to be necessary. In routine care data, therefore, results of diagnostic tests are often missing simply because the decision whether or not to perform the test is based on clinical judgement of the patient by the physician (Figure 1). [24] Missing data in routine care tend not to occur at random, but for a reason, e.g. 'on indication'.

Imputation techniques may serve to overcome the selection bias due to missing data in diagnostic research using routine patient care data and to increase the efficiency of the analysis. Frequently applied methods, e.g. imputation of mean values of available data or the so-called 'indicator method', however, may also lead to biased estimates. [50-52] More recent methods, i.e. the maximum-likelihood method and multiple imputation, have been proposed which seem to yield valid estimates. These imputation methods use all information available from the actually documented data to impute the missing values. Furthermore, multiple imputation allows to incorporate the uncertainty among the imputed value. [50-52] By multiple imputation each missing data is imputed more than once in a Bayesian way, such that multiple databases with complete data are obtained. Repeating the analyses on each of the imputed datasets and averaging the results according to standard statistical techniques [50] will result in unbiased estimates of the regression coefficients and their standard errors. The number of repeated imputations depends on the fraction of missing data. In case of missing values up to 50%, reliable inferences can be obtained by using five imputations. [52] The multiple imputation method is an accepted and valid statistical method for the problem of missing data, as long as the probability of missing depends on observed values only. [50-52] The allowable proportion of missing data in order to obtain valid results using routine care data in diagnostic research, however, is not known. It may be argued that diagnostic items with a very high proportion of missing data should be excluded from the analysis anyway, since they are presumably difficult to obtain in practice, often unavailable or not considered clinically important.

Given a complete dataset after proper imputation, routinely documented data including the entire, stepwise, diagnostic work-up and the clinical course facilitate proper analysis of diagnostic tests in the sequence as they commonly occur in routine practice. In contrast to single test evaluation or test research, multivariate logistic regression modelling allows for probability estimation of the presence of a disease as a combined function of available characteristics from patient history, examination and additional laboratory tests. [1,2,25,31,49] This probability estimation based on all diagnostic information together, directly coheres with the diagnostic process in practice. Moreover, the logistic model obviates the need for sensitivity, specificity or likelihood ratio. The discriminative value of a diagnostic model can be expressed by the area under the Receiver Operator Characteristic curve (ROC-area). [53,54] From such a logistic model a prediction or decision rule can be derived, that is easy applicable in practice. Of course, before introducing a diagnostic rule in clinical practice, prospective application of the rule in a new group of similar patients is necessary to get insight in the rule's usefulness and its impact on the diagnostic process in practice. [25,49] For specific details on methods of analysis we refer to the statistical literature. [1,2,31,53-59]

Conclusion

For meaningful and valid inference, diagnostic research needs to reflect the sequential diagnostic work-up of clinical practice. It starts with patients selected on their disease suspicion, who underwent all clinically relevant steps in the diagnostic work-up. Preferably, the reference test is interpreted independently from the preceding information. Commonly, the diagnostic added value of tests is of interest, with reference to the preceding information available from patient history and physical examination. After some adjustments such as imputation of missing data if necessary, valid and useful diagnostic research may be based on routinely documented data including the whole diagnostic, therapeutic and prognostic phase as recorded in routine practice.

References

1. Moons KGM, van Es GA, Deckers JW, Habbema JDF, Grobbee DE. Limitations of sensitivity, specificity, likelihood ratio, and Bayes' theorem in assessing diagnostic probabilities: a clinical example. Epidemiology 1997;8:12-17.
2. Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Redundancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
3. Begg CB. Biases in the assessment of diagnostic tests. Stat Med 1987;6:411-23.
4. Diamond GA. Selection bias and the evaluation of diagnostic tests: a metadissent. J Chron Dis 1986;39:359-360.
5. Knottnerus JA, Leffers JP. The influence of referral patterns on the characteristics of diagnostic tests. J Clin Epidemiol 1992;45:1143-1154.
6. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med 1978;299:926-30.
7. Sackett DL. A primer on the precision and accuracy of the clinical examination. JAMA 1992;267:2638-2644.

8. van der Schouw YT, van Dijk R, Verbeek ALM. Problems in selecting the adequate patient population from existing data files for assessment studies of new diagnostic tests. J Clin Epidemiol 1995;48:417-422.
9. Jaeschke R, Guyatt G, Sackett DL. Users'guides to the medical literature. III: How to use an article about a diagnostic tests. A. Are the results ofthe study valid? JAMA 1994;271:389-391.
10. Feinstein AR. Clinical Epidemiology: the architecture of clinical research. Philadelphia: WB Saunders Company; 1985.
11. Grobbee DE, Mietingen OS. Clinical epidemiology introduction to the discipline. Neth J Med 1995;47:2-5.
12. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. Jama 1999;282:1061-6.
13. Dalla-Palma L, Dixon AK, Durand-Zaleski I, Reiser M, Soimakallio S. An overview of cost-effective radiology. Eur Radiol 1997;7:147-50.
14. Mackenzie R, Dixon AK. Measuring the effects of imaging: an evaluative framework. Clin Radiol 1995;50:513-18.
15. Guyatt GH, Tugwell PX, Feeny DH, Haynes RB, Drummond M. A framework for clinical evaluation of diagnostic technologies. Can Med Assoc J 1986;134:587-594.
16. Sackett DL, Haynes RB, Tugwell P. Clinical epidemiology; a basic science for clinical medicine. Boston: Little, Brown & Co; 1985.
17. Oostenbrink R, Moons KGM, Twijnstra MJ, Grobbee DE, Moll HA. Children with meningeal signs: indication for therapeutic interventions. submitted for publication 2001.
18. Oostenbrink R, Theunissen CCW, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Signs of meningeal irritation at the emergency department; how often bacterial meningitis? Ped Emerg Care, in preparation 2001.
19. Oostenbrink R, Moons KGM, Donders ART, Grobbee DE, Moll HA. Prediction of bacterial meningitis in children with meningeal signs: reduction of lumbar punctures. Acta Paediatrica, in preparation 2001.
20. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
21. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr (Phila) 1990;29:254-5, 258-61.
22. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11:88-94.
23. Moons KGM, Stijnen T, Michel BC, Büller HR, Grobbee DE, Habbema JDF. Treatment thresholds in diagnostic test evaluation: an alternative approach to the comparison of areas under the receiver operating characteristic curve. Med Decis Making 1997;17:447-454.
24. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980;302:1109-1117.
25. Sox HC, Jr. Probability theory in the use of diagnostic tests. An introduction to critical study of the literature. Annals of Internal Medicine 1986;104:60-6.
26. Hoen B, Viel JF, Paquot C, Gerard A, Canton P. Multivariate approach to differential diagnosis of acute meningitis. Eur J Clin Microbiol Infect Dis 1995;14:267-74.
27. Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics 2000;105:316-319.
28. Isaacman DJ, Shults J, Gross TK, Davis PH, Harper M. Predictors of bacteremia in febrile children 3 to 36 months of age. Pediatrics 2000;106:977-982.
29. Panzer RJ, Suchman AL, Griner PF. Workup bias in prediction research. Med Decis Making 1987;7:115-119.
30. Diamond GA, Rozanski A, Forrester JS, Morris D, Pollock BH, Staniloff HM, et al. A model for assessing the sensitivity and specificity of tests subject to selection bias. Application to exercise radionuclide ventriculography for diagnosis of coronary artery disease. J Chron Dis 1986;39:343-355.
31. Miettinen OS, Henschke CI, Yankelevitz DF. Evaluation of diagnostic imaging tests: diagnostic probability estimation. J Clin Epidemiol 1998;51:1293-1298.
32. Begg CB, McNeil BJ. Assessment of radiologic tests: control of bias and other design considerations. Radiology 1988;167:565-569.
33. Randolph AG, Guyatt GH, Calvin JE, Doig G, Richardson WS. Understanding articles describing clinical prediction tools. Crit Care Med 1998;26:1603-1612.

34.Riordan FA, Thomson AP, Sills JA, Hart CA. Bacterial meningitis in the first three months of life. Postgrad Med J 1995;71:36-8.
35.Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
36.Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-9.
37.Braitman LE, Davidoff F. Predicting clinical states in individual patients. Annals of Internal Medicine 1996;125:406-12.
38.van Steensel-Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, Dekker A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics II. [in Dutch]. Tijdschr Kindergeneesk 1996;64:99-104.
39.Derksen-Lubsen G, Jongkind CJ, Kraayenoord S, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics I. [in Dutch]. Tijdschr Kindergeneesk 1996;64:93-98.
40.Alonzo TA, Pepe MS. Using a combination of reference tests to assess the accuracy of a new diagnostic test. Statistics in Medicine 1999;18:2987-3003.
41.Reid MC, Lachs MS, Feinstein AR. Use of methodological standards in diagnostic test research. Getting better but still not good. JAMA 1995;274:645-651.
42.Bates AS, Margolis PA, Evans AT. Verification bias in pediatric studies evaluating diagnostic tests. J Pediatrics 1993;122:585-590.
43.Weller SC, Mann NC. Assessing rater performance without a "gold standard" using consensus theory. Medical Decision Making 1997;17:71-9.
44.Hoes AW, Grobbee DE, Valkenburg HA, Lubsen J, Hofman A. Cardiovascular risk and all-cause mortality; a 12 year follow-up study in The Netherlands. Eur J Epidemiol 1993;9(3):285-92.
45.PIOPED investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 1990;263:2753-2759.
46.Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
47.Saywer MH. Enterovirus infections: diagnosis and treatment. Ped Inf Dis J 1999;18:1033-1040.
48.Bergus GR, Chapman GB, Levy BT, Ely JW, Oppliger RA. Clinical diagnosis and the order of information. Med Decis Making 1998;18:412-417.
49.Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
50.Little RA. Regression with missing X's: A review. J Am Stat Assoc 1992;87:1227-1237.
51.Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255-1264.
52.Schafer JL. Multiple imputation: a primer. Stat Methods Med Res 1999;8:3-15.
53.Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
54.Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-843.
55.Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. Journal of Clinical Epidemiology 1996;49:1373-9.
56.Hosmer DW, Lemeshow S, editors. Applied logistic regression. New York: John Wiley & Sons, Inc; 1989.
57.Centor RM, Schwartz JS. An evaluation of methods for estimating the area under the receiver operating characteristic (ROC) curve. Med Decis Making 1985;5:149-156.
58.Feinstein AR. Clinical biostatistics. XLI. Hard science, soft data, and the challenges of choosing clinical variables in research. Clinical Pharmacology & Therapeutics 1977;22:485-98.
59.Knottnerus JA. Application of logistic regression to the analysis of diagnostic data: exact modeling of a probability tree of multiple binary variables. Medical Decision Making 1992;12:93-108.

6 Summary

Summary and future perspectives

6.1

Introduction

A child with meningeal signs poses a diagnostic dilemma. Meningeal signs are indicative of bacterial meningitis, but a large part of the children with these signs have less serious diseases. [1,2] Missing the diagnosis of bacterial meningitis will lead to delayed treatment, and thereby increasing the risk of mortality and morbidity. [3,4] The aim of this thesis is to determine whether systematic diagnostic research, using data that are routinely obtained from clinical practice, can optimise the diagnostic work-up of patients with meningeal signs. In particular the diagnostic and prognostic aspects of children suspected of bacterial meningitis are at issue in this thesis and are used to illustrate the more general methodological principles and methods of diagnostic and prognostic research. In addition, we address the issues of health-related quality-of-life and economic evaluation of clinical practice.

All studies in this thesis have been performed on patients aged from one month up to 15 years, with 'meningeal signs' as the main reason of visiting the paediatric emergency department. These patients could be traced retrospectively, using a problem-oriented patient classification system as applied in the Sophia Children's hospital since 1988. [5] In the retrospective studies (chapter 2.1, 2.2, 2.3, 3.1, 3.2 and 4.1), we used data collected from children visiting the emergency department of the Sophia Children's hospital, Rotterdam between 1988 and 1998. Chapter 3.2 used data from similar patients from the Juliana Children's Hospital, The Hague as well. Chapter 2.4 used data of similar patients visiting the Sophia and Juliana Children's Hospital, the Sint Fransiscus Hospital, Rotterdam, and the Reinier de Graaf Hospital, Delft, between 1999 and 2000. All data were collected from the paediatric patient record, which has a standardised format. The data included patients' general characteristics, and information obtained from patient history and physical examination, from the clinical course and from outpatient follow-up. Laboratory and radiographic test results were retrieved from the hospital information system.

Diagnostic dilemmas in children with meningeal signs

Differential diagnoses in children with meningeal signs

The diagnoses, as assessed in children visiting the emergency department with meningeal signs, have been described in *chapter 2.1.* Corresponding to previous studies [1,2], a large diversity in final diagnoses was found in these children: 30% bacterial meningitis, 13% viral or aseptic meningitis, 11% other serious bacterial infections and 46% upper respiratory tract infections, or other self-limiting diseases. This reflects the diagnostic dilemma for the physician faced with a child with meningeal signs: because of the serious consequences of missing the diagnosis bacterial meningitis, even children with very low risk will be referred to the paediatrician to rule out this diagnosis.

In practice, meningeal irritation is considered if Brudszinky signs 1 or 2, Kernig sign, nuchal rigidity or the tripod phenomenon are positive, but not all signs need to be present. In children younger than one, symptoms of irritability during manipulation of head or legs and a bulging fontanel are additional signs of meningeal irritation. Some studies have found some signs to be better predictors than others have. [2,6,7] In our study (*chapter 2.1*), we could not identify one of the signs as mentioned above, nor combinations of them, that predicted the presence or absence of bacterial meningitis better than the other could.

Predictors of bacterial meningitis

In *chapter 2.2* we have studied clinical characteristics, obtained at admission, that independently contributed to the discrimination between the presence or absence of bacterial meningitis in children with 'meningeal signs'. These predictors are: duration of the complaint (in days) and vomiting in history, presence of meningeal irritation, cyanosis, disturbed consciousness and petechiae at physical examination and the serum C-reactive protein concentration (CRP). The serum CRP is the only laboratory test that contributed to the information already available from patient history and physical examination. Meningeal irritation at physical examination is one of the strongest predictors in our model. This concords with clinical practice, in which most doctors will perform a lumbar puncture in everyone with meningeal irritation. The other clinical characteristics included in our rule provide additional help to discriminate between the presence of bacterial meningitis versus the absence. A prediction rule including all these independent predictors achieved a discriminative value (ROC-area) of 0.92 for the presence or absence of bacterial meningitis. With this rule, patients could be classified into categories of increased risk of bacterial meningitis. Since clinicians do not want to miss a single case of bacterial meningitis, we have defined a threshold value for the clinical score (score = 9.5) to ascertain the indication for a lumbar puncture. Using the rule with this threshold score, a lumbar puncture could be withheld in 35% of children with meningeal signs, without missing one case of bacterial meningitis.

In those patients in whom a lumbar puncture is indicated by their clinical profile, we have assessed the cerebrospinal fluid (CSF) indices that independently contributed to the assessment of the diagnosis bacterial meningitis in *chapter 2.3*. No CSF index could solely discriminate between patients with and without bacterial meningitis, since the ranges of CSF cell count, glucose etc. as found in patients with viral meningitis largely overlapped possible ranges found in those with bacterial meningitis. We have shown that the CSF polymorphonuclear cell count and the glucose ratio of CSF and blood independently contributed to the clinical profile as assessed by clinical risk score (chapter 2.2), in diagnosing bacterial meningitis. Using the clinical score and CSF score together, 30% of the patients with a lumbar puncture could be identified in whom empirical antibiotic treatment could be withheld, without missing one case of bacterial meningitis. Combining the CSF score with the clinical score reflects clinical practice, in which laboratory tests are always judged in view of clinical signs and symptoms in a particular patient.

In *chapter 2.4* the actual performance of the diagnostic decision rule in clinical practice has been validated prospectively in four hospitals: one academic paediatric hospital, one paediatric hospital, and two general hospitals. For each patient, the variables of the decision rule were prospectively assessed by one of the paediatricians (in training) of the participating hospitals using a scoring form, providing a description of the variable definitions. Of course, some variability between clinicians occurred when assessing the variables, due to lack of standardised definitions of recording data. This, however, will occur in future practice as well, and thus informs on the practical applicability of the rule. Application of the rule in 176 new patients, who initially presented themselves with meningeal signs, showed a similar performance of the clinical score (ROC-area: 0.87) as in the derivation population (chapter 2.2). The discriminative value of the CSF score in patients with an indication for lumbar puncture (based on the clinical score) was 0.95. In the new population, however, some patients with bacterial meningitis had lower clinical and CSF scores than in the derivation population. Therefore, we adjusted the threshold values for the indication of a lumbar puncture or empirical treatment, in order not to misdiagnose one child with bacterial meningitis.

Implications of the rule for clinical practice

The decision rule aims to guide decisions on two sequential steps in the care of children with meningeal signs: whether or not to perform a lumbar puncture and whether or not to initiate empirical treatment. The value of the scores, assigned to each predictor in the rule, indicates how the presence or absence of one characteristic influences the risk of bacterial meningitis in particular. The scoring rule enables the physician to classify patients into categories of increased risk of bacterial meningitis. We have recommended threshold values in the decision rule to decide upon the need of a lumbar puncture or initiating empirical treatment, such that no case of bacterial meningitis will be missed in its use. Using these threshold values, the diagnostic rule increased the prior probability of bacterial

meningitis in all children with meningeal signs from 11% to 20% in those selected for a lumbar puncture and to 39% in those selected for empirical treatment.

In some clinical circumstances, physicians may hesitate to withhold a lumbar puncture although it is not indicated by the rule. Therefore, we have evaluated the performance of the decision rule in all patients who actually underwent a lumbar puncture on the physician's decision. The same clinical and CSF characteristics were applicable and a similar number of patients was selected for empirical treatment. Therefore, we state that the rule can validly be applied in patients with meningeal signs and undergoing a lumbar puncture based on the physician's decision only, as well.

In developing our decision rule, the outcome diagnosis was presence or absence of bacterial meningitis. Therefore, the rule will miss the diagnosis of some cases of viral or aseptic meningitis. The question is, however, why diagnostic tests are performed: for therapeutic reasons or also for 'the sake of knowing' without clear therapeutic consequences. In the first case, a lumbar puncture is not indicated in order to detect viral or aseptic meningitis, since these patients generally require symptomatic treatment only. [8] Of course, this view may change whenever antiviral treatments become available.

Some generalising aspects of the rule need to be discussed. First; the rule has been derived on data from patients in the Sophia Children's Hospital, which is an academic paediatric hospital, situated in the inner city of Rotterdam. It receives about 2,500 new patients at the emergency department annually; of whom 90% needs basic-paediatric care. [9] Therefore, we expect the results to apply to general hospitals as well. Application of the rule in three other hospitals with their particular patient populations (chapter 2.4) indeed showed good performance of the rule. Second, the data on which the rule has been derived partly included the period before the routine *H. influenzae* type b (HIB) immunisation of infants. [10] Since the diagnostic decision rule may be implemented in a future era without HIB, we performed a separate analysis with exclusion of the HIB cases. This resulted in the same predictors with a similar rule. In addition, the prospective application of the rule during 1999 and 2000 appeared to be valid. Third, our study has been based on patients selected on their clinical presentation, i.e. 'meningeal signs'. Since meningeal signs are less prominent in young children [11,12], the age distribution in our study population is probably influenced by selection on 'meningeal signs'. Of course, our population did not reflect all cases of bacterial meningitis, since patients with a dominance of other symptoms of meningitis (such as seizures, or coma [11,12]) did not meet our inclusion criteria. This, however, does not affect the generalisability of the rule, as long as it is used in populations selected on the same clinical presentation.

The principle aim of the development of diagnostic protocols or decision rules is to apply them and optimise clinical practice. In the implementation of a rule, however, some barriers are met. Although a majority of paediatricians is familiar

with decision rules or guidelines, only one third uses them frequently in practice. [13] Preferably, decision rules should be simple and easy applicable, but should allow flexible patient management also. [14] Furthermore, information to physicians on the effectiveness of the rule compared to actual practice may improve its use. [15]

Prognosis

Description of outcome after bacterial meningitis

Despite adequate treatment and intensive care support, bacterial meningitis still causes mortality and morbidity in 5% and 10 - 15%, respectively. [16] In *chapter 3.1* we assessed the frequency of sequelae occurring after bacterial meningitis in children initially presenting with meningeal signs. Among 103 children with bacterial meningitis, two died (2%), seven had permanent neurological sequelae (7%) and in seven hearing impairment was detected during follow-up (7%). In concordance with previous studies, hearing impairment occurred most frequently isolated from neurological sequelae in our study; only one child had a combination of hearing impairment and neurological sequelae. In two children, multiple neurological sequelae were present. The main problem in studies on the prognosis of bacterial meningitis is the diversity of sequelae and the low frequency of severe sequelae, requiring large study populations for correct estimates. An overview of the characteristics of studies on the long-term prognosis of bacterial meningitis is presented in Table 1. These studies substantially differ in study design or population, age or pathogen distribution, duration of follow-up or the definition of end-points. Due to these differences, the results are difficult to compare.

The risk of sequelae is known to be related to pathogen type. [16] We have found a 10% mortality after pneumococcal meningitis and sequelae occurring in 56%. After meningococcal and HIB-meningitis, sequelae occurred in 6% and 12%, respectively. The introduction of routine HIB-vaccination in infants has substantially changed the pathogen spectrum of childhood bacterial meningitis. [10,17,18] In our study on children with meningeal signs, we included 25 cases of bacterial meningitis between July 1993 and December 1998, which is only one third of the number included between January 1988 and June 1993 (78 cases of bacterial meningitis). The relative frequency of sequelae, however, was similar in both periods: 13% (95% CI: 6 - 22%) and 20% (95% CI: 7 - 41%), respectively.

Prediction of an adverse outcome

To determine the independent associates of sequelae or death, we have performed a multivariate analysis of potential prognostic indicators in *chapter 3*. From information available within the first 24 hours of presentation, we have found male gender, atypical seizures in recent history, and low body temperature at admission, to be independently associated with an adverse outcome. A prediction

Table 1 Overview of long-term prognostic studies of childhood bacterial meningitis (1984 – 2000)

Author[$]	Study type	Total number of patients	Age	Duration of follow-up	Adverse outcome*	Pathogen type			
						HIB	NM	SP	Other
Antila (1994)[20]	Prospective	134	31% < 1 yr	12 months	29 (22%)*	100 (75%)	18 (13%)	9 (7%)	7 (5%)
Akpede (1999)[19]	Prospective	109[§]	34% < 1 yr	Unknown	47 (43%)	2 (2%)	43 (39%)	5 (5%)	13 (12%)
Lin (1984)[93]	Retrospective	476	6 w – 11 yr	Discharge	71 (15%)	335 (70%)	62 (13%)	45 (10%)	34 (37%)
Madagame (1995)[25]	Retrospective	32	Median 9.8 m	Median 41.5 m	21 (69%)	14 (44%)	6 (19%)	9 (28%)	3 (9%)
Pomeroy (1990)[27]	Prospective	186	Median 10 m	Median 10 yrs	26 (14%)†	118 (64%)	20 (11%)	30 (16%)	17 (9%)
Pikis (1995)[26]	Retrospective	90	63% < 1 yr	Mean 12.3 yrs	14 (16%)†			90 (100%)	
Kornelisse (1995)[24]	Retrospective	83	54% < 1 yr	Discharge	39 (47%)			83 (100%)	
Kaaresen (1995)[22]	Retrospective	92	Median 1.9 yr	1 yr	18 (20%)	45 (49%)	21 (23%)	7 (8%)	19 (21%)
Grimwood (1996)[21]	Prospective	138	38% < 1 yr	5-9 yr	19 (14%)	104 (75%)		21 (15%)	13 (10%)
Woolley (1999)[30]	Retrospective	432	Median 7.7 m	1-5 yr	59 (14%)‡	177 (41%)	49 (11%)	63 (15%)	143 (33%)
Valmari (1987)[11]	Retrospective	123	Median 20 m	Mean 2 m	19 (15%)	80 (65%)	23 (19%)	7 (6%)	13 (10%)
Oostenbrink (2000)[¶]	Retrospective	103	25% < 1 yr	Median 7 m	15 (15%)	34 (32%)	51 (50%)	10 (10%)	8 (8%)

[$] all studies were performed on patients of the paediatric ward, except for Madagame et al.[25] including intensive care patients only
* defined as mortality or neurological/audiological sequelae except for †: neurological/audiological sequelae among survivors only and ‡: hearing loss only
[§] in 46 bacterial meningitis was confirmed by CSF pleocytosis and depressed glucose levels in absence of pathogens identified on Gram-stain or culture
[¶] Chapter 3.2 of this thesis

model including these variables has a prognostic value (ROC-area) of 0.82 (95% CI: 0.72 - 0.93). From the variables obtained later during hospitalisation, only the pathogen type is of added prognostic value and increases the prognostic value of the model to 0.87 (95% CI: 0.78 - 0.96). In this final model the pathogen type has the largest prognostic impact, with an odds ratio of 22.6 if *S. pneumoniae* is present. Other characteristics from the clinical course, such as fever pattern or persistence of meningeal signs are not of prognostic added value.

Although several studies have been performed on the long-term prognostic characteristics of children with bacterial meningitis [19-30], their conclusions are different and sometimes contradicting, as we showed in *chapter 3.2* This may result from differences in study population (defined by e.g. presenting symptoms, age, pathogen type or disease severity) as presented in Table 1 and from different statistical methods (uni-or multivariate, or stratified analysis). Furthermore, the number of patients with sequelae in the study populations is often limited, which decreases the power of the study to select important predictors.

Since presence of neurological sequelae may not be clear at the moment of discharge, but become visible during follow-up, a short follow-up may underestimate the occurrence of sequelae, in young children in particular. In our study, the median duration of follow-up was seven months. Half of the children younger than one year, however, had a follow-up of more than nine months. Therefore, the duration of follow-up appeared not to bias the incidence of sequelae in this study.

Implications for clinical practice

Based on independent prognostic predictors of bacterial meningitis, a prediction rule has been formulated. With this rule, the physician can estimate the probability of an adverse outcome after bacterial meningitis based on observations in the individual patient. The predictors in the rule are all available within three days, and therefore the probability on an adverse outcome can be assessed in an early phase of the clinical course. This information may help the physician in parental counselling and in guiding plans for long-term follow-up for specific subgroups. Unfortunately, the prediction rule can not predict the specific type of sequelae, probably due to different causal processes underlying audiological sequelae and neurological sequelae. Audiological sequelae are probably due to the toxic effect of the pathogen and of inflammatory mediators on inner ear hair cells. Neurological sequelae, in contrast, result from direct parenchymal damage. [4,31,32]

In the studies of chapter 3, the minor sequelae after bacterial meningitis, such as mild behavioural problems, learning disabilities and attention deficits, are not addressed. Information on mild sequelae is often not routinely included in the patient record and thus not available for us, using routinely collected data from the patient record. Moreover, these mild sequelae may remain unnoticed until

schoolgoing-age, requiring a long period of follow-up of children with bacterial meningitis, using neuropsychological tests for detection. [33,34]

The duration of follow-up may depend on the characteristics of the individual patient. Frequently, sequelae present at discharge recover spontaneously. [27] On the other hand, seizures may occur after a disease free interval, in particular in patients with focal neurological deficits during the acute phase of meningitis. These late seizures rarely occur after a disease free interval of two years or more. [27]

Quality-of-life in children after bacterial meningitis

Additional to categorising patients according to their type of sequelae, the health state associated with a particular sequelae can be valued, to express the relative severity of the sub-optimal health state with reference to perfect health or death. For cost-utility analysis of the diagnostic rule, we needed such values (preference scores) for permanent disabling sequelae after bacterial meningitis. Some studies have assessed parents' preference values for outcomes of bacteraemia or neonatal care, but the values substantially varied between studies and did not include all possible health states following bacterial meningitis. [35-37] Empirical description of health-related quality-of-life (HRQoL) in children raises some problems. Due to their age-related development, children are a heterogeneous group, which has important consequences for description of HRQoL. First, children may be too young to provide their own estimation of quality-of-life, since it requires the cognitive ability of filling in forms, understanding the questionnaires and responding. [38] This problem may be solved by using measures adapted to their level of communicative and cognitive development or by using a proxy (e.g. a parent or teacher). In general, proxies can reliably describe the child's physical, psychological and social functioning (which are at issue in health-related quality-of-life) [37-39], in contrast to describing the affective dimensions, as at issue in the broader 'quality-of-life'. [40-42] Second, some dimensions included in the health status measure may not yet be appropriate for children, such as school performance, independence in daily life or fertility issues. [38,43] This requires adaptation of the contents of the physical, psychological and social domain in the instrument. Finally, the prognostic value of health status is of additional importance in the measurement of HRQoL in children.

Two generic instruments are available in Dutch for measuring health-related quality-of-life, i.e. EQ-5D and the Health Utilities Index (HUI), that both yield a preference score (utility) reflecting the severity of the sub-optimal health state related to perfect health and death. [44-46] No empirical information existed, however, on their relative performance. Evaluating these measures, substantial differences can be found, with regard to the derivation of their algorithms, dimensional contents of the instrument, scaling and underlying concept of health. In *chapter 3.3* we have studied the differences between the preference scores obtained by the two instruments for seven health states associated with neurological sequelae of bacterial meningitis. No differences were found with

regard to the feasibility of the instruments. The preference scores obtained by the HUI were substantially lower than those obtained by the EQ-5D. The largest differences in preference scores were found for health states associated with 'deafness' and 'mental retardation'. The differences in preference scores obtained by the two instruments lead to a different ranking order of the vignettes, as well. These differences in preference scores and ranking order may result from the fact that the EQ-5D does neither contain a dimension for hearing function nor for cognition, in contrast to the HUI. This lack of cognition illustrates one of the disadvantages of the EQ-5D for populations characterised (in part) by cognitive dysfunction. [47] Evaluation of the variance components of the preference scores obtained by the instruments showed that the interaction between the health states and instruments substantially influenced the value of the preference scores: one instrument values some health states different from others. Because of the impact of the dimensional contents of instruments on the value of preference scores for particular health states, the type of sequelae at interest should guide decisions on the particular instrument for quality-of-life measurement to be used in future studies.

Economic evaluation

The effects of the use of the decision rule on the number of lumbar punctures performed, the number of empirical treatments initiated and the associated cost expenditures of interventions have been assessed in *chapter 4*.

The possible cost savings following the application of the decision rule compared to actual practice are estimated in *chapter 4.1* Since in practice a physician does not want to miss a single case of bacterial meningitis, we have chosen for a cost minimisation study, involving a comparison of costs of two strategies with a similar outcome. Using the rule without misdiagnosing a single case of bacterial meningitis, reduced total costs by 10%: a mean cost saving of € 292 per patient. As could be expected from the high nursery costs compared to those of diagnostic tests, the largest costs savings by the rule were achieved in the therapeutic phase (90% of total reduction), and only 10% of the total reduction in the diagnostic phase. This may suggest that introducing more diagnostic tests, in order to rule out some diagnoses and subsequent therapies, increases the cost-effectiveness of clinical practice. Diagnostic tests, however, are not always conclusive and will yield some false positives and false negatives. [48,49] These figures will increase by increasing the number of tests, and subsequently reduce the cost-effectiveness. The study of chapter 4.1 underlines the importance of taking the complete therapeutic course into account, instead of the diagnostic tests only. Cost evaluation of diagnostic tests only, without their therapeutic consequences may lead to false conclusions.

Of course, the cost estimates in chapter 4.1 concern the net cost reduction as estimated for the Sophia Children's Hospital. The cost savings may be different for

hospitals that are more or less reluctant to perform diagnostic tests or to start therapeutic interventions. To extrapolate the results to other hospitals, we have identified key determinants of changes in the cost estimates by sensitivity analysis. The cost savings mainly depend on the inpatient nursing costs, the frequency distribution of bacterial meningitis and self-limiting diseases among patients with meningeal signs and the hospitalisation rate of the latter group. Using these determinants, with corresponding values for one's own hospital, one can roughly estimate the possible cost savings following the application of the decision rule in one's own hospital.

In *chapter 4.2* we introduce a model to estimate the consequences of adequate diagnosis and treatment in patients with meningeal signs in terms of quality-adjusted-life-years (QALYs) and costs. This model takes into account the entire course of diagnosis, treatment and management of long-term sequelae. To incorporate the downstream consequences of bacterial meningitis, the model includes a time horizon of 15 years. The costs associated with long-term morbidity after bacterial meningitis constitute 65% of all costs. The model is sensitive in particular for the prior probability of bacterial meningitis in patients with meningeal signs, the risk of neurological sequelae after meningitis, and the costs associated with long-term neurological sequelae. Costs of diagnostic tests hardly influence the model outcomes. Different diagnostic strategies (ranging from a very conservative to a more reluctant approach), however, have a large impact on the costs and QALYs of the model by increasing the risk of morbidity. In the management of the patient, the physician implicitly considers the trade-offs that influence the decision whether to withheld therapy, order another test, or to start therapy. [49,50] The study in chapter 4.2 has explicitly shown, from a cost perspective, that it is not worth running the risk of missing one case of bacterial meningitis by reducing diagnostic tests. Furthermore, the model may allow cost-effectiveness analysis of future interventions affecting the diagnostic, therapeutic or prognostic course of children with meningeal signs, incorporating the long-term costs and QALYs. This is illustrated by a cost-utility analysis of new vaccination strategies in chapter 4.2. Although some previous studies have estimated the expected cost-effectiveness of vaccination programmes [51-53], the long-term consequences on quality-of-life and costs have not been considered so far. The reduction of the prior risk of bacterial meningitis due to vaccination strategies substantially reduced costs and increased QALYs in our model. This long-term benefit should be taken into account in studies on the effect of future vaccination strategies. Of course, reduction of other invasive infections, due to vaccination, such as pneumococcal pneumonia and otitis, or meningococcal septicaemia, were not included in our model. Therefore, this study is not conclusive on the cost-effectiveness of new vaccination strategies. Our model, however, informs on associated costs and effects of prevention of meningitis, which is a major component of the potential cost-effectiveness of vaccination programmes. The increase in costs due to vaccination should be considered in view of the gain in quality adjusted life-years (incremental cost-utility ratio). Some authors have proposed criteria for introduction of new technology. Strong

evidence for adoption would exist for technologies with incremental cost-utility ratios of 20,000 €/QALY or less, and a moderate evidence for those with incremental cost-utility ratios of 100,000 €/QALY or less. [54] A recently introduced Dutch guideline measure on prevention of diabetic nephropathy for type 2 diabetes had a cost-utility ratio of 14,000 €/QALY. [55] These values may serve as a raw indication of acceptable incremental cost-utility ratios of new interventions to be introduced. League tables, ranking selected health care interventions by their incremental cost-utility ratios, may additionally help to place the results of a particular study in a broader context. [56] Decisions on whether or not to introduce a new technology, however, may be influenced by other considerations than the economic aspects, such as emotional, ethical or political reasons, or personal preferences, as well.

Methodological aspects of diagnostic research

In practice, diagnosis starts with a patient with a clinical problem (symptoms or signs) who is suspected of having a particular disease, the so-called target disease. [57-59] The physician commonly applies a phased work-up starting with patient history and physical examination. Subsequent steps may be additional laboratory tests of e.g. blood or urine, imaging tests or invasive tests such as a lumbar puncture in our example. After each phase the physician will consider the available diagnostic information to implicitly estimate the probability of the target disease. [57,60] In patients with a very low probability of the target disease, the physician will refrain from further diagnostic testing and discharge the patient. As long as insecurity remains, further diagnostic tests are applied until a treatment decision (including no treatment) can be made. [50,61,62] Ideally, diagnostic research should reflect this sequential diagnostic process in clinical practice and evaluate which of the findings contribute to the estimation of the diagnostic probability. [57,63,64]

According to practice, we have selected in this thesis patients on their symptoms or signs by which they came to the physician's attention, i.e. children with meningeal signs, suspected of having bacterial meningitis. We collected all data of these children that were routinely documented in practice and were relevant to set a diagnosis. Such data allow for a stepwise analysis of predictors in the sequence as they occur in routine practice. While performing our study on routinely documented data, we have encountered several methodological problems as described in *chapter 5*. Although much has been written on methods [57,58,60,65-71], and various authors have proposed guidelines [72-74], still no general framework exists for diagnostic research.

Study populations selected on the patient's signs and symptoms may still be subject to verification and incorporation bias. The first arises, when the reference standard to set the final diagnosis has not been performed in all patients, as is often the case in clinical practice. [65,67,68,75,76] It can be prevented by using an

outcome diagnosis that is rapidly progressing if left untreated, only. Incorporation bias occurs when the reference test is interpreted using information from preceding tests, such that the diagnostic value of the preceding test is overestimated. [64,68,70,77] Since blinding the observer of the reference test for preceding tests is not feasible in routinely documented databases, an objective reference tests is preferred. Routinely documented data are likely to have missing data, due to actual practice of the physician. The problem of missing data can be solved reliably by multiple imputation techniques, incorporating the uncertainty among the imputed values. [78-80]

Given a complete dataset after imputation, routinely documented data including the whole diagnostic and therapeutic phase facilitate proper analysis of predictors in the sequence as they occur in routine practice. Multivariate logistic regression analysis allows for probability estimation of the presence of a disease as a combined function of available characteristics from patient history, examination and additional laboratory tests. [50,57,63,81,82] In contrast to single test evaluation, the logistic model makes no use of sensitivity, specificity or likelihood ratio and its discriminative value can be expressed by the area under the Receiver Operator Characteristic curve (ROC-area). [83,84] Unfortunately, the multivariate logistic regression analysis as most frequently applied, requires a dichotomous outcome, i.e. presence or absence of the disease under study. [81,85] In some situations, however, one may prefer to discriminate more than two groups of diagnostic outcome. This discrimination between three groups of patients, however, requires more complicated analytic methods, such as polytomous modelling, and larger patient groups. [85]

The principle aim of the development of diagnostic protocols is to apply them in clinical practice and influence actual clinical practice. Usually, the performance of a diagnostic protocol in a new group of patients is lower than if applied to the patients on which the model has been derived. [81,86-88] Therefore, estimation of the actual performance of the diagnostic protocol in a new group of similar patients is recommended before its implementation in routine practice.

Future perspectives

Diagnosis

During the prospective application of our decision rule in chapter 2.4, we focussed on how the rule itself performed in similar new patients. Aspects of actual use of the rule by clinicians, and its impact on the diagnostic process were not included in this thesis yet and may be subject of future studies. The fact that the rule performed well in a prospective cohort of patients in four hospitals, now justifies to initiate the actual implementation process of the rule. As a first step we suggest the introduction of the rule in hospitals within the adherence of the Sophia Children's Hospital. To improve the implementation, information on the practical use of the rule to paediatricians should be accompanied by information on its

development, validation and effectiveness as presented in chapter 2.2, 2.3 and 4.1.

When antiviral treatments become available, a clinician may want to diagnose children with viral meningitis additional to determining the presence and the absence of bacterial meningitis in children with meningeal signs. Only the latter was enabled by our prediction rule. Future studies may focus on the development of a model that allows for discrimination between three groups of diagnoses in children with meningeal signs: bacterial meningitis, viral meningitis and absence of meningitis.

Prognosis

Due to routine vaccination of H. influenzae in infants the risk of meningitis in childhood and its pathogen spectrum has changed substantially. To gain insight into the subsequent alterations of the prognosis after childhood bacterial meningitis, larger studies on populations with the present spectrum of pathogens are necessary.

Only few studies have focussed on minor sequelae after childhood bacterial meningitis, such as mild behavioural problems, learning disabilities and attention deficits and uncertainty remains about their frequency. [34] To obtain detailed information on these mild sequelae after bacterial meningitis, standardised clinical follow-up after bacterial meningitis preferably should include neuropsychological functioning tests, besides hearing function tests and neurological examination and continue until school-going age.

In chapter 3.2 we presented a prognostic scoring rule for children with bacterial meningitis. Internal validation of the rule by bootstrapping techniques showed that the rule was robust. A prospective validation study, however, is necessary before implementation of this rule in practice, to inform about the actual performance of the rule in new similar patients.

Bacterial meningitis most frequently occurs in young children, for whom most questionnaires to measure health-related quality-of-life are still not suitable. Very recently, some generic questionnaires have been developed for young children (so-called 'toddler versions'), such as the TAPQoL (Dutch origin) and the Child Health Questionnaire (CHQ; American origin). [89,90] Both instruments lead to a multidimensional profile score. An algorithm leading to a preference score, as is required in cost-utility analysis, however, is not available for these instruments and has to be developed. The Dutch translation of the CHQ is currently being validated in healthy children. Translations in other languages are also available, such that the CHQ allows for international comparison of health-related quality-of-life. Future studies should inform on its applicability to measure the consequences of HRQoL after e.g. meningitis in children.

Economic evaluation

Cost estimation of tests or treatments are often locally performed and can not easily be extrapolated to other clinical settings. Furthermore, discrepancies in the methods employed by economic investigators still remain. Consequently, the ability to draw general conclusions from cost-effectiveness analysis results is usually rather limited. [91,92] Generalisation of the results to other hospitals requires general standards for techniques of cost assessment, and use of standard values, which are still lacking.

The unit costs of the diagnostic tests and therapeutic interventions as estimated in chapter 4.1 can be used in future economic evaluations of management of other acute paediatric diseases as well. The relative contribution of determinants of cost savings as we assessed in chapter 4.1 may help to define key parameters in future economic studies of paediatric care. Since costs of in-patient nursery and therapeutic interventions mainly determined the total costs, we recommend to focus on these components in economic studies in particular.

Most new interventions are associated with increased costs and a gain in quality adjusted life-years compared to the existing practice. A norm for incremental cost-utility ratios that are considered cost-effective such that new interventions deserve to be introduced, has not been defined yet and remains to be discussed by experts and policy makers. A league table ranking health care interventions by their incremental cost-utility ratios may be helpful in this debate.

Methodology

Selection of patients on their clinical profile is often not feasible in retrospective studies using routine care data, since most patients classification systems in hospitals are based on the diagnosis. The presence of a problem oriented patient classification system in the Sophia Children's Hospital since 1988 allowed to perform a retrospective diagnostic study with patients selected on their clinical profile (e.g. meningeal signs). Implementation of such a classification system may be recommended to hospitals interested in diagnostic research. Of course, when such a system is available, other diagnostic problems can be attacked by a similar study using routinely documented data to develop a practical applicable diagnostic rule.

Although much has been written on methodology of diagnostic research, no general framework exists until now. Future studies are required to inform about principles and methods for study design and statistical analyses in diagnostic research using existing databases. Polytomous regression analysis offers a promising tool for diagnostic research, but has hardly been used so far. Imputation techniques seem a valid solution for missing data that are likely to occur in routinely documented data. Future studies are necessary to inform on the value and limitations of methods for handling missing data and how these methods best can be integrated in analysis of diagnostic research.

References

1. Barnett ED, Bauchner H, Teele DW, Klein JO. Serious bacterial infections in febrile infants and children selected for lumbar puncture. Pediatr Infect Dis J 1994;13:950-3.
2. Levy M, Wong E, Fried D. Diseases that mimic meningitis. Analysis of 650 lumbar punctures. Clin Pediatr 1990;29:254-5, 258-61.
3. Lebel MH, McCracken GH, Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989;83:161-167.
4. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11:785-814.
5. Derksen-Lubsen G, Jongkind CJ, Kraayenoord S, Aarsen RSR, de Goede-Bolder A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics I. [in Dutch, English summary]. Tijdschr Kindergeneesk 1996;64:93-98.
6. Attia J, Hatala R, Cook DJ, Wong JG. Does this adult patient have acute meningitis? JAMA 1999;282:175-181.
7. Verghese A, Gallemore G. Kernig's and Brudzinski's signs revisited. Rev Infect Dis 1987;9:1187-92.
8. Saywer MH. Enterovirus infections: diagnosis and treatment. Ped Inf Dis J 1999;18:1033-1040.
9. van Steensel-Moll HA, Jongkind CJ, Aarsen RSR, de Goede-Bolder A, Dekker A, van Suijlekom-Smit LWA, et al. A problem oriented patient classification system for general pediatrics II. [in Dutch, English summary]. Tijdschr Kindergeneesk 1996;64:99-104.
10. Conyn-van Spaendonck MA, Veldhuijzen IK, Suijkerbuijk AW, Hirasing RA. Significant decline of the number of invasive Haemophilus influenzae infections in the first 4 years after introduction of vaccination against H. influenzae type B in children [in Dutch, English summary]. Nederlands Tijdschrift voor Geneeskunde 2000;144(22):1069-73.
11. Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. Eur J Pediatr 1987;146:515-8.
12. Riordan FA, Thomson AP, Sills JA, Hart CA. Bacterial meningitis in the first three months of life. Postgrad Med J 1995;71:36-8.
13. Flores G, Lee M, Bauchner H, Kastner B. Pediatricians' attitudes, beliefs, and practices regarding clinical practice guidelines: a national survey. Pediatrics 2000;105(3 Pt 1):496-501.
14. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. Jama 1999;282(15):1458-65.
15. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature. XXII: How to use articles about clinical decision rules. JAMA 2000;284:79-84.
16. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993;12:389-94.
17. Dawson KG, Emerson JC, Burns JL. Fifteen years of experience with bacterial meningitis. Ped Infect Dis J 1999;18:816-822.
18. Adams WG, Deaver KA, L. CS, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood haemophilus influenzae type b (Hib) disease in the Hib vaccine era. JAMA 1993;269:221-226.
19. Akpede GO, Akuhwa RT, Ogiji EO, Ambe JP. Risk factors for an adverse outcome in bacterial meningitis in the tropics: a reappraisal with focus on the significance and risk of seizures. Ann Trop Paediatr 1999;19:151–159.
20. Anttila M. Clinical criteria for estimating recovery from childhood bacterial meningitis. Acta paediatr 1994;83:63-67.
21. Grimwood K, Nolan TM, Bond L, Anderson VA, Catroppa C, Keir EH. Risk factors for adverse outcomes of bacterial meningitis. J Paediatr Child Health 1996;32:457-462.
22. Kaaresen PI, Flaegstad T. Prognostic factors in childhood bacterial meningitis. Acta Paediatr 1995;84:873-8.
23. Kilpi T, Anttila M, Kallio MJ, Peltola H. Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. Pediatr Infect Dis J 1993;12:184-8.
24. Kornelisse RF, Westerbeek CM, Spoor AB, van der Heijde B, Spanjaard L, Neijens HJ, et al. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis 1995;21:1390-7.

25.Madagame ET, Havens PL, Bresnahan JM, Babel KL, Splaingard ML. Survival and functional outcome of children requiring mechanical ventilation during therapy for acute bacterial meningitis. Crit Care Med 1995;23:1279-1283.
26.Pikis A, Kavaliotis J, Tsikoulas J, Andrianopoulos P, Venzon D, Manios S. Long-term sequelae of pneumococcal meningitis in children. Clincial Pediatrics 1996;35:72-78.
27.Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990;323:1651-7.
28.Radetsky M. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. Pediatric Infectious Disease Journal 1992;11(9):694-8; discussion 698-701.
29.Valmari P, Makela M, Kataja M, Peltola H. Multivariate prognostication in bacterial meningitis of childhood. Scand J Infect Dis 1987;19:29-34.
30.Woolley AL, Kirk KA, Neumann AM, Mc Willams SM, Freind D, Wiatrak BJ. Risk Factors for Hearing Loss From Meningitis in Children. Arch Otolaryngol Head Neck Surg 1999;125:509-514.
31.Leib SL, Tauber MG. Pathogenesis of bacterial meningitis. Infectious Disease Clinics of North America 1999;13(3):527-48, v-vi.
32.Richardson MP, Reid A, Tarlow MJ, Rudd PT. Hearing loss during bacterial meningitis0000. Arch Dis Child 1997;76:134-8.
33.Grimwood K, Anderson VA, Bond L, Catroppa C, Hore RL, Keir EH, et al. Adverse outcomes of bacterial meningitis in school-age survivors. Pediatrics 1995;95:646-56.
34.Grimwood K, Anderson P, Anderson V, Tan L, Nolan T. Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. Arch Dis Child 2000;83:111-116.
35.Bennet JE, Sumner W, Downs SM, Jaffe DM. Parents' utilities for outcomes of occult bacteremia. Arch Pediatr Adolesc Med 2000;154:43-48.
36.Kramer MS, Etezadi-Amoli J, Ciampi A, Tange SM, Drummond KN, Mills EL, et al. Parents' versus physicians' values for clinical outcomes in young febrile children. Pediatrics 1994;93:697-702.
37.Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, Rosenbaum PL, et al. Differences in preferences or neonatal outcomes among health care professionals, parents, and adolescents. JAMA 1999;281:1991-1997.
38.Jenney ME, Campbell S. Measuring quality of life. Arch Dis Child 1997;77:347-50.
39.Gemke RJ, Bonsel GJ. Reliability and validity of a comprehensive health status measure in a heterogeneous population of children admitted to intensive care. J Clin Epidemiol 1996;49:327-33.
40.Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998;7:387-97.
41.Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, Cummings BJ. Whose utilities for decision analysis? Med Decis Making 1990;10:58-67.
42.Eiser C. Children's quality of life measures. Arch Dis Child 1997;77:350-4.
43.Theunissen NCM, Vogels AGC, Koopman HM, Verrips GH, Zwinderman AH, Verloove-Vanhorick SP. Measuring health-related quality of life in a child population. Eur J Public Health 1999;9:188-193.
44.Dolan P. Modeling valuations for the EuroQol health states. Med Care 1997;35:1095-1108.
45.Feeny DH, Furlong WJ, Barr RD. Multiattribute approach to the assessment of health-related quality of life: Health Utilities Index. Med Pediatr Oncol 1998;Suppl:54-9.
46.Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702-22.
47.Krabbe PFM, Stouthard MEA, Essink- Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol 1999;52:293-301.
48.Kassirer JP. Our stubborn quest for diagnostic certainty. A cause of excessive testing. N Engl J Med 1989;320:1489-1491.
49.DeKay ML, Asch DA. Is the defensive use of diagnostic tests good for patients, or bad? Med Decis Making 1998;18:19-28.

50.Sox HC, Jr. Probability theory in the use of diagnostic tests. An introduction to critical study of the literature. Annals of Internal Medicine 1986;104:60-6.
51.Bovier PA, Wyss K, Au HJ. A cost-effectiveness analysis of vaccination strategies against N. Meningitidis meningitis in sub-Saharan African countries. Soc Science Medicine 1999;48:1205-1220.
52.Fendrick AM, Lee JH, LaBarge C, Glick HA. Clinical and economic impact of a combination Haemophilus influenzae and Hepatitis B vaccine: estimating cost-effectiveness using decision analysis. Archives of Pediatrics & Adolescent Medicine 1999;153(2):126-36.
53.Lieu TA, Ray GT, Black SB, Butler JC, Klein JO, Breiman RF, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. Jama 2000;283(11):1460-8.
54.Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J 1992;146:473-481.
55.van Os N, Niessen LW, Bilo HJG, Casparie AF, van Hout BA. Diabetes nephropathy in the Netherlands: a cost effectiveness analysis of national clinical guidelines. Health Policy 2000;51:135-147.
56.Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. second edition. 2nd ed. Oxford: Oxford University Press; 1997.
57.Moons KGM, van Es GA, Michel BW, Büller HR, Habbema JDF, Grobbee DE. Reduncancy of single diagnostic test evaluation. Epidemiology 1999;10:276-281.
58.Sackett DL. A primer on the precision and accuracy of the clinical examination. JAMA 1992;267:2638-2644.
59.Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11:88-94.
60.Grobbee DE, Mietingen OS. Clinical epidemiology introduction to the discipline. Neth J Med 1995;47:2-5.
61.Moons KGM, Stijnen T, Michel BC, Büller HR, Grobbee DE, Habbema JDF. Treatment thresholds in diagnostic test evaluation: an alternative approach to the comparison of areas under the receiver operating characteristic curve. Med Decis Making 1997;17:447-454.
62.Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980;302:1109-1117.
63.Miettinen OS, Henschke CI, Yankelevitz DF. Evaluation of diagnostic imaging tests: diagnostic probability estimation. J Clin Epidemiol 1998;51:1293-1298.
64.Begg CB, McNeil BJ. Assessment of radiologic tests: control of bias and other design considerations. Radiology 1988;167:565-569.
65.Begg CB. Biases in the assessment of diagnostic tests. Stat Med 1987;6:411-23.
66.Diamond GA. Selection bias and the evaluation of diagnostic tests: a metadissent. J Chron Dis 1986;39:359-360.
67.Knottnerus JA, Leffers JP. The influence of referral patterns on the characteristics of diagnostic tests. J Clin Epidemiol 1992;45:1143-1154.
68.Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med 1978;299:926-30.
69.van der Schouw YT, van Dijk R, Verbeek ALM. Problems in selecting the adequate patient population from existing data files for assessment studies of new diagnostic tests. J Clin Epidemiol 1995;48:417-422.
70.Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III: How to use an article about a diagnostic tests. A. Are the results of the study valid? JAMA 1994;271:389-391.
71.Feinstein AR. Clinical Epidemiology: the architecture of clinical research. Philadelphia: WB Saunders Company; 1985.
72.Fryback DG. Bayes' theorem and conditional nonindependence of data in medical diagnosis. Comput Biomed Res 1978;11:423-34.
73.Dalla-Palma L, Dixon AK, Durand-Zaleski I, Reiser M, Soimakallio S. An overview of cost-effective radiology. Eur Radiol 1997;7:147-50.
74.Mackenzie R, Dixon AK. Measuring the effects of imaging: an evaluative framework. Clin Radiol 1995;50:513-18.
75.Alonzo TA, Pepe MS. Using a combination of reference tests to assess the accuracy of a new diagnostic test. Statistics in Medicine 1999;18:2987-3003.

76.Reid MC, Lachs MS, Feinstein AR. Use of methodological standards in diagnostic test research. Getting better but still not good. JAMA 1995;274:645-651.
77.Guyatt GH, Tugwell PX, Feeny DH, Haynes RB, Drummond M. A framework for clinical evaluation of diagnostic technologies. Can Med Assoc J 1986;134:587-594.
78.Little RA. Regression with missing X's: A review. J Am Stat Assoc 1992;87:1227-1237.
79.Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995;142:1255-1264.
80.Schafer JL. Multiple imputation: a primer. Stat Methods Med Res 1999;8:3-15.
81.Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
82.Moons KGM, van Es GA, Deckers JW, Habbema JDF, Grobbee DE. Limitations of sensitivity, specificity, likelihood ratio, and Bayes' theorem in assessing diagnostic probabilities: a clinical example. Epidemiology 1997;8:12-17.
83.Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
84.Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-843.
85.Harrell FE, Jr., Margolis PA, Gove S, Mason KE, Mulholland EK, Lehmann D, et al. Development of a clinical prediction model for an ordinal outcome: the World Health Organization Multicentre Study of Clinical Signs and Etiological agents of Pneumonia, Sepsis and Meningitis in Young Infants. WHO/ARI Young Infant Multicentre Study Group. Stat Med 1998;17:909-44.
86.Efron B. Estimating the error rate of a prediction rule: improvement on Cross-Validation. J Am Stat Ass 1983;78:316-331.
87.Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985;313:793-9.
88.Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. Jama 1997;277(6):488-94.
89.Theunissen NCM. Health related quality of life in children . Leiden: University of Leiden; 1999.
90.Landgraf JM. Measuring pediatric outcomes in applied clinical settings: an update about the Child Health Questionnaire (CHQ). Quality of Life Newsletter MAPI Research Institute 1999;23:5-6.
91.Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. Jama 1996;276(15):1253-8.
92.Bonsel GJ, Rutten FFH, Uyl-de Groot CA. Economic evaluation alongside cancer trials: Methodological and practical aspects. Eur J Cancer 1993;29A, suppl. 7:S10-S14.
93.Lin TY, Nelson JD, McCracken GH, Jr. Fever during treatment for bacterial meningitis. Pediatr Infect Dis 1984;3:319-22.

Samenvatting

6.2

Dit proefschrift beschrijft diagnostisch en prognostisch onderzoek op routinematig verzamelde gegevens van kinderen die zich presenteren met meningeale prikkeling op de acute hulp, met als doel het huidig klinisch beleid te optimaliseren. Ook aspecten van gezondheidsgerelateerde kwaliteit van leven van kinderen, verdacht van meningitis, en de economische effecten van verschillen in de klinische praktijk worden hierin belicht. Tevens komen algemene methodologische principes van diagnostisch en prognostisch onderzoek aan de orde.

Introductie

Hoofdstuk 1 beschrijft de klinische presentatie en het diagnostisch probleem bij een kind met meningeale prikkeling. Alhoewel meningeale prikkeling een belangrijk symptoom is van bacteriële meningitis, heeft een groot deel van de kinderen met dit symptoom een andere (veel minder ernstige) diagnose. Vanwege het verhoogde risico op sterfte en morbiditeit bij een vertraagde behandeling van kinderen met bacteriële meningitis, hanteren artsen in de praktijk een lage drempel om een lumbaal punctie te verrichten en empirische behandeling te starten.

Kenmerkende symptomen van bacteriële meningitis bij kinderen zijn o.a. koorts, braken, hoofd- en nekpijn en een gestoord bewustzijn. Bij zuigelingen staan vaak meer aspecifieke symptomen zoals prikkelbaarheid en lethargie op de voorgrond. Afwijkende liquor parameters verdacht voor bacteriële meningitis zijn een verhoogd celgetal, een laag glucose en een verhoogd eiwit gehalte. De waarden voor deze variabelen, zoals gevonden bij kinderen met bacteriële meningitis overlappen echter de waarden zoals gevonden bij kinderen met b.v. een virale meningitis. De meeste onderzoeken naar diagnostische kenmerken van bacteriële meningitis zijn verricht op geselecteerde patiëntengroepen (b.v. kinderen geselecteerd op hun diagnose of bij wie een lumbaal punctie is uitgevoerd), zodat de resultaten niet altijd even goed te vertalen zijn naar de klinische praktijk.

Bacteriële meningitis gaat gepaard met ongeveer 5% mortaliteit en 15% morbiditeit. Gehoorverlies treedt frequent op na meningitis (10%). Andere neurologische restverschijnselen zijn cognitieve stoornissen, locomotore afwijkingen en epilepsie, welke vaak gecombineerd voorkomen. Verschillende voorspellers voor een slechte prognose van bacteriële meningitis worden in de literatuur beschreven. De prognose wordt vooral bepaald door de verwekker.

Door de verbeteringen in de medische zorg krijgen niet alleen morbiditeit, maar ook de psychologische en sociale gevolgen van een aandoening toenemend de aandacht. Gezondheidsgerelateerde kwaliteit van leven (HRQoL) geeft een kwantitatieve maat voor iemands functioneren op fysiek, mentaal en sociaal gebied met een bepaalde beperking ten opzichte van perfecte gezondheid en dood. Er zijn verschillende instrumenten beschikbaar voor het kwantificeren van HRQoL, maar er is weinig inzicht in de vraag of ze tot dezelfde resultaten en conclusies leiden. Deze instrumenten zijn in het algemeen weinig geschikt voor jonge kinderen.

In de beoordeling van veranderingen in de klinische praktijk worden veelal de gezondheidseffecten afgewogen tegen de financiële aspecten van medisch handelen. Over de juiste methoden voor kostenonderzoek bestaat nog discussie, en resultaten van economische studies zijn daarom moeilijk te generaliseren naar andere klinische omstandigheden. De vraag is welke componenten van een bepaald klinisch beleid de kosten het meest beïnvloeden.

Diagnostiek bij kinderen met meningeale prikkeling

Hoofdstuk 2 richt zich op de diagnostiek bij kinderen met meningeale prikkeling. Hierbij zijn routinematig verzamelde gegevens gebruikt uit het medisch dossier van kinderen die de acute hulp van het Sophia Kinderziekenhuis bezochten tussen 1988 en 1998 met het probleem 'meningeale prikkeling'. De probleemcode 'meningeale prikkeling' werd toegekend aan kinderen met pijn in de nek in anamnese, of die zijn verwezen met (verdenking) meningeale prikkeling door de huisarts, of bij wie de kinderarts dit vaststelt bij lichamelijk onderzoek. In hoofdstuk 2.1 worden de uiteindelijke diagnoses beschreven die werden gesteld bij deze kinderen: 30% bacteriële meningitis, 13% virale of aseptische meningitis, 11% andere ernstige bacteriële infecties en 46% bovenste luchtweginfecties of andere onschuldige ziekten. In tegenstelling tot enkele andere studies bleek in ons onderzoek geen enkele van de kenmerken van meningeale prikkeling zoals Brudzinsky 1 of 2, Kernig, het driepootfenomeen, nekstijfheid, de bomberende fontanel of luierpijn, noch combinaties van deze kenmerken, de aan- of afwezigheid van bacteriële meningitis beter te voorspellen.

In *hoofdstuk 2.2* worden klinische kenmerken bij presentatie bestudeerd die onafhankelijk bijdragen aan het voorspellen van de aan- of afwezigheid van bacteriële meningitis bij kinderen met meningeale prikkeling (periode 1988-1995). Deze voorspellers waren: de duur van de hoofdklacht (relatief risico (RR):

1.5 per dag) en braken (RR: 2.3) in de anamnese, meningeale irritatie (RR: 21.1), cyanose (RR: 13.0), petechiën (RR: 4.9) en een verminderd bewustzijn (RR: 21.8) bij lichamelijk onderzoek en het serum CRP (RR: 1.1 per 10 mg/l). Met deze voorspellers werd de volgende diagnostische regel ontwikkeld:

Score= 1 × duur van de klacht (in dagen) + 2 × braken + 7.5 × meningeale prikkeling + 6.5 × cyanose + 4 × petechiën + 8 × verminderd bewustzijn + 0.1 × serum CRP (per 10 mg/l)

In de onderzoekspopulatie varieerde de totale score van 0.5 tot 31 punten. Deze diagnostische regel had een onderscheidend vermogen (ROC-area) van 0.92 voor de aan- of afwezigheid van bacteriële meningitis. Met deze regel konden patiënten worden ingedeeld in groepen met een toenemend risico op bacteriële meningitis. Er werd een drempelwaarde vastgesteld voor de klinische score (score ≥ 9.5) voor de indicatie van een lumbaal punctie. Deze drempelwaarde voorkwam een lumbaal punctie bij 35% van de kinderen met meningeale prikkeling zonder eenmaal de diagnose bacteriële meningitis te missen. Het toepassen van de klinische score op gegevens uit het medisch dossier van vergelijkbare kinderen uit latere jaren (1996 - 1998) leidde tot dezelfde resultaten.

Bij patiënten met een indicatie voor een lumbaal punctie op basis van de klinische score, is in *hoofdstuk 2.3* de onafhankelijke diagnostische waarde onderzocht van liquor parameters voor de diagnose bacteriële meningitis. Voorspellers die onafhankelijk bijdroegen aan de klinische score (hoofdstuk 2.2) voor het stellen van de diagnose bacteriële meningitis waren het aantal polymorfonucleaire cellen (PMN) in de liquor (RR: 3.0 per ^{10}log-toename van PMN/µl) en de liquor/bloed glucose ratio (RR: 0.6 per 0.1 ratio toename). Met deze twee parameters werd de volgende CSF score geformuleerd:

CSF score = 1.0 × (^{10}log absoluut PMN celgetal) – 5 × (CSF/bloed glucose ratio)

Gecombineerd gebruik van de klinische en liquor score selecteerde 30% van de patiënten met een lumbaal punctie bij wie empirische behandeling voor bacteriële meningitis achterwege gelaten kon worden.

In *hoofdstuk 2.4* is de effectiviteit van de toepassing van de diagnostische regel vastgesteld in de klinische praktijk van vier ziekenhuizen in de periode van november 1999 tot november 2000: in het Sophia kinderziekenhuis (academisch kinderziekenhuis), in het Juliana kinderziekenhuis, Den Haag (algemeen kinderziekenhuis) en op de kinderafdeling van het Sint Fransiscus Gasthuis, Rotterdam en het Reinier de Graaf Gasthuis, Delft (algemene ziekenhuizen). Het functioneren van de regel in 176 nieuwe patiënten die zich in de ziekenhuizen presenteerden met meningeale prikkeling was vergelijkbaar met die in de populatie waarin de regel was ontwikkeld, zoals beschreven in hoofdstuk 2.2 en 2.3. In de nieuwe populatie was het onderscheidend vermogen (ROC-area) van

de klinische en CSF score respectievelijk 0.82 en 0.95. Er bleken echter lagere klinische scores en CSF scores voor te komen bij patiënten met bacteriële meningitis dan in de ontwikkelingsset. Daarom werden de drempelwaarden voor de indicatie van lumbaal punctie en empirische behandeling aangepast, zodat ook in de toekomst geen enkele patiënt met bacteriële meningitis zal worden gemist.

Prognose van bacteriële meningitis
In *hoofdstuk 3* wordt de prognose van bacteriële meningitis bij kinderen met meningeale prikkeling beschreven. Hierbij zijn gegevens van kinderen met bacteriële meningitis uit hoofdstuk 2 gebruikt en die van vergelijkbare kinderen uit het Juliana kinderziekenhuis, Den Haag. Twee van de 103 kinderen met bacteriële meningitis (2%) overleden tijdens de acute ziektefase (*hoofdstuk 3.1*). Bij zeven kinderen (7%) werden permanente neurologische afwijkingen vastgesteld en bij zeven bleek het gehoor afwijkend in de follow-up (7%). Evenals in eerder onderzoek trad gehoorverlies in onze studie vooral op als een geïsoleerde afwijking: slechts één kind had zowel gehoorverlies als neurologische afwijkingen. Bij twee kinderen waren er multipele neurologische afwijkingen aanwezig.

In *hoofdstuk 3.2* zijn kenmerken vastgesteld die onafhankelijk gerelateerd waren aan permanente restverschijnselen of sterfte na meningitis. Uit de beschikbare gegevens in de eerste 24 uur van presentatie bleken het mannelijk geslacht (RR: 4.4), atypische convulsies in de recente anamnese (RR: 9.7), en een lage lichaamstemperatuur bij presentatie (RR: 0.5 voor elke toename in graden Celsius) een slechte prognose te voorspellen. Uit kenmerken verkregen tijdens opname bleek alleen de verwekker hieraan verder bij te dragen (RR: 22.6 voor *S. pneumoniae* en RR: 4.4 voor *N. meningitidis* ten opzichte van de andere verwekkers). In het uiteindelijke model had de verwekker (met name *S. pneumoniae*) de grootste invloed. Andere kenmerken uit het klinisch beloop, zoals het koortsbeloop of het persisteren van meningeale prikkeling waren van geen aanvullende prognostische betekenis. Met het model kon echter het type neurologische restafwijking niet specifiek worden voorspeld. Dit prognostisch model, waarvan alle voorspellers beschikbaar zijn binnen de eerste 3 dagen, stelt de arts in staat de kans op een slechte prognose (sterfte of permanente restverschijnselen) in een vroeg stadium in te schatten voor de individuele patiënt met meningeale prikkeling. Deze informatie draagt bij aan een goede voorlichting aan ouders en helpt in het bepalen van het lange termijn beleid.

Hoofdstuk 3.3 beschrijft de waardering van kwaliteit van leven (HRQoL) van gezondheidstoestanden gerelateerd aan restverschijnselen na meningitis. Hierbij werd gebruik gemaakt van twee generieke meetinstrumenten voor HRQoL, te weten de EQ-5D en de Health Utilities Index (HUI), die beiden een wegingsfactor (utiliteit) opleveren voor de relatieve ernst van de sub-optimale gezondheidstoestand ten opzichte van 'gezond' en 'dood'. Deze wegingsfactoren voor permanente restverschijnselen na bacteriële meningitis waren nodig voor

de kosten utiliteitsanalyse van de diagnostische regel zoals beschreven in hoofdstuk 4.2, maar waren niet beschikbaar in de huidige literatuur. Dergelijke wegingsfactoren worden idealiter verkregen middels een classificatie van gezondheidstoestanden door patiënten zelf een vragenlijst in te laten vullen, waarna aan elk van deze classificaties een waardering van de gezondheidstoestanden door de algemene bevolking wordt toegekend. De studieopzet in dit proefschrift, gebaseerd op retrospectieve gegevens, stond een dergelijke empirische waardering van gezondheidstoestanden door patiënten niet toe. Tevens ging het voornamelijk om gegevens van jonge kinderen, voor wie de meeste vragenlijsten naar kwaliteit van leven niet geschikt zijn. Daarom werden van de zeven meest voorkomende ernstige restverschijnselen na meningitis representatieve casusbeschrijvingen gemaakt. Deze restverschijnselen waren: doofheid, mild gehoorverlies, ernstige retardatie met tetraplegie, epilepsie, locomotore stoornissen, milde mentale retardatie, en een combinatie van deze laatste drie. Vervolgens werd aan een panel van 28 kinderartsen gevraagd om de vragenlijsten van de EQ-5D en HUI voor elk van deze zeven casusbeschrijvingen in te vullen. Er werd geen verschil gevonden in toepasbaarheid tussen de instrumenten. De wegingsfactoren verkregen met de HUI waren echter aanzienlijk lager dan die van de EQ-5D. Het grootste verschil werd gevonden voor gezondheidstoestanden gerelateerd aan doofheid en mentale retardatie. De verschillen in wegingsfactoren verkregen met de twee instrumenten leidden ook tot een verschillende rangorde van de gezondheidstoestanden. Deze verschillen konden vooral worden verklaard door verschil in gezondheidsdimensies tussen de twee instrumenten, waardoor bepaalde gezondheidstoestanden anders werden gewaardeerd door een bepaald instrument dan andere. Dit leidde tot de conclusie dat het van belang is om de keuze voor het meetinstrument voor kwaliteit van leven te laten leiden door het type restverschijnsel dat bestudeerd wordt.

Economisch evaluatie van de klinische praktijk

In *hoofdstuk 4.1* wordt de mogelijke kostenbesparing van de beslisregel ingeschat ten opzichte van de huidige praktijk. Omdat in de praktijk de arts geen enkele patiënt met bacteriële meningitis zal willen missen, werd gekozen voor een kosten minimisatie studie, die kosten van twee strategieën met eenzelfde gezondheidseffect vergelijkt. De beslisregel leidde tot een 10% vermindering van de totale kosten (gemiddeld € 2976 per patiënt) zonder de diagnose bacteriële meningitis eenmaal te missen. De meeste kosten werden bespaard in de behandelingsfase (90% van het totaal) en slechts 10% in de diagnostische fase. De kostenbesparing werd voornamelijk bepaald door de verpleegdagprijs, de frequentieverdeling van bacteriële meningitis en zelf-limiterende ziektes bij kinderen met meningeale prikkeling en de opnamefrequentie van deze laatste groep.

In *hoofdstuk 4.2* wordt een model geïntroduceerd om de lange termijn gevolgen van adequate diagnostiek en behandeling van kinderen met meningeale prikkeling in te schatten in termen van levensjaren gecorrigeerd voor kwaliteit

van leven (QALYs) en kosten. Dit model omvatte de gehele diagnostische en behandelingsfase en de lange termijn gevolgen van bacteriële meningitis. Over een tijdsspanne van 15 jaar bedroegen de gemiddelde kosten per patiënt € 8393, en de gezondheidseffecten 11.2 QALYs. De kosten van lange termijn morbiditeit na bacteriële meningitis omvatten tweederde van alle kosten in het model. De model uitkomsten (i.e. kosten en gezondheidseffecten) bleken gevoelig voor de voorafkans op bacteriële meningitis bij kinderen met meningeale prikkeling (i.e. prevalentie), het risico op restverschijnselen na meningitis en de kosten van deze lange termijn morbiditeit. Kosten van diagnostiek hadden nauwelijks invloed op de modeluitkomsten. Verschillende diagnostische strategieën hadden grote invloed op de lange termijn kosten en gezondheidseffecten van het model. Het model gaf ook inzicht in de lange termijn gevolgen van eventuele preventieve interventies en diagnostische of therapeutische strategieën bij kinderen met meningeale prikkeling, in termen van kosten en QALYs. Dit werd geïllustreerd aan de hand van een kosten utiliteitsanalyse van de introductie van nieuwe vaccinatieprogramma's. Daling van de voorafkans op bacteriële meningitis door vaccinatie reduceerde de kosten en verhoogde de gezondheidseffecten in ons model aanzienlijk.

Methodologie van diagnostisch onderzoek

In *hoofdstuk 5* worden een aantal problemen van diagnostisch onderzoek op routinematig verzamelde gegevens, zoals ondervonden in boven beschreven studies, toegelicht en mogelijke oplossingen hiervoor aangedragen. In de praktijk is het stellen van de diagnose een gefaseerd proces, dat begint bij een patiënt met een bepaalde klacht of een symptoom, verdacht voor een bepaalde ziekte (waarschijnlijkheidsdiagnose). De arts zal allereerst een anamnese afnemen en een lichamelijk onderzoek verrichten. Vervolgstappen zijn aanvullend laboratoriumonderzoek van bloed of urine, beeldvorming of invasieve testen zoals b.v. een lumbaal punctie. Overeenkomstig met deze klinische praktijk dient diagnostisch onderzoek zich te richten op het vaststellen van de toegevoegde diagnostische waarde van een test bij de al beschikbare informatie. Het gebruik van gegevens van routinematige patiëntenzorg lijkt geschikt voor dergelijk diagnostisch onderzoek. Een valide schatting van de diagnostische waarde van een test vereist echter selectie van patiënten op hun klinische presentatie, n.l. de symptomen of klachten waarmee ze de arts bezoeken. Daarom is het van belang om in de database de patiënten te labelen met hun klinisch probleem bij verwijzing, en niet alleen op basis van hun einddiagnose. In onderzoeken op routinematig verzamelde gegevens van populaties geselecteerd op een klinisch probleem kan zich echter nog steeds een aantal problemen voordoen. Het diagnostisch proces wordt in de praktijk bepaald door eerdere onderzoeksgegevens. Daarom zijn routinematig verzamelde gegevens gevoelig voor 'verificatie-bias' en 'work-up' bias. Verificatie bias kan worden voorkomen door gebruik van een uitkomst diagnose die een snel progressief beloop kent bij uitblijven van behandeling. Work-up bias kan zoveel mogelijk vermeden worden door het gebruik van een objectieve referentie test. Bij het gebruik van routinematig verzamelde gegevens bestaat

een grote kans op ontbrekende waarden. Multipele imputatie technieken lijken voor dit probleem een geschikte oplossing te bieden.

In *hoofdstuk 6* worden de resultaten van dit proefschrift samengevat en bediscussieerd. Tevens worden aanbevelingen gedaan voor vervolgonderzoek. Het gebruik van routinematig verzamelde gegevens lijkt geschikt voor het ontwikkelen van diagnostische richtlijnen voor de klinische praktijk. In het diagnostisch probleem, zoals in dit proefschrift beschreven, blijkt de doelmatigheidswinst bij optimalisering van de diagnostiek beperkt te zijn. Dit probleem biedt echter een goede illustratie van de methoden en het potentieel van diagnostisch onderzoek.

List of co-authors

SE Bleeker, MD
Department of General Paediatrics
Sophia Children's Hospital
Rotterdam, The Netherlands

G Derksen-Lubsen, MD, PhD
Department of General Paediatrics
Juliana Children's Hospital
The Hague, The Netherlands

ART Donders, PhD
Julius Centre for General Practice and Patient oriented research /
Department of BioStatistics
University Medical Centre
Utrecht, The Netherlands

ML Essink-Bot, MD, PhD
Department of Public Health
Erasmus University
Rotterdam, The Netherlands

DE Grobbee, MD, PhD
Julius Centre for General Practice and Patient oriented research
University Medical Centre
Utrecht, The Netherlands

M Maas, MD
Department of General Paediatrics
Sophia Children's Hospital
Rotterdam, The Netherlands

HA Moll, MD, PhD
Department of General Paediatrics
Sophia Children's Hospital
Rotterdam, The Netherlands

KGM Moons, PhD
Julius Centre for General Practice and Patient oriented research
University Medical Centre
Utrecht, The Netherlands

JB Oostenbrink, MSc
Institute for Medical Technology Assessment
Erasmus University
Rotterdam, The Netherlands

WK Redekop, PhD
Institute for Medical Technology Assessment
Erasmus University
Rotterdam, The Netherlands

CCW Theunissen, MD
Department of General Paediatrics
Sophia Children's Hospital
Rotterdam, The Netherlands

MJ Twijnstra, MSc
Julius Centre for General Practice and Patient oriented research
University Medical Centre,
Utrecht, The Netherlands

Dankwoord

Onderzoek doen is een stukje teamwork en ik wil alle medespelers heel hartelijk bedanken voor hun inzet. De enthousiaste samenwerking met velen vanuit verschillende disciplines heb ik als een groot voorrecht ervaren.

Dr. H. A. Moll, co-promotor, beste Henriëtte, met jou enthousiasme en optimisme heb je me als student al warm gemaakt voor het doen van wetenschappelijk onderzoek. Ik wil je heel hartelijk bedanken voor de stimulerende begeleiding in de afgelopen jaren, zodat zowel het onderzoek als de onderzoeker konden groeien.

De promotoren Prof. Dr. D. E. Grobbee en Prof. Dr. H. A. Büller dank ik voor hun begeleiding en constructieve ideeën. Beste Rick, je wist de vragen toch altijd vanuit hun oorsprong te verduidelijken, wanneer ik als onderzoeker te dicht op de resultaten zat. Bedankt voor je verhelderende visie!

Prof. R. de Groot, Prof. Dr. W. F. M. Arts, Prof. Dr. F. F. H. Rutten, en Prof Dr. J. Lubsen, leden van de promotiecommissie, wil ik bedanken voor de beoordeling van dit proefschrift en voor hun bijdrage aan de definitieve versie. Beste Ronald, ook heel hartelijk bedankt voor de gezellige infectie-uitjes en congressen, die ik met de subafdeling infectie- en immuunziekten mocht delen!

Dr. K. G. M. Moons, beste Carl, heel hartelijk bedankt voor de intensieve en gezellige begeleiding in de afgelopen jaren. Je hebt me geleerd dat onderzoek nooit af is, en dat de motivatie om verder te gaan daar ook uit voortkomt. Lang leve de electronische snelweg tussen Utrecht en Rotterdam voor de vele vraag-en antwoordmailtjes.

Sacha Bleeker, Carola Bouwhuis, Monique Kromhout en Ezra Piepers, lieve kamergenoten, hartelijk bedankt voor de leuke tijd en steun bij onderzoeksperikelen. Sacha, bedankt voor je inbreng als onderzoeksmaatje binnen het project en natuurlijk dat je als paranimf naast me staat! Chantal Theunissen en Marielle Maas wil ik hartelijk bedanken voor hun bijdrage tijdens het onderzoek. Willy Atema, bedankt voor de gezelligheid, steun en betrokkenheid tijdens de projectjaren.

Dr. G. Derksen-Lubsen, beste Arda, dank voor je inspirerende ideeën en je inzet om het project letterlijk en figuurlijk in een breder perspectief te plaatsen. Drs. I. Hiemstra, beste Idske, bedankt voor de prettige samenwerking.

Mw Dr. M. L. Essink-Bot, beste Marie-Louise, je introduceerde me in de veelzijdigheid van kwaliteit van leven onderzoek. Bedankt voor de leuke samenwerking en hopelijk nog veel 'kinderQol' in de toekomst!

Dr. W. K. Redekop en Drs. J. B. Oostenbrink, beste Ken en Jan, jullie plaatsten de medische zorg in een economisch perspectief. Bedankt voor de prettige samenwerking. Beste Jan, bedankt dat je je nichtje ter zijde staat als paranimf!

Dr. A. R. T. Donders, beste Rogier, dank voor je hulp en creatieve adhoc oplossingen als het project om nieuwe statistische inzichten vroeg.

Drs M. J. Twijnstra, beste Minke, hoe hadden al die statusgegevens zonder jou in een bruikbaar bestand moeten komen? Dank je voor het databeheer en inzet als er toch nog even iets tussendoor moest.

Mede-onderzoekers in het Sophia, beste Dick, Edwin, Geert, Jan Erik, Jeroen, Laurens, Leon, Marcel, Paul, Pieter, Theo, Ward, Annemarie, Annemarie (F), Barbara, Clementien, Daphne, Debby, Ester, Hannerieke, Hestien, Hettie, Inge, Jessie, Jose, Karen, Maartje, Margriet, Marja, Nicolette, Saskia, Sophie, Venje, en Yvonne bedankt voor de gezellige WP-uurtjes, aio-weekenden en discussies over en tijdens het onderzoeksleven.

Onderzoekers en epidemiologen van het Julius Centrum, beste Julianen, dank jullie voor de samenwerking en gezelligheid tijdens mijn 'Utrecht-dagen', het WEON en op de cursussen.

De arts-assistenten en artsen van het Sophia en Juliana kinderziekenhuis en van de afdeling kindergeneeskunde van het Sint Franciscus Gasthuis en Reinier de Graaf Gasthuis wil ik hartelijk bedanken voor hun bijdrage in de prospectieve fase van het onderzoek.

Lieve papa en mama, om iets zelf te doen moet je wel de nodige bagage meegekregen hebben. Bedankt voor jullie steun die altijd zo vanzelfsprekend lijkt.

Tot slot, lieve Arre, dank je wel voor je support en aanwezigheid om altijd weer op terug te vallen. Zoals je weet is een twee-cilinder zo handig omdat eentje het altijd nog wel doet. En nu in volle vaart samen de toekomst tegemoet..!

Bedankt!

Rianne

Curriculum vitae

The author of this thesis was born on May 14th, 1972, in Culemborg. She attended the secondary school Scholengemeenschap Melanchthon in Rotterdam and passed the VWO exam in 1990. She started her medical training in 1990 at the Faculty of Medicine and Health Sciences of the Erasmus University, Rotterdam. During her study, she was a member of the Netherlands Medical Student Committee and the Dutch national student co-ordinator of the Erasmus student exchange program. As a student, she participated in a study on diagnostic procedures in children with a urinary tract infection, supervised by Dr. H. A. Moll at the outpatient department of the Sophia Children's Hospital, Rotterdam. During the internships, she stayed three months at the paediatric department of the Hospital Santo Antonio, Porto Alegre, Brasil. She obtained her medical degree in March 1997. From May till December 1997 she worked as a resident at the paediatric department of the Albert Schweitzer Hospital, Dordrecht. In December 1997 she started working as a research physician at the Ontwikkelingsgeneeskunde project 'Systematic diagnostic evaluation in paediatrics' as presented in this thesis, performed at the Sophia Children's Hospital, Rotterdam and the Julius Centre for General Practice and Patient Oriented Research, University Medical Centre, Utrecht, and supervised by Dr. H. A. Moll and Prof. Dr. D. E. Grobbee. She obtained her MSc in Clinical Epidemiology at the Netherlands Institute for Health Sciences, Erasmus University Rotterdam in June 2000. In February 2001 she started her training in paediatrics (first as agnio) at the Sophia Children's Hospital, Rotterdam (head Prof. Dr. H. A. Büller).