Children´s Hospital

Helsinki University Central Hospital

University of Helsinki, Finland

Paediatric Graduate School

University of Helsinki, Finland

Improving outcome of childhood bacterial meningitis by simplified treatment

- Experience from Angola

Tuula Pelkonen

ACADEMIC DISSERTATION

To be publicly discussed by permission of the Faculty of Medicine of the University of Helsinki, in the Niilo Hallman Auditorium of the Children´s Hospital, on June 3, 2011 at 12 noon.

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Supervised by	Professor Heikki Peltola, MD, PhD, DTM & H
	University of Helsinki
	Children´s Hospital, Helsinki University Central Hospital
Reviewed by	Professor Jussi Mertsola, MD, PhD
	University of Turku, Faculty of Medicine, Department of Paediatrics
	Docent Marjo Renko, MD, PhD
	University of Oulu, Department of Paediatrics
Official opponent	Professor Elizabeth Molyneux, FRCP, FRCPCH, FRCPCH (Hons),
	FCEM, OBE
	Paediatrics, College of Medicine, Blantyre, Malawi

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This book is dedicated to the children of Angola.

Table of Contents

1. Abstract

Background Acute bacterial meningitis (BM) continues to be an important cause of childhood mortality and morbidity, especially in developing countries. Prognostic scales and the identification of risk factors for adverse outcome both aid in assessing disease severity. New antimicrobial agents or adjunctive treatments - except for oral glycerol - have essentially failed to improve BM prognosis. A retrospective observational analysis found paracetamol beneficial in adult bacteraemic patients, and some experts recommend slow β-lactam infusion. We examined these treatments in a prospective, double-blind, placebo-controlled clinical trial.

Patients and methods A retrospective analysis included 555 children treated for BM in 2004 in the infectious disease ward of the Paediatric Hospital of Luanda, Angola. Our prospective study randomised 723 children into four groups, to receive a combination of cefotaxime infusion or boluses every 6 hours for the first 24 hours and oral paracetamol or placebo for 48 hours. The primary endpoints were 1) death or severe neurological sequelae (SeNeSe), and 2) deafness.

Results In the retrospective study, the mortality of children with blood transfusion was 23% (30 of 128) *vs.* without blood transfusion 39% (109 of 282; p=0.004). In the prospective study, 272 (38%) of the children died. Of those 451 surviving, 68 (15%) showed SeNeSe, and 12% (45 of 374) were deaf. Whereas no difference between treatment groups was observable in primary endpoints, the early mortality in the infusion-paracetamol group was lower, with the difference (Fisher's exact test) from the other groups at 24, 48, and 72 hours being significant (p=0.041, 0.0005, and 0.005, respectively). Prognostic factors for adverse outcomes were impaired consciousness, dyspnoea, seizures, delayed presentation, and absence of electricity at home (Simple Luanda Scale, SLS); the Bayesian Luanda Scale (BLS) also included abnormally low or high blood glucose.

Conclusions New studies concerning the possible beneficial effect of blood transfusion, and concerning longer treatment with cefotaxime infusion and oral paracetamol, and a study to validate our simple prognostic scales are warranted.

Resumo

Introdução Meningite bacteriana aguda (MB) continua a ser uma causa importante da mortalidade e morbilidade infantil, especialmente nos países em via de desenvolvimento. Escalas de prognóstico e a identificação de factores de risco de mau prognóstico ajudam a estimar a gravidade da doença. Novos antibióticos ou tratamentos adjuntos, exepto o glicerol via oral, essencialmente falharam em melhorar o prognóstico da MB. Num estudo retrospectivo observador, paracetamol revelou-se benéfico nos adultos com bacteriemia, e alguns peritos recomendam infusão lenta de β-lactam. Nós estudamos estes tratamentos num ensaio clínico prospectivo, duplo-cego, placebo-controlado.

Pacientes e métodos A análise retrospectiva incluiu 555 crianças tratadas contra MB em 2004 na enfermaria de infecciologia do Hospital Pediátrico de Luanda, Angola. O nosso estudo prospectivo randomizou 723 crianças em quatro grupos, para receberem uma combinação de infusão ou boluses de 6 em 6 horas de cefotaxima durante as primeiras 24 horas e paracetamol ou placebo via oral durante 48 horas. Os eventos observados primários eram 1) mortalidade ou sequelas neurológicas severas (SeNeSe), e 2) surdez.

Resultados No estudo retrospectivo, a mortalidade de crianças com transfusão de sangue foi 23% (30 de 128) e sem transfusão 39% (109 de 282; p=0.004). No estudo prospectivo, 272 (38%) crianças morreram. Das 451 sobreviventes, 68 (15%) apresentaram SeNeSe, e 12% (45 de 374) foram surdas. Embora não fosse observada nenhuma diferença entre os grupos de tratamento nos eventos primários, a mortalidade inicial no grupo de infusão-paracetamol foi mais baixa, com uma diferença significante (teste exacto de Fisher) dos outros grupos nas horas 24, 48 e 72 (p=0.041, 0.0005, e 0.005, respectivamente). Factores prognósticos de mau prognóstico eram consciência alterada, dispneia, convulsões, atraso de comparência, e falta de electricidade em casa (Escala Simples de Luanda, ESL); a Escala Bayesiana de Luanda (EBL) incluiu também glicose no sangue baixa ou alta.

Conclusões Novos estudos a respeito de possíveis efeitos benéficos de tranfusão de sangue e do tratamento mais longo com infusão de cefotaxima e paracetamol via oral, e um estudo para validação das nossas escalas simples de prognóstico são justificados.

Yhteenveto

Taustaa Äkillinen bakteerin aiheuttama aivokalvotulehdus (bakteerimeningiitti, BM) on yhä tärkeä lapsikuolleisuuden ja sairastavuuden syy, erityisesti kehitysmaissa. Prognostiset pisteytyssysteemit ja riskitekijöitten tunnistaminen auttavat taudin vakavuuden arvioimisessa. Uudet antibiootit tai liitännäishoidot, suun kautta annettavaa glyserolia lukuun ottamatta, eivät ole parantaneet BM:n ennustetta. Takautuva, havainnoiva tutkimus on osoittanut parasetamolin hyödylliseksi aikuisilla bakteremiapotilailla, ja jotkut asiantuntijat suosittelevat β-laktaamiantibioottien antoa hitaana infuusiota. Me tutkimme näitä hoitoja prospektiivisessa, plasebokontrolloidussa kaksoissokkotutkimuksessa.

Potilaat ja menetelmät Retrospektiivisessa tutkimuksessa analysoitiin 555:n vuonna 2004 BM:iin sairastuneen lapsen hoitotuloksia Luandassa, Angolassa. Sen jälkeen toteutimme prospektiivisen tutkimuksen, jossa 723 lasta satunnaistettiin neljään eri hoitoryhmään, saamaan hidasta kefotaksiimi-infuusiota tai boluksia kuuden tunnin välein (ensimmäisten 24 tunnin ajan) yhdessä suun kautta annettavan parasetamolin tai plasebon kanssa (48 tunnin ajan). Hoidon päätetapahtumia olivat 1) kuolema tai vakava neurologinen vammautuminen (VaNeVa) sekä 2) kuurous.

Tulokset Retrospektiivisessä tutkimuksessa verensiirron saaneista lapsista kuoli 23% (30/128) ja verensiirtoa saamattomista lapsista 39% (109/282; p=0.004). Prospektiivisessa tutkimuksessa 272 (38 %) lasta menehtyi. 451 eloonjääneestä 68:lla (15 %) oli VaNeVa, ja 12 % (45/374) kuuroutui. Vaikka hoitoryhmien välillä ei lopulta ollut tilastollista eroa, infuusio-parasetamoli -ryhmän kuolevuus oli merkitsevästi pienempi (Fisherin tarkka testi) kuin muissa ryhmissä 24, 48 ja 72 tunnin kohdalla (p-arvot 0.041, 0.0005 ja 0.005). Kehittämämme Yksinkertainen Luanda-skaala tunnisti alentuneen tajunnantason, hengitysvaikeudet, kouristukset, viiveen hoitoon tulossa ja kodin sähköttömyyden liittyvän huonoon ennusteeseen. Toinen pisteytysjärjestelmistämme, Bayesilainen Luanda-skaala identifioi yhden lisäennustetekijän: pienen tai suuren verenglukoosipitoisuuden.

Johtopäätelmät Uudet tutkimukset verensiirron sekä pidemmän kefotaksiimi-infuusion ja suun kautta annettavan parasetamolin mahdollisesta hyödystä sekä uusien prognostisten pisteytysskaalojemme validoimiseksi ovat aiheellisia.

2. Original publications

This thesis is based on the following articles which are referred to in the text by Roman numerals [I-V].

I. Pelkonen T, Roine I, Monteiro L, João Simões M, Anjos E, Pelerito A, Pitkäranta A, Bernardino L, Peltola H. Acute childhood bacterial meningitis in Luanda, Angola. Scand J Infect Dis 2008; 40: 859-866.

II. Pelkonen T, Roine I, Monteiro L, Correia M, Pitkäranta A, Bernardino L, Peltola H. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. Clin Infect Dis 2009; 48: 1107-1110.

III. Pitkäranta A, Pelkonen T, de Sousa e Silva MO, Bernardino L, Roine I, Peltola H. Setting up hearing screening in meningitis children in Luanda, Angola. Int J Pediatr Otorhinolaryngol 2007; 71: 1929-1931.

IV. Pelkonen T, Roine I, Leite Cruzeiro M, Pitkäranta A, Kataja M, Peltola H. Slow initial β-lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial. Lancet Infect Dis. 2011; 11: 000-000.

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V. Pelkonen T, Roine I, Monteiro L, Leite Cruzeiro M, Pitkäranta A, Kataja M, Peltola H. Prognostic accuracy of five simple scales in childhood bacterial meningitis. Submitted.

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In addition, some unpublished data are presented.

3. Abbreviations

AIDS	acquired immunodeficiency syndrome
AUC	area under the curve
BBB	blood-brain barrier
BCS	Blantyre Coma Scale
BERA	brain stem evoked response audiometry
BLS	Bayesian Luanda Scale
BM	bacterial meningitis
Cbp A	choline binding protein A
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
dB	decibel
DNA	deoxyribonucleic acid
ECW	extracellular water
GCS	Glasgow Coma Scale
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HTS	Herson-Todd Scale
IL	interleukin
IMCI	Integrated Management of Childhood Illness
ISRCTN	International Standard Randomised Controlled Trial Number Register
iv	intravenous
LP	lumbar puncture
MBC	minimal bactericidal concentration
MIC	minimal inhibitory concentration
MRI	magnetic resonance imaging
NMDA	*N*-Methyl-D-aspartic acid
OR	odds ratio
PBP	penicillin-binding protein
PCR	polymerase chain reaction
PCT	procalcitonin
SD	standard deviation
SeNeSe	severe neurological sequelae
SIADH	syndrome of inappropriate secretion of antidiuretic hormone

SLS	Simple Luanda Scale
TEOE	transient evoked otoacoustic emissions
TNF-α	tumor necrosis factor-α
WBC	white blood cell count
WFA	weight for age
WHO	World Health Organization

4. Introduction

Acute bacterial meningitis (BM) continues to be an important cause of child mortality globally, being responsible for 2% of all deaths in children younger than 5 years.[1] Still, survivors of BM have an about 20% risk of long-term disabling sequelae and impaired quality of life.[2] BM is at least ten times as common in developing countries - where its mortality rates are much higher than in industrialized countries.[3-6] Likewise, the risk of sequelae is highest in developing countries where disabled children can be subjected to stigma and neglect and hidden from view.[2]

The introduction of *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* vaccines has changed the epidemiology of BM in industrialized countries. These vaccines are increasingly being applied throughout the world, but further efforts are needed, especially in developing countries.[7]

Overall, child mortality has been declining worldwide, whereas the number of deaths caused by BM has decreased very slowly.[8] Because new antibiotics have not improved the prognosis, research has focused on adjunctive medications. However, the benefit of dexamethasone is controversial.[9, 10] Instead, glycerol has proved efficacious in reducing severe neurological sequelae (SeNeSe).[11] Angola, a sub-Saharan country with population of 18 million, has a high steady incidence and prevalence of BM. In the Paediatric Hospital of Luanda, the capital, 50% of the 5847 BM patients in 1998-2002 died.[12]

Our retrospective study described the realities of BM in Luanda. In our prospective, randomised clinical trial in the same hospital we aimed to find treatments to improve the prognosis of the disease.

5. Review of the Literature

5.1 Definition, incidence, and epidemiology of childhood bacterial meningitis

Bacterial meningitis is a bacterial infection which inflames the membranes that surround the brain and spinal cord. Although the frequency of acute BM in industrialized countries has declined, it continues to be a significant cause of childhood morbidity and mortality globally. In the United States, the overall incidence of BM is about 2 to 10 cases per 100,000 population per year. The incidence is greatest in neonates with about 400 per 100,000; this is followed by children younger than 3 years with 20 per 100,000, and is lowest in adults with 1 to 2 per 100,000.[13] In developing countries the incidence of meningitis in children is about 10 times as great as in industrialized countries.[6, 8]

The aetiology of BM is affected most by the age of the child, but also by the geographical area where the child lives (Table 1[11, 12, 14-19]). In the neonatal period, group B streptococci and coliform bacilli cause most BM in industrialized countries.[20] In developing countries, in babies aged less than 1 week, *E.coli* and other Gram-negative bacteria such as the species *Klebsiella*, *Enterobacter*, and *Salmonella*, and in neonates older than 1 week, *Streptococcus pneumoniae* are the leading causes of meningitis.[21-23] In infants and small children, before the introduction of Hib vaccination, *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* were the leading agents. In children older than 5 years and in adolescents, *S. pneumoniae* and *N. meningitidis* are the predominant causes.[20, 24] In developing countries, before Hib vaccination, *S. pneumoniae* seemed to be the leading causative agent of paediatric meningitis, followed by Hib, *N. meningitidis*, and *Salmonella*.[25-27]

In the Paediatric Hospital of Luanda, Angola, of the 246 bacterial agents identified in CSF samples from children aged 0-8 years with pyrexia and neurological signs, 82 (33%) were pneumococci, 68 (28%) *H. influenzae,* 50 (20%) meningococci, and 14 (6%) *Salmonella* spp.[12] Meningococcal disease occurs sometimes as extensive epidemics, especially in the meningitis belt in sub-Saharan area.[28, 29] Some Angolan provinces have also reported *N. meningitidis* epidemics.[30] In children with immunodeficiency or cerebrospinal fluid (CSF) shunt, various different bacteria, such as *Staphylococcus* species, Gram-negative enteric bacilli, or *Pseudomonas aeruginosa* can cause BM.[31]

Factors that predispose the child to the development of infection at other sites predispose the child to the development of BM, as well. An increased incidence is observable in the very young; and boys are affected more frequently

Country/Area	Age of patients	Pre-admission antibiotics, %	Bacteria identified/ patients studied	*Haemophilus influenzae*, %	*Streptococcus pneumoniae*, %	*Neisseria meningitidis*, %	Gram-negative rods, %	*Streptococcus* agalactiae, %	Other %	Reference
Finland	Mean + SD 31.6 + 36.0 mo	23	193/200 = 97%	76 type b	7	16			1	Peltola 1989 [14]
United Kingdom	Median (range) 11 mo (6d-14y)	30	197/197 = 100%	27	11	56		4	2	Molyneux 2006 [15]
Greece, 1974-1984	1 mo – 14 y		605/1319 = 46%	16 type b	15	64			5	Theodoridou 2007 [16]
1985-1994			394/600 = 66%	35 type b	12	50			3	
1995-2005			332/558 = 59%	4 type b	15	77			4	
Papua New Guinea	Median 5.8-7.0 mo	49	260/357 = 73%	45	48	0.3	3		4	Duke 2002 [17]
Korea	Mean 25 mo; median 3 mo		402/402 = 100%	17	23	5		25	30	Cho 2010 [18]
Latin America	Median (range) 12 mo (2-184)	33	484/654 = 74%	46	27	23			4	Peltola 2007 [11]
Malawi	Median (range) 6 mo (1d-14y)	24	175/175 = 100%	25	35	4	18	10	8	Molyneux 2006 [15]
Malawi	Median (range) 13-14 mo (2-168)	36	520/598 = 87%	33 type b	46	13	6		2	Molyneux 2002 [19]
Angola	0-8 y		246/799 = 31%	28 type b	33	20	6		13	Bernardino 2003 [12]
Angola	Median (range) 11 mo (2-150)	42	412/553 = 75%	60 type b	24	10	2	1	3	Pelkonen, et al, Retrospective
Angola	Median (range) 14 mo (1-157)	60	453/723 = 63%	41.5 type b	40.5	11			7	Pelkonen, et al, Prospective

Table 1. Causative organisms in childhood bacterial meningitis.

d=day, mo=month, y=year

than girls.[8] Congenital or acquired abnormalities of the immune system, especially of the complement system, may predispose the child to BM.[8, 32] Anatomical or functional asplenia increases the risk for meningitis by *S. pneumoniae*, *H. influenzae* or Gram-negative enteric bacteria. Children with malignant neoplasms with or without neutropenia, with systemic diseases, and with bacterial infections at other sites are also at increased risk. Malnutrition also predisposes children to BM.[8] Neurosurgical procedures or cochlear implants, penetrating head injuries or CSF leaks increase the risk of BM, as well.[24]

5.1.1 Epidemiology of *Haemophilus influenzae* meningitis

H. influenzae type b meningitis affects mainly children aged 3 months to 3 years.[20] Before the advent of Hib vaccines, the incidence of *H. influenzae* meningitis varied worldwide. In Scandinavia the incidence was estimated to be 16 to 28 cases per 100,000 children younger than age 5 years,[33] but in non-industrialized populations like Alaskan Eskimos, Native Americans, Australian aboriginals, and African populations, the incidence was 3 to 10 times higher.[8, 34] Before the introduction of conjugate vaccines, the incidence of Hib meningitis in the industrialized regions was estimated to be 32 cases per 100,000 children younger than 5 , causing 27,000 cases and 1,300 deaths per year; in developing regions the figures were 60 cases per 100,000, meaning 330,000 cases and 100,000 deaths annually.[35] In another review, based on surveillance studies and laboratory-confirmed cases that are likely to underestimate the burden of the disease, the estimate for the incidence of Hib meningitis in children younger than 5 years in Europe in 2000 was 16, in Africa 46, and globally 31 per 100,000, causing a respective 5,200, 51,300, and 173,000 cases, which resulted in 2,000, 34,600, and 78,300 deaths (mortality 22–67%).[4] Highly effective and safe conjugate Hib vaccines have almost eliminated Hib disease and meningitis in countries where they are routinely used.[36-40]

The risk of spread of severe *H. influenzae* illness is increased especially in young household contacts, in day care centres, and in enclosed hospital populations.[34] In the USA the incidence of *H. influenzae* meningitis used to be greater in blacks and in the rural white population, a fact explained by poverty and lack of access to early medical care.[8] The risk for invasive Hib infection in African people with sickle cell disease is 13-fold that of those without sickle cell disease.[41]

5.1.2 Epidemiology of *Streptococcus pneumoniae* meningitis

In a review of pneumococcal disease based on surveillance studies and laboratory-confirmed cases—which are likely to underestimate the burden of the disease—the

estimate for incidence of pneumococcal meningitis in children younger than 5 years of age in Europe in 2000 was 6, in Africa 38, and globally 17 per 100,000, causing respectively 3,300, 43,100, and 103,000 cases, which resulted in 1,300, 31,700, and 60,500 deaths (mortality 29-73%).[5] In many countries where routine Hib vaccination has been implemented, *S. pneumoniae* has become the leading causative agent of BM.[42] In a few countries with routine vaccination with 7-valent pneumococcal conjugate vaccine, a 56–69% reduction in childhood BM has been reported.[43-45] Pneumococcal meningitis generally occurs sporadically, but in recent years, countries located in the African meningitis belt have reported highly lethal epidemics.[46-48] Similar to meningococcal meningitis, pneumococcal meningitis occurs there primarily in the dry season.[49]

The risk of developing meningitis depends somewhat upon the serotype of the pneumococcus. Although >90 serotypes exist, meningitis is most commonly associated with serotypes 14, 6B, 19, 18C, 23, 4, 9V, 3, and 1.[24, 34] In Africa, the most common serotypes are type 1, 5, and 6.[6] The risk of pneumococcal meningitis is greater in indigenous people, in blacks, and is independent of income or population density.[8, 50] Pneumococcal meningitis is 36 times greater in African people with sickle-cell disease than in those without sickle-cell disease.[41] Moreover, HIV infection predisposes to invasive pneumococcal infection.[51, 52] Children with cochlear implants have more than a 30-fold increased incidence of pneumococcal meningitis.[53] The incidence of systemic infection with penicillin-resistant *S. pneumoniae* (MIC $\geq$2 µg/L) has been increasing since the 1960s. Resistance to third-generation cephalosporins has emerged more recently.[8] Alterations in one or more penicillin-binding proteins (PBP) reduce their affinity for penicillin and other β-lactams, thus causing resistance. Several clones carrying altered PBP genes have spread in many parts of the world.[54]

5.1.3 Epidemiology of *Neisseria meningitidis* meningitis

Serogroups A, B, and C are responsible for most cases of meningococcal disease and meningitis globally, with serogroups B and C predominating in Europe and the Americas and serogroups A and C in Asia and Africa.[55] In the USA the incidence of endemic meningococcal disease has been 0.9 to 1.5 cases per 100,000 per year. The rates are highest during infancy, adolescence, and early adulthood.[56] In the African meningitis belt, from Ethiopia to Senegal, the incidence of endemic meningococcal disease is much higher. In addition, every 8 to 12 years occur outbreaks during which the rates can climb to 500 to 1000 cases per 100,000 population.[55] The outbreaks occur during the hot and dry season; some suggest that the adverse climatic conditions damage local defences of the nasopharynx and thus predispose to the infection.[6]

The carriage rate for *N. meningitidis* in populations has been estimated to be between 1 and 15 percent. Carriers are usually school-age children and young adults. Higher carriage rates appear in lower socioeconomic classes,[28] in patients´ household members, and kissing contacts.[57] In most persons, carriage results in a systemic protective antibody response. Why, in a small number of carriers, *N. meningitidis* causes a systemic disease is unknown.[55, 58]

The risk of acquisition of infection is increased in family members, in blacks, and in persons of low socioeconomic status, with exposure to tobacco smoke, or concurrent viral infection.[55, 59, 60] New military recruits or college freshmen have a higher risk of sporadic and epidemic disease, which has been explained by crowded living conditions.[55] In high school students, male gender, upper respiratory tract infection, marijuana use, and disco attendance associate with increased risk of meningococcal disease.[61] Children with immunodeficiency or sickle cell disease are more susceptible to invasive meningococcal disease. Paediatric patients with meningococcal diseases should be screened for complement deficiency.[8] HIV-positive children are probably also at increased risk.[55]

5.2 Pathogenesis and pathophysiology of childhood bacterial meningitis

Bacteria enter the central nervous system (CNS) either by haematogenous spread or by direct extension from a contiguous site (Figure 1[54, 62, 63]). In the neonatal period, bacteria are acquired mainly during birth from maternal genital secretions.[24] In infants and children, the organisms that cause meningitis colonize the upper respiratory tract by attaching to the nasopharyngeal mucosal epithelium. All meningeal bacterial pathogens express various surface proteins that facilitate pathogen-host cell interaction. *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* all produce immunoglobulin A proteases, which support colonization.[13] Choline-binding protein A (Cbp A) and neuraminidase NanA are other pneumococcal proteins that aid the colonization of the nasopharynx.[54] *N. meningitidis* uses fimbria or pili to adhere to the host´s mucosal epithelial cells.[55] If the ciliated epithelial cells are damaged, as in viral infection or with smoking, their ability to prevent mucosal adhesion of invading bacteria is weakened.[13]

S. pneumoniae uses Cbp A that binds to the polymeric immunoglobulin receptor to traverse the mucosal barrier.[54] The bacteria traverse the endothelium by endocytosis (meningococci) or by separating tight junctions (*H. influenzae*) to invade intravascular space.[13] Once in the bloodstream, encapsulated bacteria (eg. *H. influenzae*, *S.pneumoniae*, and *N. meningitidis)* avoid the host defence mechanisms, because their polysaccharide capsule inhibits neutrophil phagocytosis and complement-mediated bactericidal activity.[13] The organisms then cross the vulnerable sites of the blood–brain barrier (BBB, e.g. cerebral capillaries and

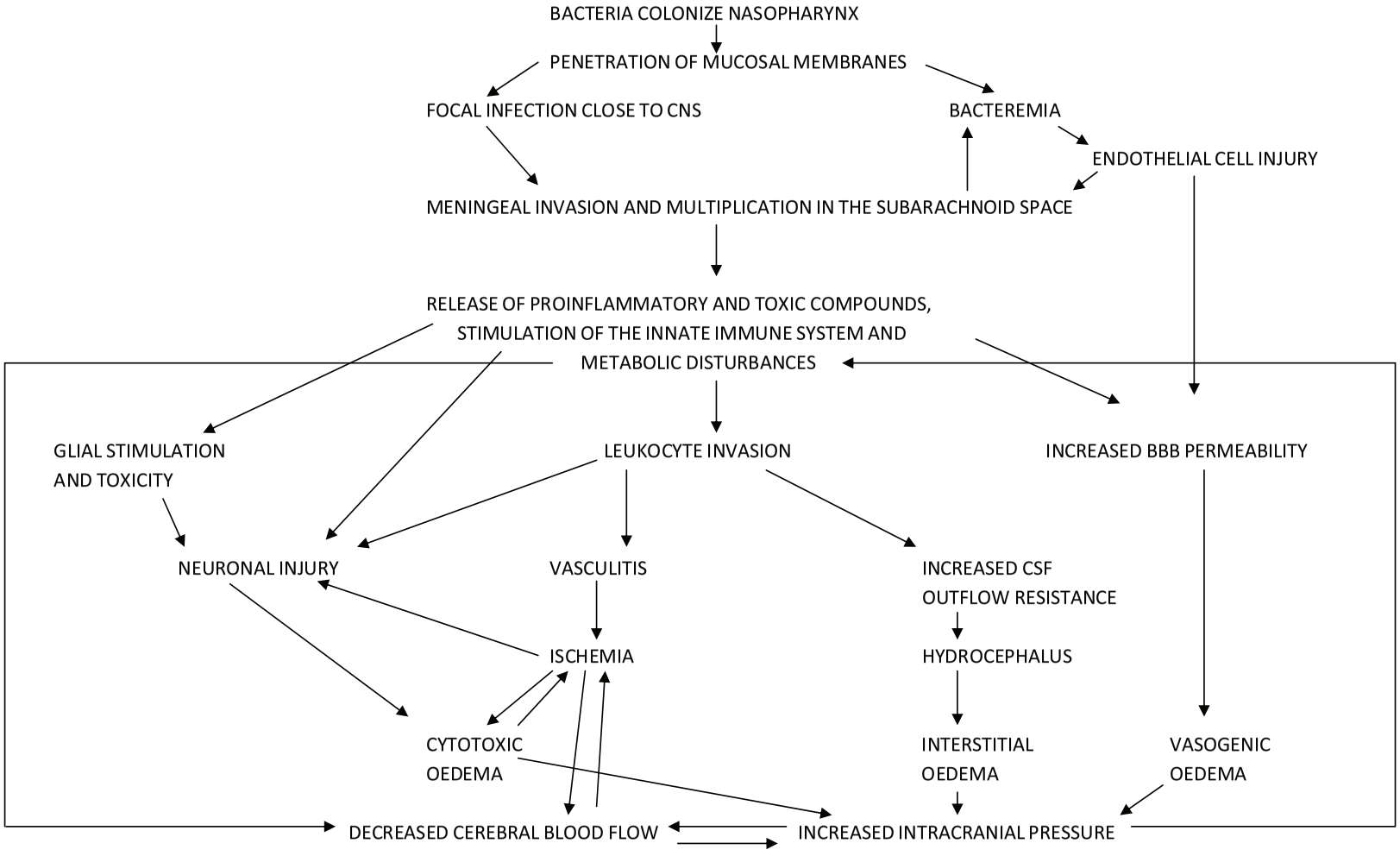


Figure 1. Pathophysiological alterations in bacterial meningitis (Adapted from Tunkel ,[62] Koedel ,[54] and Gerber.[63])

choroid plexus) and reach the subarachnoid space.[64] In the CSF, the organisms multiply rapidly because the host lacks defence mechanisms.[62]

Meningitis can also develop by direct spread of bacteria from a paranasal sinus or from the middle ear through the mastoid process. Severe head trauma with a skull fracture or penetrating wounds can also lead to meningitis. Congenital dural defects such as dermal sinuses or meningomyelocele, or neurosurgical procedures can directly inoculate bacteria into the CSF.[20]

When the pathogens have entered the CSF, they release active cell wall- or membrane-associated components; gram-positive bacteria liberate lipoteichoic acid and peptidoglygan, and gram-negative bacteria liberate lipopolysaccharide. β-lactam antibiotics that act on cell walls and cause rapid lysis of bacteria can in the beginning of the treatment cause a burst of release of these active bacterial products.[65-70] The interaction of bacterial products with host pattern recognition receptors, such as Toll-like receptors, initiates the inflammatory reaction.[71] As a consequence, CNS macrophages, astrocytes, ependymal, glial and endothelial cells release proinflammatory cytokines: interleukin (IL)-1β, IL-6, and tumour necrosis factor-α (TNF-α).[24, 72] These cytokines stimulate chemotactic cytokines called chemokines (IL-8, macrophage inflammatory proteins), other chemotactic substances (complement factor C5a, platelet-activating factor), and adhesion molecules (intercellular adhesion molecule-1) which facilitate the passage of leukocytes from the circulation into the subarachnoid space.[54, 72] Plasma and cerebrospinal concentrations of endotoxin and IL-1β, but not of IL-6 and TNFα, correlate with severity or adverse outcome of BM.[8, 73-76]

Consequently, leukocytes release nitric oxide, toxic oxygen metabolites, matrix metalloproteinases, and prostaglandins, which results in injury to the vascular endothelium and alteration of the BBB permeability (Figure 1[54, 62, 63]). Penetration of low molecular-weight serum proteins into the CSF leads to vasogenic oedema. Bacteria and neutrophils release cytotoxic substances causing cytotoxic oedema. Increased CSF volume due to a blockade of CSF resorption across the inflamed arachnoid villi causes interstitial oedema. Cerebral oedema and intracranial hypertension contribute to neuronal damage. Cerebral blood flow increases early in meningitis, but decreases later, which can aggravate the neurological damage. In recent years research has focused on Toll-like receptors, reactive oxygen and nitrogen substances, excitatory aminoacids (glutamate, aspartate), matrix metalloproteinases, and caspases in mediating cellular apoptosis and neuronal death.[20, 54, 63, 71, 72]

5.3 Clinical manifestations of childhood bacterial meningitis

Bacterial meningitis can be insidious and develop progressively over one or several days. As it may be preceded by a nonspecific febrile illness, to define the exact

onset of meningitis is therefore difficult. Another pattern of the disease is acute and aggressive; the signs of sepsis and meningitis develop in a few hours.[77]

Meningitis is generally associated with nausea, vomiting, anorexia, irritability, headache, confusion, back pain, and nuchal rigidity (Figure 2). However, especially in young children, the symptoms and signs are often non-specific. The classic combination of manifestations: fever, neck stiffness, and altered mental status, is not always seen in infants. In infants, only irritability, restlessness, and poor feeding may be noticeable. Increased intracranial pressure may cause headache and vomiting in older children, and bulging fontanel and diastasis of sutures in infants.[34]

In children and adults nuchal rigidity can associate with Kernig´s and Brudzinki´s signs. Kernig´s sign is positive when the leg is flexed 90 degrees at the hip and cannot be extended more than 135 degrees. Brudzinki´s sign is positive if the thighs and legs are flexed involuntarily when the neck is flexed.[8] However, these signs are neither sensitive nor specific. In Kenya, only 40% of hospital-admitted children with neck stiffness had BM.[78]

Petechial or purpuric lesions of the skin may accompany BM caused by any bacteria, but are more common in meningococcal meningitis. *H. influenzae, S. pneumoniae,* and *N. meningitidis* can attack joints, thus causing suppurative arthritis early, or reactive arthritis later during the disease.[20] Facial cellulitis, endophthalmitis, pneumonia, and other suppurative manifestations can associate with bacteremia and meningitis.[8]

In industrialized countries, seizures before or within 2 days of hospitalization occur in 20 to 30% of children with BM. Focal neurological signs, such as mono-, hemi-, or quadriparesis, facial palsy, ptosis (Figure 3), or strabismus, occur in about 15% of patients with BM. Sometimes, ataxia or behavioural abnormalities are the presenting sign of meningitis. Subdural effusions, which are not generally associated with signs and symptoms and resolve spontaneously, can be

Figure 2.

Figure 3.

demonstrated in up to half of infants and children during acute illness. Rarely, a brain abscess appears as a complication of meningitis.[8, 77]

Table 2 describes characteristics of children with BM in different geographical areas.[11, 14, 15, 17, 19, 79, 80] In Africa, the diagnosis of BM is difficult partly because the clinical features overlap with those of malaria.[25, 81, 82] At the initial clinical assessment, a diagnosis of meningitis is correctly included in only 30-40% of admissions for whom a final diagnosis of meningitis is recorded.[25, 81, 83, 84] The Integrated Management of Childhood Illness (IMCI) guidelines advise primary care workers to refer all children with general danger signs or a stiff neck as potential meningitis cases.[85, 86] In Gambia, a simplified set of IMCI signs (convulsions, lethargy, unconsciousness, or stiff neck) had a sensitivity of 98% and a specificity of 72% to predict BM.[87] However, in Kenya, 96% of children who met the IMCI referral criteria did not have meningitis. Their indicators for lumbar puncture (LP) or presumptive treatment were bulging fontanel, neck stiffness, cyanosis, impaired consciousness, partial seizures, and seizures outside the febrile convulsion age range, giving a sensitivity of 79% and specificity of 80%.[88] Researchers from Papua New Guinea, also an area of malaria endemicity, recommend an LP in children with impaired consciousness, meningism, and multiple seizures, but not in a child with a single simple febrile seizure.[89] Recent European guidelines agree with those preceding, but emphasize that some children with BM present with non-spesific signs which makes the diagnosis more difficult. [90, 91]

5.4 Diagnosis of childhood bacterial meningitis

LP and examination of CSF are necessary for a definite diagnosis of BM. Physicians should always perform an LP immediately when they suspect the diagnosis (Figure 4). Sometimes LP is delayed or cancelled when concern about the risk of cerebral herniation has risen, in patients with papilloedema, focal neurological signs, impaired consciousness, immunocompromise, coagulation abnormalities, or cardiovascular instability.[90, 91] Abnormalities on computed tomography (CT) do not reliably predict cerebral herniation, and a normal CT does not exclude the risk of herniation; therefore, CT should not be used to decide whether it is safe to perform LP.[90-92] CT plays a role in suspicion

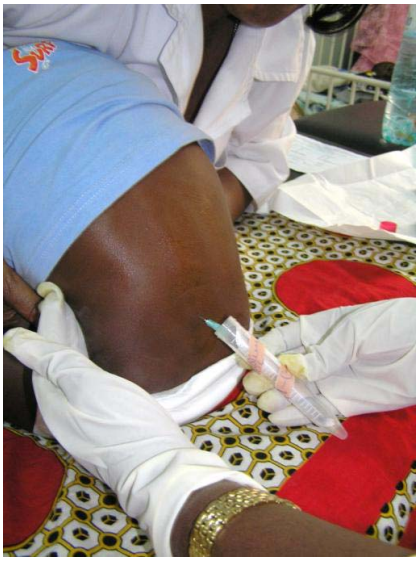


Figure 4.

Country/ Area	Age of patients	Delay in presentation	Poor general condition	Abnormal status of consciousness	Seizures prior or at admission	Focal neurological signs	Dyspnoea	Another focus of infection	Malnutrition	Dehydration	Shock or delayed capillary filling	Malaria	Haemoglobin	HIV-positive of tested	Reference
Finland	Mean + SD 31.6 + 36.0 mo	>72 hours 28%	83%	80%	19%		40%		-	-		-	-	-	Peltola 1989 [14]
United Kingdom	Median (range) 11 mo (6d-14y)	Median (range) 1d (0-10)		GCS <8 8%	23%				-	-		-	<10 g/dL 15%		Molyneux 2006 [15]
Papua New Guinea	Median 5.8-7.0 mo	Mean 6d			67%	16%			WFA<80% 27%	12%					Duke 2002 [17]
Latin America	Median (range) 12 mo (2-184)	>48 hours 12%		GCS<13 39%	32%				z score < -1 31%				Median 9.0-9.4		Peltola 2007, [11, 79] Roine 2010 [80]
Malawi	Median (range) 6 mo (1d-14y)	Median (range) 3d (1-30)		GCS <8 19%	40%				WFA<80% 49%			19%	<10 g/dL 48%	7%	Molyneux 2006 [15]
Malawi	Median (range) 13-14 mo (2-168)	Median (range) 3d (0-60) >48 hours 56%		BCS <2 35%	48%			18%	WFA 79.8-78.9%		9%	16%	Median 8.5-8.7	34%	Molyneux 2002 [19]
Angola	Median (range) 11 mo (2-150)	Median (range) 7d (1-150)	29%	61%	65%	23%	52%	38%	WFA<-2SD 32%	13%		33%	Median (range) 6.8 (1.5-16.5) <10 g/dL 90%	11%	Pelkonen, et al, Retrospective
Angola	Median (range) 14 mo (1-157)	Median (range) 5d (1-180) >72 hours 63%	52%	69% GCS<8 21% GCS<13 56%	70%	24%	46%	25%	WFA<-2SD 32%	16%		32%	Median (range) 7.7 (2.3-15.6) <10 g/dL 88%	8%	Pelkonen, et al, Prospective

Table 2. Characteristics of children with bacterial meningitis.

d=day, mo=month, y=year

of an underlying cause such as mastoiditis, and magnetic resonance imaging (MRI) in detecting and monitoring the complications of BM.[93]

Analysis of CSF should include glucose and protein concentrations, white blood cell (WBC) count and differential, and Gram stain and cultures.[20] Opening pressure is usually elevated; the average pressure is 300 mm H_2O.[8] The gross appearance of CSF is often used to determine the likelihood of BM. Turbid or cloudy CSF implies the presence of WBCs, red blood cells, bacteria, or protein. In BM, the leukocyte count is elevated, usually 1000-5000 cells/mm^3, but can be <100 or >10,000 cells/mm^3. Usually neutrophils predominate, but about 10% of patients present with lymphocyte predominance. The CSF glucose concentration is <40 mg/dL (2.2 mmol/L) in more than half of BM patients. A CSF to serum glucose ratio of ≤0.6 in neonates and ≤0.4 in older children is considered abnormal. Low CSF glucose concentration virtually excludes viral meningitis. In BM, the CSF protein concentration is elevated usually to 1,000 to 5,000 mg/L.[8, 34, 94]

Where laboratory facilities are inadequate, urinary reagent strips have been tried as a means of low-cost CSF testing,[95, 96] but in some studies their sensitivity has been low.[97] In Kuwait, urine dipsticks identified all patients with normal CSF and 97% of patients with abnormal CSF, and could distinguish viral from bacterial meningitis in 98%.[98] By adding a test for nitrites, the sensitivity can be improved.[99]

CSF culture is clearly the ideal, the "gold standard" for the diagnosis of BM,[100] but when antibiotics have been given, it lacks sensitivity (falls from 70-85% to below 50%[20]); and the culture facilities are expensive and difficult to maintain in developing countries. Pre-presentation antibiotics can alter other CSF parameters, as well: leukocyte counts can be reduced, lymphocytes predominate, and glucose concentrations rise.[78, 101] As even oral antibiotics reduce CSF bacterial concentrations and yields of Gram stain and culture, parenteral antibiotics may sterilize CSF cultures within 1 hour for meningococcal meningitis and within 4 hours for pneumococcal meningitis.[102]

Gram staining of the CSF is 60-90% sensitive and 97% specific in diagnosis of BM. However, the likelihood of visualizing bacteria depends on the concentration of bacteria. Concentration techniques of the CSF, like centrifugation, enhance the probabilities of detecting bacteria.[100, 103] Gram staining is positive in up to 15% of CSF that yield a negative culture result. Antibiotics before admission reduce the yield of Gram stain by 20%. Gram stain is rapid, inexpensive, and highly specific; it should direct initial therapy, especially where culture is unavailable.[94, 101]

Several rapid bacterial-antigen detection tests have been developed to aid in the aetiologic diagnosis of BM. Latex agglutination is simple, does not require any special equipment, and gives results in 15 minutes, but requires a considerable amount of CSF, and the reagents are not cheap. Some authors have reported good sensitivity,[104] increased sensitivity compared with culture in antibiotic-treated patients,[105] and high specificity for the common meningeal pathogens. Its routine use has been questioned, but it might prove useful in patients pre-treated with antibiotics, or when Gram staining and culture results are negative or unavailable.[94, 101] The polymerase chain reaction (PCR) amplifies DNA from CSF of BM patients

to detect common meningeal pathogens.[8] The results have been associated with high sensitivity, specificity, and predictive values. This method could prove useful in cases when Gram staining and culture remain negative. However, the method is expensive and rarely obtainable in developing countries.[94] For study purposes, filter paper strips have proved an easy way to store CSF. The strips can be transported by regular mail to a centre with facilities for PCR.[106]

Acute-phase reactants that have been used in the diagnosis of BM are not specific for BM. C-reactive protein (CRP) is useful in distinguishing bacterial from viral meningitis.[107] CRP may help in cases in which CSF is suggestive of meningitis, but the Gram stain remains negative; normal CRP has a high negative predictive value in the diagnosis of BM.[94] Procalcitonin (PCT) is also useful in distinguishing bacterial from viral meningitis; it increases in septic infection and decreases during antibiotic therapy rapidly.[108, 109] It is, however, more expensive than CRP. In Malawian children, both CRP and PCT proved good predictors of serious bacterial infection, and BM; PCT had some value in predicting death, as well.[110]

Complex predictive models have been developed in industrialized countries to distinguish between bacterial and viral meningitis. The Bacterial Meningitis Score has generally performed well but missed rare patients with BM.[111] The Meningitest added procalcitonin and has showed 100% sensitivity and 52% specificity.[112, 113]

Differential diagnosis of BM includes aseptic meningitis, brain abscess, epidural abscesses, bacterial endocarditis with embolism, subdural empyema, and brain tumours.[8] Both BM and cerebral malaria cause fever, headache, and altered consciousness. In Kenya, 14% of comatose infants with positive malaria smear had proven BM; in sub-Saharan Africa even if malarial parasites are seen in the blood of comatose children, BM must be excluded.[82] Partially treated BM is a diagnostic challenge in many developing countries where antibiotics can be bought freely over the counter. Differentiation between partially treated BM and tuberculous or viral meningitis is difficult with limited diagnostic resources. Viral aetiology (mostly enteroviruses) may account for 14-25% of all meningitis cases in Africa.[101, 114] A rapid HIV test is important in areas of high prevalence. If the test is positive, *Cryptococcus neoformans*, *Mycobacterium tuberculosis,* and *Toxoplasma gondii* should be born in mind.[101] In some areas of Africa, also trypanosomiasis, "sleeping sickness," can cause meningoencephalitis.[115] In some parts of Europe or North America, children with neuroborreliosis can present with subacute meningitis, facial or other cranial nerve palsies.[116]

5.5 Treatment of childhood bacterial meningitis

5.5.1 Antimicrobials

Factors in choosing an antimicrobial for BM are its activity against the probable pathogens and its ability to gain adequate bactericidal activity in CSF. Meningitis causes increased permeability of the BBB to most antibiotics. The concentrations of β-lactam antibiotics in CSF are 5 to 20% of respective serum values.[24] Experimental models have shown that prompt bacterial killing in CSF is reached with antibiotic concentrations 4 to 5 times the minimum inhibitory concentration (MIC) of the specific pathogen.[117]

The pharmacokinetic and dynamic properties of antimicrobials differ – and affect their bacteriologic efficacy. Aminoglycosides, fluorokinolones, and metronidazol are concentration-dependent agents; i.e. their effectiveness depends on the ratio between the peak concentration or area under the concentration curve of the antibiotic and the minimal bactericidal concentration (MBC) of the pathogen. β-lactam antibiotics, aztreonam, and vancomycin exhibit time-dependent bactericidal activity; i.e. the time their plasma concentrations remain above the MIC determines their efficacy.[118-120]

Traditional intermittent drug administration results in high peak and low trough serum levels and can result in concentrations below the MIC over a long period. Several animal studies suggest that it is efficacious to administer β-lactams continuously.[121-124] In rabbits with group B streptococcal meningitis, cefotaxime infusion kills the bacteria effectively.[125] The first reports of continuous antibiotic administration in humans included small numbers of patients,[117, 126] until a meta-analysis of randomised controlled trials suggested that continuous infusion of antibiotics is at least as efficacious as intermittent administration.[127] In recent years, studies in critically ill patients have shown β-lactam infusion to equal an intermittent administration.[128-130] In a randomised controlled study in COPD patients with respiratory tract infections, continuous cefotaxime administration led to greater proportions of concentrations >MIC and >5 x MIC compared with intermittent dosing.[131] Some centres in Germany and Austria have since 1980s treated childhood pneumococcal meningitis with slow penicillin infusion.[132]

The initial empiric antibiotics should cover the most likely pathogens for the age group of the patient. In neonates with early-acquired meningitis, the initial therapy is ampicillin with an aminoglycoside or cefotaxime. In late-onset neonatal infection, the therapy should cover staphylococci and include nafcillin or vancomycin, plus cefotaxime or ceftazidime. In infants of 1-3 months of age, ampicillin and a third-generation cephalosporin (ceftriaxone or cefotaxime) is recommended, because of the probability of *Listeria* or enterococci in this age-group. After that age, monotherapy with a third-generation cephalosporin suffices.[20, 133] However, in areas with pneumococcal resistance to penicillin and cephalosporins, addition of

vancomycin to the third-generation cephalosporin is a practice guideline. Moreover, in patients with basilar skull fracture the combination of vancomycin and third-generation cephalosporin can be used. However, in patients with penetrating trauma, CSF shunt, or having had neurosurgery, the initial therapy should include vancomycin plus cefepime, ceftazidime, or meropenem.[94, 134]

Treatment can be modified when the disease-causing pathogen is identified, and its antimicrobial susceptibilities are known. Penicillin G or ampicillin is still the standard therapy for susceptible (MIC ≤0.06 μg/mL) strains of *S. pneumoniae* or *N. meningitidis*; a third-generation cephalosporin is an alternative.[135] A third-generation cephalosporin is indicated if the organism is not susceptible to penicillin (MIC ≥0.1 μg/mL), but is susceptible to the cephalosporin (MIC ≤0.5 μg/mL). If the strain of *S. pneumoniae* is not susceptible to penicillin, and its MIC to the third-generation cephalosporin is ≥1.0 μg/mL, the patient should be treated with a combination of vancomycin and a third-generation cephalosporin. If the MIC to the third-generation cephalosporin exceeds 2 μg/mL, the addition of rifampin should be considered.[50] The standard therapy for β-lactamase-negative *H. influenzae* is ampicillin; a third-generation cephalosporin is an alternative. If the strain produces β-lactamase, the therapy should be with a third-generation cephalosporin—chloramphenicol, fluoroquinolones, and meropenem being alternatives.[94, 136]

WHO recommends the use of ceftriaxone as first-line therapy in Africa.[137] This is, however, expensive, and therefore benzylpenicillin or ampicillin and chloramphenicol are still popular in many countries.[101] A Cochrane meta-analysis found no significant difference in risk of death, deafness, or treatment failure between the third-generation cephalosporins and conventional antibiotics. The authors concluded, however, that the antimicrobial resistance has to be monitored.[138] Drug resistance is a major problem especially in developing countries, where facilities for culture and susceptibility testing lack and second-line antibiotics are too expensive.[27, 101]

Duration of the antimicrobial treatment depends on the age of the patient, the causative bacteria, and the clinical course. In the past, when resistance was not a problem, BM was treated successfully with only one injection of long-acting sulfonamide,[139] penicillin,[140] or chloramphenicol, which was effective also against Hib and pneumococcus.[141] Currently, for neonates with group B *Streptococcus* or *Listeria monocytogenes,* 10 to 14 days is recommended, and for Gram-negative enteric meningitis, a minimum of 3 weeks is necessary.[24] In many parts of the world meningococcal meningitis is treated for 4 to 7 days; *H. influenzae* for 7 to 10 days; and *S. pneumoniae* for 10 to 14 days.[24] However, a meta-analysis demonstrated no difference between short-course (4-7 days) and long-course (7-14 days) treatment with intravenous ceftriaxone regarding clinical success or long-term neurological or hearing sequelae.[142]

In developing countries, the WHO recommends shorter courses.[137] One intramuscular dose of ceftriaxone or oily chloramphenicol can effectively treat uncomplicated meningococcal meningitis.[143] In meningitis caused by other bacteria, the WHO recommends 5 days of therapy for immunocompetent patients with

uncomplicated recovery. However, in immunocompromised patients, HIV patients, or in patients with persistent fever, seizures, and coma, therapy should be extended.[101, 137] Salmonella meningitis requires at least 2 weeks of intravenous therapy.[144]

The introduction of sulphonamides in the 1930s reduced mortality in bacterial meningitis from 98% to 25 %. The introduction of penicillin brought, however, only a modest decline in the mortality.[145] Newer and more potent antimicrobial agents have failed to produce any further reductions in morbidity and mortality, except in cases caused by resistant bacteria.[14] This unexpected outcome may result from the host´s inflammatory response to invading bacteria.[54, 72]

5.5.2 Adjunctive Treatment

Corticosteroids have been suggested as an adjunct to therapy of BM because they may reduce intracranial pressure [9] and modulate the production of cytokines.[9, 70, 76, 146, 147] Limiting dexamethasone therapy to 2 days seemed to be optimal.[148] However, studies from developing countries have given differing results. In a prospective study in Pakistan, dexamethasone even proved harmful,[149] and in Malawi no benefit was observable.[19] A study in Latin America showed very little benefit even in Hib meningitis.[11] Finally, in a recent meta-analysis (2010) of 2029 patients for which raw data were available, dexamethasone reduced any hearing loss among survivors of BM (OR 0.77, 0.60–0.99, p=0.04), but no significant effects occurred as to mortality or neurological sequelae, or in any subgroups (causative organisms, prior antibiotic treatment, HIV status, or age). The authors state that the benefit of adjunctive dexamethasone in BM remains unproven.[10] In the latest Cochrane review (2010) of 4041 patients, dexamethasone reduced hearing loss and neurological sequelae in high-income countries. In low-income countries no beneficial effect appeared. Subgroup analysis of high-quality studies showed dexamethasone to be beneficial only in preventing severe hearing loss.[150]

Glycerol (glycerine, 1, 2, 3-propanetriol), which is a naturally occurring trivalent alcohol, an essential compound of the human cell-membrane, an hyperosmolar agent and osmotic diuretic, was used for decades in neurosurgery and in neurological disorders, as well as in Ménière's disease.[151-155] In one Finnish study, oral glycerol suggested a beneficial effect on neurologic sequelae of paediatric BM,[156] and later a very large (n=654) study in Latin America clearly showed reduced risk of severe neurological sequelae of paediatric BM.[11] The mechanism by which glycerol works is increase in serum osmolality and cerebral blood flow, and thus improved brain oxygenation. Osmotic diuresis plays a minor or no role.[11, 157-159]

Non-steroidal anti-inflammatory drugs (NSAID) relieve the host´s inflammatory response.[72] The inhibition of the cyclooxygenase (COX, prostaglandins, and thromboxans) pathway of arachidonic acid metabolism by NSAIDs (oxindanac,

indomethasin and diclofenac) has reduced inflammation in animal studies of meningitis.[160, 161] In adults with clinical sepsis, ibuprofen reduced levels of prostacyclin and thromboxane and reduced fever, tachycardia, oxygen consumption, and lactic acidosis, but did not prevent shock or acute respiratory distress syndrome and did not improve survival.[162, 163]

Some NSAIDs seem, however, to inhibit inflammatory reactions, also ones other than those mediated by inhibition of arachidonic acid metabolism, namely activation of neutrophils.[164] Paracetamol (acetaminophen) is an inexpensive, effective, and safe antipyretic and analgesic drug much used in children.[165-173] It has weak anti-inflammatory activity and inhibits COX enzymes, especially COX3, and thus prostaglandin synthesis in the CNS, and NMDA (*N*-Methyl-D-aspartic acid) receptors in the hypothalamus.[174-177] One observational study, a retrospective analysis of 809 adult patients with *S. pneumoniae, S. aureus, E. coli, or P. aeruginosa* bacteraemia in Helsinki, found paracetamol, in the final logistic regression analysis, to be independently associated with a reduced risk of death (odds ratio 0.24, 95% CI 0.11-0.51 and p value <0.001).[178-180]

5.5.3 Supportive therapy

Previously, fluid restriction has been the practise in BM to prevent the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). SIADH causes hyponatraemia, which is common in BM, and is thought to worsen cerebral oedema and thus the outcome of BM.[8] However, this viewpoint has been challenged.[181-183] Fluid restriction can result in decreased systemic blood pressure and impaired cerebral perfusion.[184] Singhi and colleagues examined fluid restriction in BM children with or without hyponatraemia. Children with restricted fluids showed significant decreases in total body water and extracellular water (ECW). Children with ECW reduction of ≥10 ml/kg had higher mortality than children with <10 ml/kg or no ECW reduction. Low plasma osmolality, low ECW at admission, and ECW reduction correlated with poor outcome.[181]

A randomised trial in Papua New Guinea found fewer seizures after 72 hours, reduced spasticity at 14 days, and reduced neurological sequelae at 4 weeks in BM children with intravenous fluid at maintenance volumes *vs.* those with oral fluid restriction. Sunken eyes and reduced skin turgor associated with adverse outcome, especially in the fluid-restricted group.[17] A recent meta-analysis preferred maintaining intravenous fluids rather than restricting them in the first 48 hours, in settings with high mortality rates and where patients present late. However, in industrialized countries, evidence was insufficient to guide practice.[185] A recent European guideline recommends correction of dehydration with intravenous isotonic fluids, and fluid restriction only when evidence shows raised intracranial pressure or SIADH. [90, 91] In developing countries, nasogastric tube and enteral

hydration are used instead of intravenous fluids, which are more expensive and require skilled staff and more intensive supervision.[101]

Possible hypovolaemia and shock should be checked for and if present, corrected urgently with isotonic intravenous fluids.[17] In industrialized countries, vasoactive agents such as dopamine or dobutamine are infused to maintain normal blood pressure and to ensure sufficient cerebral circulation.[8] Guidelines have been developed especially for treatment of meningococcal disease.[90, 91, 186]

Simple measures such as attempts to reduce intracranial pressure include 30° bed head elevation and avoidance of head tilting and vigorous procedures. Control and prevention of seizures can be achieved with anticonvulsant medications: benzodiazepines, phenobarbital, and phenytoin.[24] In Malawi, easy-to-use intranasal lorazepam was as effective and safe as intramuscular paraldehyde in children with protracted convulsions.[187] In Ugandan children, buccal midazolam was as safe as—and in children without malaria also more effective than—rectal diazepam for the treatment of prolonged seizures.[188] The high cost, however, of midazolam may prevent its use in developing countries.

5.6 Prognosis and sequelae of childhood bacterial meningitis

5.6.1 Prognosis

The outcome of BM in developing countries is much worse than in industrialized countries (Table 3[11, 14, 15, 17, 19, 80]). Mortality is approximately 5% in industrialized countries and 12-60% in resource-poor countries.[3, 8, 15, 20, 26, 34] In 2000, Hib meningitis was estimated to have caused globally 78,300 deaths in children younger than 5 years, of which 34,000 were in Africa and 2,000 in Europe; the case fatality estimates were 43, 67, and 27%, respectively.[4] The same estimates for pneumococcal meningitis were 60,500 deaths globally of which 31,700 were in Africa and 1,300 in Europe, case fatality estimates being 59, 73, and 38%, respectively.[5] In a recent review of BM among African children, the reported in-hospital mortality in pneumococcal, Hib, and meningococcal meningitis was 35, 25, and 4 %. Of children followed up after discharge, 10% died. [189]

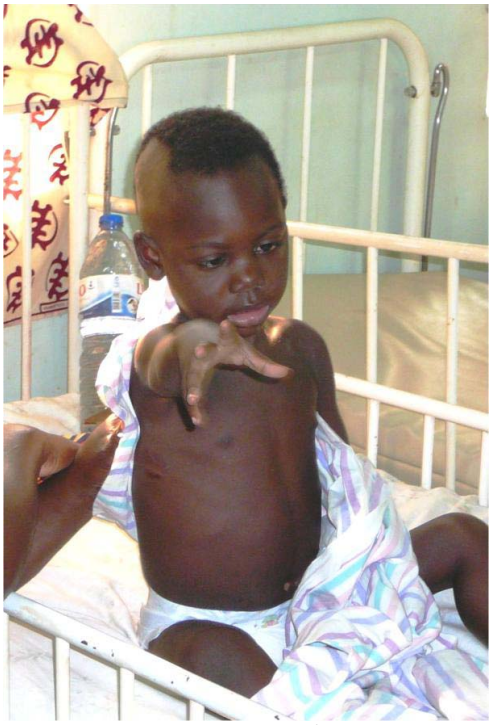
Sequelae of BM include sensorineural hearing loss, decreased cognitive function, dizziness, seizures, motor deficits, focal neurological deficits, paralysis, blindness (Figure 5), and hydrocephalus.[13] Less severe or minor sequelae documented are transient ataxia, behavioural problems, learning difficulties, unilateral hearing loss, hypotonia, and diplopia.[2, 190]

Sequelae are reported in 15-20% of survivors of childhood BM in industrialized countries and in 25-50% in developing countries.[3, 8, 26, 34] In a prospective study in

Country/Area	Pathogen	Number of patients	Death	NeSeq	HeSeq	Seq	Death or Seq	Reference
Finland	All	200	4.5%	A 7%	6 mo, A 5%		ANe 8%	Peltola 1989 [14]
United Kingdom	All	197	7%			A 10%	A 17%	Molyneux 2006 [15]
	Haemophilus influenzae	53	6%			A 6%	A 11%	
	Streptococcus pneumoniae	22	0%			A 23%	A 23%	
	Neisseria meningitidis	111	10%			A 8%	A 17%	
Papua New Guinea	All	346	17%	Se 16%			SeNe 29%	Duke 2002 [17]
Latin America	All	654	13%	Se 8%	Se 8%		SeNe 20%	Peltola 2007,[11] Roine 2010 [80]
	Haemophilus influenzae	221	14%	Se 7%	Se 12%		SeNe 21%	
	Streptococcus pneumoniae	132	23%	Se 13%	Se 9%		SeNe 33%	
	Neisseria meningitidis	110	1%	Se 1%	Se 3%		SeNe 2%	
Malawi	All	175	41%			A 17%	A 33%	Molyneux 2006 [15]
	Haemophilus influenzae	44	43%			A 31%	A 59%	
	Streptococcus pneumoniae	62	46%			A 23%	A 56%	
	Neisseria meningitidis	7	28%			A 0%	A 28%	
Malawi	All	598	31%	A 30%			ANe 52%	Molyneux 2002 [19]
	Haemophilus influenzae	170	29%	A 34%			ANe 53%	
	Streptococcus pneumoniae	238	39%	A 33%			ANe 59%	
	Neisseria meningitidis	67	4%	A 14%			ANe 18%	
Angola	All	555	35%	Se 23%			SeNe 52%	Pelkonen, et al, Retrospective
	Haemophilus influenzae	247	33%	Se 27%			SeNe 52%	
	Streptococcus pneumoniae	98	38%	Se 27%			SeNe 56%	
	Neisseria meningitidis	42	12%	Se 12%			SeNe 23%	
Angola	All	723	38%	Se 15% A 53%	Se 12% A 27%	Se 26% A 68%	SeNe 47% Se 56% A 80%	Pelkonen, et al, Prospective
	Haemophilus influenzae	188	33%	Se 13% A 57%	Se 13% A 34%	Se 26% A 72%	SeNe 42% Se 54% A 82%	
	Streptococcus pneumoniae	184	45%	Se 19% A 65%	Se 17% A 30%	Se 30% A 78%	SeNe 55% Se 64% A 86%	
	Neisseria meningitidis	49	14%	Se 2% A 21%	Se 7% A 19%	Se 11% A 36%	SeNe 16% Se 24% A 45%	

Table 3. Outcome of childhood bacterial meningitis by region. A = any, He=hearing, Ne=neurological, Se=severe, Seq=sequelae

Figure 5.



urban Senegal, the 66 survivors of BM had three times greater odds (65%) of major sequelae than did their 66 controls (41%); 52% had hearing, 40% cognitive, and 21% motor deficits, 21% seizures, and 35% multiple impairments.[191] In a recent meta-analysis (2010), the median risk of at least one major or minor sequela from BM was 20%. The risk of at least one major sequela (cognitive or motor deficit, bilateral hearing loss, visual impairment, and hydrocephalus) was 13%; 25% in pneumococcal, 10% in Hib, and 7% in meningococcal meningitis. In Africa, the risk of a major sequela was 25% *vs.* 9% in Europe.[2]

Deafness is the most common serious complication of BM in children; deafness comprises one third of all major sequelae.[2] In industrialized countries, approximately 6-14% of survivors are left with permanent sensorineural hearing loss.[2, 3, 192-197] Hearing loss seems to develop during the acute stage of meningitis, but progression and fluctuation of hearing loss occur.[193, 198-200] The inner ear is the site of the auditory lesion.[200, 201] *S. pneumoniae* causes hearing loss in 8-50%, *H. influenzae* in 3-40%, and *N. meningitidis* in 3-25% of the cases.[2, 197, 201, 202] Up to 25% of the children do not undergo any formal hearing test after BM, even in industrialized countries,[192, 203] and the situation is much worse in developing countries.[204] Brain stem-evoked response audiometry (BERA, ABR, BSA),[196, 205] which measures the stimulus-evoked electrophysiological response of the VIIIth cranial nerve and brainstem, is useful in hearing assessment of childhood BM,[206, 207] also in developing countries (Figure 6).[208,

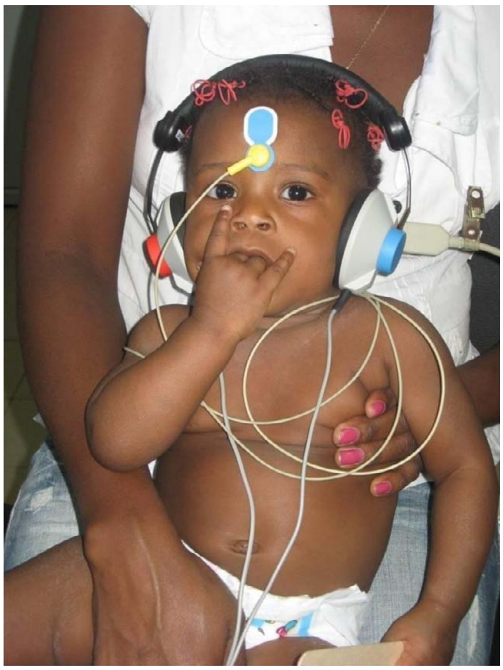


Figure 6.

[209] The transient evoked otoacoustic emission (TEOE) method is an alternative and cost-effective test for hearing screening. If TEOEs are absent, more precise methods should be used.[210, 211]

Long-term consequences of childhood BM have gained attention in recent years. BM in children is associated with a substantial excess risk of intellectual, cognitive, and auditory impairment that persists into adolescence.[212-216] In a review (2010) of 1433 survivors of childhood BM, 49% had at least one long-term sequela; 45% behavioural or intellectual, 7% auditory, and 14% gross neurologic deficits.[217]

5.6.2 Risk factors for unfavourable outcomes

The prognosis of childhood BM varies depending on multiple clinical and laboratory factors (Table 4[190, 218-222]). Identification of these factors at hospital admission or during the course of the disease aids clinicians in finding the high-risk patients who are at greatest danger of dying or developing sequelae.

Mortality is high in the neonatal period. Infections caused by Gram-negative enteric bacilli and pneumococci are, according to many studies, associated with higher mortality than those caused by *H. influenzae* or *N. meningitidis*..[13, 20] Other factors associated with high mortality rates are decreased level of consciousness, signs of increased intracranial pressure, seizures, severe respiratory distress, need for mechanical ventilation, hypotension, delayed capillary filling, hyperthermia, malnutrition, delay in initiation of treatment, low CSF leukocyte count, low CSF glucose level, high CSF protein level, low white blood cell count, and low platelet count.[13, 80, 221, 223, 224] In the USA, the death rates for *H. influenzae* meningitis used to be 3.5 times higher in blacks than in whites, which was explained by lack of access to early medical care.[225, 226]

Impaired consciousness, seizures and prolonged seizures are signs of severe disease and their presence correlates with neurological sequelae. Risk factors are young age, hyperthermia, malnutrition, male gender, low blood and CSF leukocyte count, low CSF glucose, and high CSF bacterial load.[80, 224, 227] The risk of hearing loss is increased with young age, impaired consciousness, seizures, ataxia, delay in treatment, previous antimicrobials, *S. pneumoniae* as the causative pathogen, absence of petechiae, low blood leukocyte count, low CSF glucose, and high CSF protein.[193, 195, 202, 224, 228] Furthermore, low socioeconomic status associates with poor outcome.[229, 230] Some studies have described higher risk of sequelae in indigenous than other populations.[231, 232]

Country /Area	Pathogen	Number of patients	Age of patients	Follow-up duration	Outcome	Analysis	Significant prognostic factors	Reference
Norway	All	92	Median (range) 1.9 y (1 mo – 13.8 y)	Mean 6 w	Death or any sequelae	Multi-variate	Delay >48 h, pre-hospital convulsions, peripheral vasoconstriction, temperature ≤38.0 ° C, CSF leukocytes < 1000 x 10^6/l	Kaaresen 1995 [218]
Australia	All	138	3 mo – 14 y	Mean (range) 6.7 y (5.3-9.3)	Death or any sequelae	Uni-variate	Age ≤12 months, tertiary referral, delay > 24 h, convulsions, focal neurological signs, serum sodium < 130 mmol/L, Pnc, deteriorating consciousness in hospital	Grimwood 1996 [190]
						Multi-variate	Age ≤12 months, delay > 24 h,convulsions after 72 h in hospital, focal neurological signs	
India	All	80	Mean (range) 31 mo (2 mo – 12 y)	Mean(range) 28 mo (12-44)	Any NeSeq	Multi-variate	GCS score <8, cranial nerve palsy, abnormal deep tendon reflexes	Singhi 2007 [219]
Paraguay	Pnc	72	Mean (range) 48 mo (1 mo – 15 y)	Hospital discharge	Death	Uni-variate	Age <12 mo, GCS<9, convulsions, convulsions >48 h, low CSF glucose, high CSF protein, low blood leukocytes, low haemoglobin	Lovera 2005 [220]
				Hospital discharge	Death or SeNeSe	Uni-variate	Age <12 mo, GCS<9, convulsions, convulsions >48 h, low CSF leukocytes, low CSF glucose, high CSF protein, low blood leukocytes, low haemoglobin	
Latin America	All	654	Median (range) 12 mo (2-184)	Hospital discharge	Death	Uni-variate	Young age, delay >48 h, prior convulsions, GCS, slow capillary filling, low CSF glucose, high CSF protein, low blood leukocytes, low blood glucose, Pnc, not Mnc	Roine 2008 [221]
						Multi-variate	GCS, capillary filling time >3 s, CSF protein ≥250 g/dL	
					Death or SeNeSe	Uni-variate	Young age, delay >48 h, prior convulsions, GCS, rapid pulse, slow capillary filling, low CSF glucose, high CSF protein, low blood leukocytes, low blood haemoglobin, Pnc, not Mnc	
						Multi-variate	Delay >48 h, GCS, CSF protein ≥250 g/dL, blood leukocytes <15,000/mm^3	
					Death or any NeSeq	Uni-variate	Young age, delay >48 h, prior convulsions, GCS, rapid pulse, slow capillary filling, low CSF leukocytes, low CSF glucose, high CSF protein, low blood leukocytes, low haemoglobin, Pnc, not Mnc	
						Multi-variate	Prior convulsions, GCS, capillary filling time >3, CSF glucose ≤20 mg/dL, blood leukocytes <15,000/mm^3	
Nigeria	All	109	1 mo – 15 y	Hospital discharge	Death	Uni-variate	Coma, convulsions, shock	Akpede 2002 [222]
					Any NeSeq	Uni-variate	Age <12 mo, delay >7 d, prior antibiotic treatment, coma, convulsions, focal nerve deficits, abnormal posturing, abnormal muscle tone	
					Death or any NeSeq	Uni-variate	Age <12 mo, delay >7 d, prior antibiotic treatment, coma, convulsions, focal nerve deficits, abnormal posturing, abnormal muscle tone, lack of typical meningeal signs, shock	
Angola	All	403	Median (range) 9 mo (2 mo – 12 y)	Hospital discharge	Death	Uni-variate	Prior convulsions, WFA <-2 SD, poor general condition, impaired consiousness, GCS, BCS, convulsions at admission, additional focus of	Pelkonen et al, Retrospective

							infection, severe dyspnoea, not Mnc, other bacteria	
						Multi-variate	Impaired consiousness, convulsions at admission, severe dyspnoea	
					SeNeSe	Uni-variate	Delayed presentation, prior convulsions, WFA <-2 SD, poor general condition, impaired consiousness, GCS, BCS, convulsions at admission, low CSF glucose, not Mnc	
						Multi-variate	Delay >3 days, impaired consiousness, convulsions at admission	

Table 4. Prognostic factors for unfavourable outcomes in childhood bacterial meningitis.

d=day, mo=month, w=week, y=year; NeSeq= neurological sequelae, SeNeSe= severe neurological sequelae; Mnc= *Neisseria meningitidis*, Pnc= *Streptococcus pneumoniae*

Country/Area	Finland	North America	Nigeria	Angola	Angola	Angola	Angola
Pathogen	All	*H.influenzae*	All	All	All	All	All
Outcome	Death or any seq	Death or SeSeq	Death or any NeSeq	Dismal	Death	Death or SeNeSe	Dismal
Sex	Male - 1.583 Female - 0.508						
Age		<12 mo - 1	age ≤2 y - 2				
Electricity at home				Present – 0 Absent – 2 Unknown -1		Present – 0.742 Absent – 1.276	Present – 0.778 Absent – 1.259
Delay	<24 h – 0.486 24-47 h – 0.945 48-71 h – 1.335 ≥72 h - 1.783	>3 d - 0.5	>7 d - 1.5	≤3 d – 0 4-7 – 1 ≥8 – 3 Unknown - 1	≤3 d – 0.682 4-7 – 1.001 ≥8 – 1.740	≤3 d – 0.625 4-7 – 0.999 ≥8 – 2.122	≤3 d – 0.698 4-7 – 0.957 ≥8 – 2.349
Consciousness		Severe coma - 3	Coma - 0.5	Normal – 0 Altered – 5 Coma – 10 Unknown - 1	Normal – 0.227 Altered – 1.432 Coma – 3.665	Normal – 0.216 Altered – 1.526 Coma – 6.508	Normal – 0.271 Altered – 1.514 Coma – 6.925
Seizures		On admission - 2	On admission - 2.5	On admission Absent – 0 Focal – 1 Generalized – 2 Unknown - 1		At home Absent – 0.392 Focal – 1.167 Generalized – 1.405	At home Absent – 0.455 Focal – 1.180 Generalized – 1.522
Focal neurological signs	Present – 3.241 Absent – 0.926						
Abnormal muscle tone			1				
Neck rigidity	Present – 1.150 Absent – 0.772						
Petechiae	Present – 0.864 Absent – 1.114						
Otitis media	Present – 0.442 Absent – 1.197						
Temperature		<36.6 °C - 2					
Dyspnoea				None to slight – 0 Moderate – 1 Severe – 2 Unknown - 1	None to slight – 0.698 Moderate – 1.600 Severe – 2.621	None to slight – 0.729 Moderate – 1.486 Severe – 2.970	None to slight – 0.727 Moderate – 1.687 Severe – 2.522
Shock		Syst.RR < 60 mmHg - 1	Hypovolaemic shock - 1				
CSF leukocytes	<5,000x10^6/l –1.179 5,000-9,999 - 0.926 >10,000 – 0.695	<1,000/mm^3 - 1					

CSF granulocytes	<80% - 1.389 80-89% - 1.335 90-100% - 0.775						
CSF glucose	<1.0 mmol/L– 2.206 1.0-1.9 – 0.810 ≥2.0 – 0.512	<20 mg/dL - 0.5					
CSF Gram stain	Positive – 1.158 Negative – 0.154						
Haemoglobin	≤110 g/L – 1.783 >110 – 0.782	<11 g/dL – 1					
Blood leukocytes	<5.0x10^9/L –0.972 5.0-15.0 – 1.080 15.1-25.0 – 1.006 >25.0 – 0.810						
Blood platelets	<150x10^9/L–2.493 151-300 – 1.042 >300 – 1.216						
Blood glucose					≤40 mg/dL – 1.408 41-100 – 0.700 101-120 – 3.906 ≥121 – 9.797	≤40 mg/dL – 1.446 41-100 – 0.733 101-120 – 3.518 ≥121 – 8.575	≤40 mg/dL - 1.279 41-100 – 0.803 101-120 – 3.108 ≥121 – 9.399
Serum potassium	≤3.5 mmol/L–1.297 >3.5 – 0.953						
Method	Likelihood ratios Multiplication	Adding-up	Adding-up	Multivariate analysis Adding-up	Likelihood ratios Multiplication	Likelihood ratios Multiplication	Likelihood ratios Multiplication
Highest score		12	8.5	19			
High risk score	≥2.71	≥4.5	≥2.5	≥7	≥1.08	≥1.09	≥0.82
Reference	Valmari 1987 [233]	Herson 1977 [234]	Akpede 2002 [222]	Pelkonen et al, Prospective	Pelkonen et al, Prospective	Pelkonen et al, Prospective	Pelkonen et al, Prospective

Table 5. Prognostic scales for unfavourable outcomes in childhood bacterial meningitis.

d=day, mo=month, y=year; NeSeq= neurological sequelae, SeNeSe= severe neurological sequelae, SeSeq = severe sequelae

5.6.3 Scoring systems for prognostication

Scales based on risk factors can measure illness severity, assess therapeutic requirements and efficacy, and determine prognosis (Table 5[222, 233, 234]). They are valuable in studies and in comparisons between centres. Complex scales used in intensive care units in industrialized countries are not of much use in the developing world. [235-237]

Herson and Todd created a scale with nine clinical parameters (severe coma, hypothermia, seizures, shock, age <12 months, CSF leukocytes <1,000/mm^3, haemoglobin <11 g/dL, CSF glucose <20 mg/dL, symptoms >3 days) at admission for predicting death or major sequelae after *H. influenzae* meningitis. Score >4 indicates high risk.[234] The scoring system is much used, and has proved useful in predicting major sequelae in other meningitides as well.[232] A multivariate prognostic method based on likelihood ratios was created on the basis of initial clinical and laboratory data of Finnish children with BM.[233] A Dutch scale identified male gender, atypical convulsions, low body temperature, and pneumococcal (and meningococcal) aetiology as independent predictors of death or neurological sequelae.[238] Akpede and colleagues in Nigeria have developed a simple model for prognosis of an abnormal course (seizures during treatment) or adverse outcome (death or recovery with neurological sequelae) using six bedside features: age ≤2 years, duration of illness >7 days, seizures, hypovolaemic shock, coma, and abnormal muscle tone.[222]

As the status of consciousness seems to be the most important predictor of outcome in BM, coma scales are much used in prognosis, separately or as part of another scale.[221, 239] The Glasgow Coma Scale (GCS) was developed to assess adults with cerebral trauma, and paediatric modifications soon followed.[240, 241] The Blantyre Coma Scale (BCS), originally created to predict outcome in ≥1-year-old children with malaria is simple and easy to use, as it comprises only three clinical parameters: best motor response, best verbal response, and eye movements.[242]

5.7 Prevention of childhood bacterial meningitis

5.7.1 Vaccination

Immunization is eventually the only effective method to prevent BM. Conjugated Hib vaccines have shown good protection in various studies,[20, 243-245] including studies from developing countries.[38, 40, 246, 247] Therefore, universal infant vaccination should be routine in all countries.[136] However, 17% of the world´s countries do not have Hib vaccination in their national programme,[7] and in many countries the coverage is not optimal.[248]

Pneumococcal conjugates combine 7 to 13 capsular serotypes in one vaccine.[7] A decline in invasive pneumococcal disease and meningitis has been observable after the introduction of vaccine in many areas.[43-45, 249 ,250, 251] Pneumococcal conjugate is recommended for children younger than 24 months, and for high-risk children 25 to 60 months of age,[50] but fewer than 50 countries have introduced pneumococcal vaccines into their programmes.[7] International donors and the vaccine industry should negotiate affordable prices for poor countries.[252] Serotype replacement has occurred in areas where 7-valent pneumococcal vaccines were introduced and necessitates surveillance to monitor vaccine impact and serotype distribution.[7, 249, 253] The first 7-valent conjugate did not include serotype 1, which in some areas of Africa causes almost half of all pneumococcal meningitis cases.[47]

A quadrivalent meningococcal polysaccharide vaccine against serogroups A, C, Y, and W-135 is not recommended for children because of inconsistent immunogenicity at young ages. However, it is recommended for high-risk children older than 2 years, children with asplenia, HIV, or complement deficiency; for students living in dormitories, army recruits; for travellers to endemic areas, and during outbreaks.[13, 20, 24, 254] A quadrivalent conjugate vaccine has been approved in Europe for adolescents over 10 years old, in the USA even for children over 2 years old.[135, 255] To prevent epidemics of meningococcal meningitis in sub-Saharan Africa, the WHO recommends universal vaccination with group A meningococcal polysaccharide twice in infancy, followed by the four-valent vaccine in children older than 2 years.[256] A group A meningococcal conjugate vaccine (MenAfriVac™) has been shown to be safe and effective, especially in infants.[257] Currently, there is no vaccine against group B meningococci licensed in industrialized countries. Great Britain and Canada have adopted universal vaccination with serogroup C conjugate vaccine.[20, 24]

5.7.2 Chemoprophylaxis

The risk for developing meningitis after exposure to a meningitis patient is much greater than in the general population, and chemoprophylaxis is indicated for high-risk contacts. Rifampin eradicates Hib from the pharynx in 95% of carriers [136] and reduces risk of secondary invasive illness in contacts (0/1112 in rifampin and 4/765 in a placebo group, p=0.027).[258] Chemoprophylaxis for *H. influenzae* meningitis is recommended for all household contacts, when at least one unvaccinated contact is younger than 4 years old; and for nursery or child-care contacts when at least two cases of invasive Hib disease have occurred within 60 days.[136] Rifampin is the recommended agent. Index patients who do not receive third-generation cephalosporins or are younger than age 2 should receive chemoprophylaxis to eradicate Haemophilus colonization.[136]

For meningococcal meningitis, individuals considered high-risk are those who sleep or eat in the same household, and individuals who have had direct exposure to the patient´s secretions through shared utensils or toothbrushes, kissing, and school or day-care contacts in the prior 7 days. Health-care workers who have had direct mucosal contact with the patient´s secretions (mouth-to-mouth resuscitation) require chemoprophylaxis as well. Alternative medications are rifampin, ciprofloxacin, and ceftriaxone.[13, 20, 24, 135, 245] Index patients who do not receive third-generation cephalosporins should receive chemoprophylaxis to eradicate nasopharyngeal carriage of meningococcus.[135] For pneumococcal meningitis, no chemoprophylaxis is given.[13, 24, 245] However, children with asplenia (anatomical or functional), regardless of their immunization status, should receive oral penicillin daily at least till 5 years of age to prevent pneumococcal infection.[50]

6. Aims of the Study

6.1 General aim

The aim of the study was, after gathering background data, to explore ways to improve the prognosis of childhood BM in a developing country.

6.2 Specific aims

1) To disclose the characteristics of childhood BM, its aetiology, outcomes, the sex and age distribution, and antibiotic resistance in Luanda in Angola, a sub-Saharan country [I].
2) To identify predictors of unfavourable outcomes in childhood BM in developing countries [II].
3) To assess the current knowledge about hearing loss in childhood meningitis, and to describe how hearing screening was established in Luanda [III].
4) To study whether the prognosis of childhood BM can be improved by instituting a β-lactam, such as cefotaxime, with a slow continuous infusion, instead of giving the same dose divided intermittently, and whether the prognosis would further be improved by high-dose oral paracetamol [IV].
5) To compare the value of different prognostic scales in childhood BM [V].

7. Patients and methods

7.1 Patients

The retrospective study included 555 children aged 0-12 years treated for BM in the infectious disease ward of Hospital Pediátrico David Bernardino, Luanda, Angola, in 2004 [I]. Of these children, 403 were analysed for the risk factors of death, whereas 249 children underwent an analysis of risk factors for severe neurological sequelae (SeNeSe) [II]. The prospective study enrolled and randomised 723 consecutive children with suspected BM in a 36-month period of 2005-2008 [IV] in Hospital Pediátrico David Bernardino, Luanda, Angola [IV]. Of those 723 children, 491 with confirmed BM and without an underlying condition were included in the analysis of prognostic scales [V].

7.2 Methods

7.2.1 Study design

The study was realized in Hospital Pediátrico David Bernardino which is a paediatric referral and teaching hospital in Luanda, the capital of Angola (Figure 7). The first two studies were retrospective analyses of children treated for BM during the calendar year 2004. The following three studies were prospective; the third was a descriptive study, the fourth a randomised clinical trial, and the fifth paper utilised data of the fourth study.

"Comissão de Ética do Hospital Pediátrico de Luanda" approved the prospective study on June 15, 2005, whereas the retrospective study did not require an official approval according to the local regulations. Children were included in the clinical trial only after their guardians' informed consent.

The prospective study was registered internationally as a randomised clinical trial (ISRCTN62824827). The children were randomised in blocks of 20 by use of a random number table, to one of the four groups: infusion of cefotaxime and oral paracetamol, infusion of cefotaxime and oral placebo, iv-bolus of cefotaxime and oral paracetamol, or iv-bolus of cefotaxime and oral placebo.

In the retrospective study, BM was defined as confirmed if CSF culture, latex agglutination, or PCR were positive; or CSF leukocyte count (predominantly

Figure 7.

polymorphs) was >50/mm^3, and Gram stain positive. Meningitis was defined as probable when a child with symptoms and signs of BM had either CSF leukocyte count (predominantly polymorphs) >50/ mm^3, or positive Gram stain.

In the prospective study, BM was defined as confirmed when a child with compatible symptoms and signs had 1) positive CSF culture, or 2) positive blood culture, or 3) positive PCR, or 4) at least two of the following criteria: CSF leukocytes ≥100/ mm^3 (predominantly polymorphs), positive Gram stain, positive latex agglutination test, or serum CRP ≥40 mg/L.

7.2.2 Interventions in the prospective study

When a child with probable BM arrived at the ward, a study nurse took from a box the next sealed envelope and administered the treatment as ordered by the card within. All children received cefotaxime 250 mg/kg/24 hours for 7 days. However, for the first 24 hours the children were randomised to receive cefotaxime as two 12-hour infusions, or intermittently as four boluses every 6 hours.

All children received both infusion and boluses, of cefotaxime and placebo (saline). If a child received cefotaxime as an infusion, saline was administered as boluses every 6 hours; if a child received cefotaxime as boluses, saline was administered as two 12-hour infusions. As

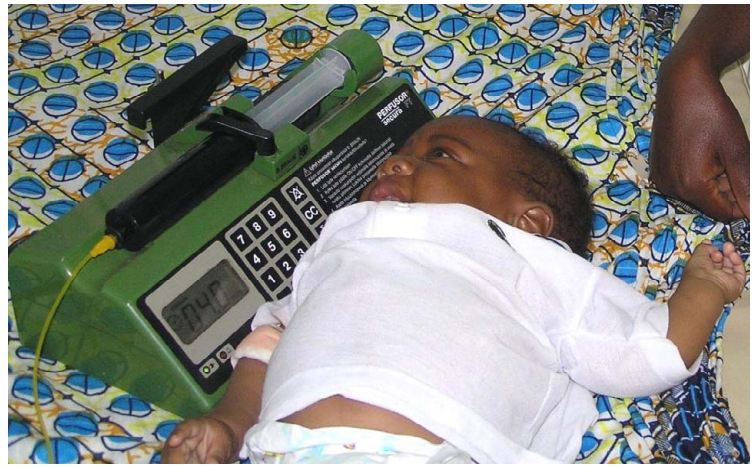


Figure 8.

ready-to-use cefotaxime is a yellowish liquid, black syringes and yellow iv-lines were used (Figure 8).

As the trial used the two-by-two factorial design, the children were also randomised to receive paracetamol or placebo (water) orally for the first 48 hours. The solution made with paracetamol effervescent tablets resembles plain water. The first dose of paracetamol was 30 mg/kg, and the following doses 20 mg/kg every 6 hours until the 48th hour.

All children received glycerol 1.5 g/kg (1.5 ml/kg, maximum 25 ml) every 6 hours for 48 hours. If the child had high fever or pain, ibuprofen was administered 15 mg/kg, and repeatedly every 12 hours, if needed. Ringer´s fluid was used to correct hypovolemia. Normal maintenance fluids were administered intravenously, orally, or through a nasogastric tube. Anaemia, hypoglycaemia, seizures, and malaria were treated according to the guidelines of the hospital.

7.2.3 Laboratory methods and follow-up

The attending physician at the emergency department performed LP if there was any suspicion of BM, when a patient presented with impaired consciousness, seizures, meningismus, bulging fontanel or prostration. CSF samples underwent microscopy for leukocyte and erythrocyte count; glucose concentration was measured. Gram staining and bacterial culture were also performed. A latex agglutination test and susceptibility testing were done in Luanda, and real-time PCR for *H. influenzae, S. pneumoniae,* and *N. meningitidis* in the Instituto Nacional de Saúde, Lisbon, Portugal, resources permitting.

When a child with BM was admitted, haemoglobin, blood glucose, malaria thick film, and CRP (prospective study) were examined immediately. Tests for full blood count, erythrocyte sedimentation rate, urea, HIV antibodies, sickle cell screening (if positive also electrophoresis of haemoglobin), urine analysis, tuberculin skin test with Mantoux technique, and (resources permitting) blood culture, were performed on the following working-day morning. Head ultrasound was carried out if a complication was suspected in an infant with a patent fontanel.

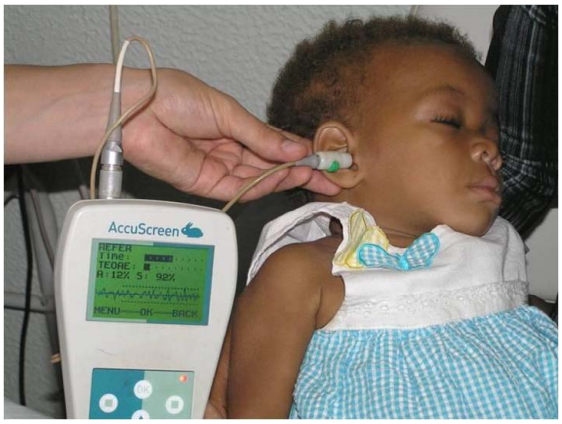


Figure 9.

Hearing was tested only in the prospective study. Transient evoked oto-acoustic emissions (Figure 9) and brain stem auditory evoked potentials were the techniques utilized immediately

after admission, and on day 7, and at the follow-up visits. In the prospective study, the physician of the infectious disease ward assessed the children daily during the hospital stay. On day 7, at discharge, and at the follow-up visits, a neurological examination was carried out. Special follow-up sheets were used. All children were called back for follow-up visits 1, 3, 6, 12, 18, 24, and 30 months after discharge.

7.2.4 Outcome measures and statistical analysis

In the prospective treatment study, the main outcome measures were 1) death in the ward or SeNeSe (blindness, quadriplegia/paresis, hydrocephalus requiring a shunt, or severe psychomotor retardation) and 2) deafness (better ear´s threshold >80 dB) at discharge. The secondary endpoint was death or any audiological (better ear´s threshold >40 dB) or neurological sequelae (in addition to SeNeSe; hemiparesis, monoparesis, any psychomotor retardation, or ataxia) [IV]. In the retrospective study, the main outcome measures were death in the ward or SeNeSe at discharge [I, II].

In the prospective study, at least 176 confirmed meningitis patients in the two main treatment arms each were required to detect a 15% decrease in the main outcome measures in favour of the infusion treatment, or of the paracetamol *vs* the placebo treatment by a two-tailed test with a power of 80%. To allow for a 5% error after adjustment for multiple testing (two endpoints and infusion *vs.* bolus, and paracetamol *vs.* placebo) we intended to enrol 750 patients.

The data were analysed with StatView 5.1 (SAS Institute). Fisher´s exact test was used to test the statistical significance for comparison of nominal and an unpaired t-test for continuous variables. The effect of blood transfusion on mortality was analysed also with logistic regression [I]. In the studies on risk factors [II, V] variables with a p value <0.1 in univariate analysis were submitted to a logistic regression model.

In the prospective randomised trial, any possible interaction between the two main treatments of infusion and paracetamol was tested with two-way analysis of variance (ANOVA). The chi square test was used to test statistical significance of the differences in the primary and secondary outcomes for infusion *vs.* bolus, and paracetamol *vs.* placebo groups. Logistic regression modeling was applied to analyse the primary and secondary outcomes in the treatment groups, using the cefotaxime boluses–oral placebo group as the reference. The predefined subgroup analyses covered the aetiology and time of death. In the exploratory analysis of time of death, survival analysis, and Fisher's exact and sign tests were used [IV].

The Simple Luanda scale (SLS) was created by using five independent predictors of dismal outcome (death, SeNeSe, or deafness): electricity at home, days of illness, seizures on admission, consciousness, and dyspnoea. The Bayesian Luanda Scale (BLS) based on likelihood ratios equalled SLS, but took into account seizures *at*

home and added blood glucose concentration. To compare five scales we determined the best cut-off point, sensitivity, specificity, efficiency, and area under the curve (AUC) [V]. Posterior probability is the likelihood used in the Bayesian method [100 x likelihood ratio / (1 + likelihood ratio)].

8. Results

8.1 Acute childhood bacterial meningitis in Luanda (retrospective series) [I]

Of the 555 children treated in 2004, 422 had confirmed and 60 probable BM. Of the 412 meningitis cases with identified bacteria, 247 (60%) were caused by Hib, 98 (24%) by pneumococcus, 42 (10%) by meningococcus, 18 (4%) by other streptococci, and 7 (2%) by other Gram-negative bacteria. Lowered sensitivity to penicillin and chloramphenicol, but not to third-generation cephalosporins was encountered.

The median age of the children was 11 months; 9 with Hib, 11 with pneumococcal, and 30 months with meningococcal meningitis. Of the whole series, 55% (283 of 510) were boys. Only 56% (165 of 294) of homes had electricity, and 14% (40 of 296) running water, facts reflecting the low socioeconomic status of the family. Of 436 children, 139 (32%) were malnourished, shown by weight-for-age (WFA) less than -2 SD below the median. The children presented late; the median length of illness before admission was 7 days. Almost all children (337 of 410, or 82%) had received some medication, 42% (131 of 313) had antibiotics before admission.

Of 364 children, 106 (29%) presented in poor general condition. Only 39% (165 of 424) were fully conscious. Seizures at home were reported in 65% (276 of 424) and were observed on admission in 34% (135 of 396). Focal neurological signs (fixed gaze, ptosis, facial paresis, hemiparesis) were reported in 23% (92 of 396). Dyspnoea was observed in 52% (205 of 398). Anaemia was very common, and 36% (113 of 312) of children had a haemoglobin level under 8 g/dL. Of the 9 children with confirmed sickle cell disease, 6 had pneumococcal, 2 Hib, and 1 *S. pyogenes* meningitis.

Of the 213 children tested, 24 (11%) were HIV-positive. Among them, 8 had pneumococcal, 6 Hib, 1 *Klebsiella pneumoniae*, 1 meningococcal, 2 unidentified streptococcal meningitis; in 6 cases the agent remained unidentified.

The most common antibiotic regimen (for 327 of 435, or 75%) was the combination of benzylpenicillin and chloramphenicol. However, ceftriaxone was instituted primarily, if Gram-negative bacilli were detected in microscopy. Malaria was treated in 55% (227 of 415), mostly with quinine. In all, 51% (204 of 399) required supplementary oxygen, and 54% (217 of 400), anticonvulsants. In the ward, still 20% (80 of 391) of children were dehydrated and needed rehydration which was generally accomplished with Ringer´s lactate.

Blood transfusion, 15 ml/kg of packed red blood cells (tested for HIV, hepatitis B, and syphilis), was given to 31% (129 of 412) of children. It was executed when a

Figure 10.

child showed haemoglobin <5 g/dL, or if especially sick, <6 g/dL. The children who received a transfusion presented more often in poor general condition or in coma, and were significantly younger.

Mortality in the ward was 35% (172 of 490); 38% from pneumococcal, 33% from Hib, 12% frǿm meningococcal, and 54% from the other types of meningitis. Death took place on the third (median) day in hospital. The children who received a blood transfusion survived significantly better than the children who did not, their mortality being 23% (30 of 128) *vs.* 39% (109 of 282; p=0.003). In logistic regression analysis with other possible risk factors, the transfused children were at significantly lower risk of death (0.41, 95% CI 0.23-0.76, p=0.004). The beneficial effect of transfusion was maintained when the bacterial aetiology was included, or when those children who died during the first day were excluded from analysis. Of the children with confirmed or probable BM, 24% were left with severe (Figure 10) and 9% with moderate sequelae.

8.2 Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in Luanda [II]

The main characteristics of the patients are described in Study I. Univariate analysis of the risk factors present at admission included 403 children and revealed the following predictors for death: seizures prior to admission, WFA <-2 SDs, poor general condition, impaired consciousness, low GCS, low BCS, seizures at hospital admission, presence of additional focus of infection, severe dyspnoea, and non-meningococcal meningitis. In logistic regression analysis, only the following three were identified as independent risk factors for death: impaired consciousness (OR 2.61, 95% CI 1.44-4.72, p=0.002), seizures during hospital admission (OR 2.49, 95% CI 1.36-4.58, p=0.003), and severe dyspnoea (OR 2.42, 95% CI 1.17-5.03, p=0.02).

Univariate analysis of factors associating with SeNeSe included 249 children and revealed the following as predictors: delay in presentation, seizures prior to admission, WFA < -2 SDs, poor general condition, impaired consciousness, low GCS, low BCS, seizures at hospital admission, low CSF glucose level, and non-meningococcal meningitis. In logistic regression analysis, only three remained as independent risk factors; convulsions during hospitalization (OR 9.34, 95% CI 3.49-25.00, p<0.001), impaired consciousness (OR 2.96, 95% CI 1.32-6.63, p=0.009), and history of symptoms >3 days (OR 3.73, 95% CI 1.24-11.26, p=0.02). Treatment with ceftriaxone instead of the primary regimen of penicillin and chloramphenicol failed to improve outcome.

8.3 Setting-up hearing screening in children with acute bacterial meningitis in Luanda [III]

Of the 238 children with confirmed BM, 155 survived and of them, 131 (85%) had BERA tested. Of them, 34 (26%) had a hearing threshold ≥80 dB at discharge. A hearing deficit was associated with SeNeSe (p=0.002) and ataxia (p=0.009).

8.4 Slow initial β-lactam infusion and paracetamol in childhood bacterial meningitis [IV]

Of the 723 children enrolled in the study, 183 were randomised to receive cefotaxime infusion and oral paracetamol, 180 cefotaxime infusion and oral placebo, 180 cefotaxime bolus and oral paracetamol, and 180 cefotaxime bolus and oral placebo. All these children were analysed on an intention-to-treat basis. As 162 children did not fulfil the criteria of BM, 34 had some exclusion criteria which were revealed only later in the ward, and 28 did not receive the complete study medication; 499 children were analysed per protocol.

The causative bacteria were identified in 453 children (63%); being Hib in 188 (41.5%), pneumococcus in 184 (40.5%), meningococcus in 49 (11%), and other, mostly Gram-negative bacteria in 32 (7%). No cefotaxime resistance was found. The median age of these children was 14 months (range 1-157 months), and of them, 386 (53%) were boys. Half the homes, 52% (379 of 722), had no electricity.

The median length of illness before admission was 5 days (range 1-180), and 63% (456 of 720) of patients had been ill for more than 3 days; 89% (636 of 718) had received some medication, 40% (271 of 679) antibiotics, 32% (230 of 723) had WFA < -2 SD. Seizures at home were reported in 70% (506 of 723) and observed on admission in 50% (360 of 722). Only 31% (224 of 723) of children were fully conscious; 24% (174 of 723) showed focal neurological signs, 25% (182/723) other

focus of infection, 16% (116/723) dehydration, and 46% (333 of 723) dyspnoea. Their median haemoglobin was 7.7 g/dL (2.3–15.6), and 88% had <10 g/dL. Median blood glucose was 119 mg/dL (18–506), 8% (60 of 715) had <40 mg/dL, and 48% (342 of 714) >120 mg/dL.

In the ward, 38% (totalling 272) of children died. Of the survivors, 15% (68 of 451) had developed SeNeSe and 53% (totalling 240) some neurological sequelae at discharge; 83% (of 374) were tested for hearing, and of those children, 27% (totalling 96) could not detect the threshold of 40 dB, 12% (45 children), not even 80 dB. With all the outcomes combined, 26% (102 of 392) had SeNeSe or deafness, 68% (268 of 393) some neurological or hearing sequelae. Death or SeNeSe occurred in 47% (340 of 723) of the patients, death, SeNeSe or deafness in 56% (374 of 662), and death or any sequela in 80% (540 of 676).

No significant differences in the treatment groups emerged in the primary or secondary outcomes: 1) death or SeNeSe, 2) deafness, or 3) death or any sequelae. However, in the subgroup analysis of pneumococcal meningitis, death or any sequelae occurred in 83% (73 of 88) among the infusion, but in 92% (81 of 88, p=0.07) of the bolus recipients. Among these children, infusion per se was beneficial, because risk of death or any sequelae was reduced in the cefotaxime infusion - oral placebo group when compared with the cefotaxime bolus - oral placebo group (OR 0.18, 95% CI 0.03-0.90, p=0.04).

Although there was ultimately no difference in total mortality, the times of death differed. In the infusion group, mortality was lowered during the 4-48 hours from the institution of the treatment (54 of 363, or 15% *vs.* 80 of 360, or 22% in the bolus group, p=0.01). However, this change was transient, as after 48 hours the mortality was even higher in the infusion group (66, or 18% *vs.* 44, or 12%, p=0.03). In the paracetamol group mortality was lower 6-60 hours after the treatment initiation (53 of 363, or 15% *vs.* 81 of 360, or 23% in the oral placebo group, p=0.006). The mortality in the cefotaxime infusion - oral paracetamol group was lower than in the other groups for 600 hours. When compared with the cefotaxime bolus - oral placebo group, the ORs were 0.45 (95% CI, 0.26 - 0.77; p=0·003) for 0-48 hours, and 0.52 (0.32 - 0.85; p=0·009) for 0–72 hours. When the cefotaxime infusion - oral paracetamol group was compared with all other groups, the difference (Fisher's exact test) was most pronounced at 24, 48, and 72 hours, the p-values being 0.041 and 0.0005, and 0.005, respectively.

8.5 Prognostic accuracy of five scales in childhood bacterial meningitis [V]

Of the 723 children in Study IV, 491 had confirmed BM and were without any underlying illness. They were analysed in the comparison of prognostic scales. Their characteristics were very similar to those of the entire series of 723 children. The

mean score on GCS, where optimal is 15, was 10.9 (SD 3.7). On BCS, where optimal is 5, the mean score was 3.4 (SD 1.4). On HTS, where 12 points is the worst grade, the mean was 4.1 (SD 1.9); 46% (219 of 474) of children were at high risk (score >4.0).

On our new scales, for SLS—where the highest and worst score is 19—the mean score was 7.2 (SD 4.0). In the comparison of scales, we used a cut-off point of 8 or 7. Regarding BLS, the likelihood ratio-derived posterior probability value (PR) for death was 46.5 (mean, SD 27.9); the cut-off point was 52. The mean PR for SeNeSe was 49.5 (SD 31.8) and the cut-off point 52. The mean PR for dismal outcome was 51.2 (SD 30.6) and the cut-off point 45.

The sensitivities of the SLS, BLS, GCS, BCS, and HTS for predicting dismal outcome were 76, 81, 81, 71, and 61%. The respective specificities were 68, 70, 67, 74, and 69%. The scales predicted dismal outcome correctly in 72, 76, 74, 74, and 65%. Of all scales, BLS proved to be the best predictor for dismal outcomes, because its AUC for death was 0.83, for death or SeNeSe 0.84, and for dismal outcome 0.82. SLS was not quite as accurate, but predicted death or SeNeSe well, its AUC being 0.82, and its specificity best of all (81%). Plain coma scales performed almost as well, HTS somewhat worse.

9. Discussion

9.1 Prevention and diagnosis of acute childhood bacterial meningitis

In the developing world, the incidence of meningitis is highest in African, mainly sub-Saharan countries.[4, 5] Angola is a classical example.[12]

It has been postulated that poverty and its consequences are responsible for the high incidence of BM in tropical Africa.[6] In our study the children came from poor socio-economic situations, crowded homes having difficulties with sanitation. Many children were malnourished; WFA < -2 SDs was found in 32%, and many were anaemic. Several had sickle cell disease (screening test was positive in 36–32% in a retrospective–prospective study and in electrophoresis, haemoglobin SS was present in 41–67% of those tested) which raised the risk of invasive bacterial infections.[41] Of the children tested, 11–8% were HIV-positive. HIV leads to increased risk of pneumococcal meningitis, recurrent BM, and mortality from BM.[52, 259] Some focus of infection other than meningitis was evident in 38–25% upon admission, and some children had developed meningitis as a complication of that infection (otitis or dental abscess). All these characteristics likely influenced the high incidence.

In our retrospective study of 2004, 60% of cases were caused by Hib, 24% by pneumococcus, and 10% by meningococcus. In our prospective study from 2005 to 2008, the corresponding figures were 42, 41, and 11%. Hib vaccinations were included in the national immunization programme at the end of 2006, and the numbers for Hib meningitis were declining. Developing countries have only a few vaccines in their national immunization programmes, because of economic constraints.[7] Meningococcal vaccinations were rarely used in Angola when epidemics broke out.[30] Pneumococcal conjugate vaccine would be highly welcomed, not only to prevent meningitis, but also pneumonia—an important killer in developing countries.[5, 252]

However, even were the national programme comprehensive, vaccinations do not materialize in remote areas. They are administered in only some health centres or hospitals in large cities. Mobile campaigns are executed rarely, and mostly against polio, which campaigns are remunerated.

In Luanda, the children with BM present very late in the disease, because the median length of time for symptoms before diagnosis is 7–5 days (retrospective – prospective study). Of these children, 82–89% had received some medication, 42–40% antibiotics. The clinical picture of malaria with fever, convulsions, and impaired consciousness overlaps that of meningitis.[81] Parents buy malaria and fever medications, or even antibiotics, in a pharmacy or market without a prescription. Many quack doctors or circulating nurses offer their unofficial services (Figure 11).

Figure 11.

Traditional medicine and witchcraft still have strong roots in African societies.[260] Even among the health care professionals, knowledge about BM is often poor.[83]

Children in our series were very ill, with 29–53% (retrospective – prospective study) in poor general condition. At the emergency department, seizures were observed in 34–50%, altered consciousness in 61–69%, focal neurological signs in 23–24%, other focus of infection in 38–25%, dehydration in 13–16%, and dyspnoea in 52–46%. These findings clearly depict the realities in developing countries where most BM cases occur. In our retrospective study, among 717 patients, 123 (17%) died immediately after reaching the hospital, in the emergency department. In contrast, in our prospective study, where the transfer to the infectious disease ward was quicker, only 8 children died before reaching the ward. Obviously, many children arrived so late that they could not be helped.

After the 27-year civil war ended in 2002, some development has taken place in Angola. The country has enormous natural resources which should be used for the benefit of her people to build up a functioning network of schools and health care facilities. Special emphasis should be put on preventive health care, education, and vaccination programmes. Educational work among parents and health care workers is needed to increase general awareness of BM (and other diseases) and to prevent delays in treatment.

Indiscriminate use of antimicrobials reduces the chances of isolating the causative bacteria and leads to resistance problems. In our two studies, an agent was identified in 74 and 63% of cases. Much of the credit goes to a fruitful collaboration with the National Health Institute of Lisbon, which helped to establish the laboratory of bacteriology, the first in Angola, in the Paediatric Hospital of Luanda in 2002. It was soon obvious that bacterial resistance to inexpensive benzylpenicillin and chloramphenicol was common. However, in our retrospective study, ceftriaxone (started when Gram-negative rods were found) instead of penicillin-chloramphenicol combination did not improve the prognosis – a finding which agrees with the Cochrane meta-analysis.[138] No resistance against third-generation cephalosporins was encountered.

9.2 Treatment of childhood bacterial meningitis

Despite expanding vaccination programs, BM continues to be among the leading causes of mortality from infectious diseases and is responsible for sequelae in survivors.[1, 2] Therefore, better treatments should be sought.

In Luanda, on arrival, 13–16% of children, but in the ward even more, 20–37%, were dehydrated. Dehydration should be corrected immediately, and in maintenance no fluid restriction should be executed.[17, 182, 185]

In our retrospective study [1], the children receiving blood transfusions survived significantly better than did those without them (p=0.003). We have found no previous reports on this potentially important observation. The transfused children presented with a poorer status, obviously. The beneficial effect of transfusion is explained by better oxygen transport, increased blood volume, and likely better cerebral circulation. This finding deserves further investigation, although immediate blood transfusions in a tropical setting always pose their own problems.

9.2.1 Slow initial β-lactam infusion and paracetamol

Our prospective, double-blind, randomised clinical trial is the first to study the effects of β-lactam infusion and paracetamol in childhood BM. Even if the treatments failed to significantly affect the primary or secondary outcomes, some differences between the treatment groups emerged. In pneumococcal meningitis, which in many countries is currently the most common type of meningitis, the risk of death or any sequelae was reduced by cefotaxime infusion. The time of death differed between the groups: In the infusion group, mortality was lower for 4-48 hours after the treatment initiation. Among the paracetamol recipients, mortality was lower for 6-60 hours. When the cefotaxime infusion - oral paracetamol group was compared with all other groups, the reduction in mortality was most pronounced at 24, 48, and 72 hours (p-values 0.041 and 0.0005, and 0.005, respectively). These are findings that merit further investigation.

The explanation for the beneficial effects of continuous infusion is that high β-lactam concentrations of antibiotic are avoided, and rapid release of toxins and pro-inflammatory bacterial cell-wall products is prevented.[69, 261] Importantly, continuous infusion has proved at least as effective and safe as traditional bolus administration in a number of studies conducted in animals and in patients.[127, 262] In the present study, the initial beneficial effect of β-lactam infusion could probably be explained by prevention of bacterial multiplication or by slower killing of bacteria, and thus a lesser inflammatory storm. However, the beneficial effect was temporary, and one explanation for this is that the slow initial killing of bacteria could cause increased mortality later.

In theory, NSAIDs could improve the outcome in BM or sepsis by reducing inflammation.[72] However, in one randomised study, ibuprofen did not improve survival.[163] Paracetamol, loosely considered as one of the NSAIDs, with its central inhibition of COX3 and NMDA receptors,[175, 177] did, on the other hand, improve survival in a retrospective study on sepsis.[178, 179] In our study, the beneficial effects of paracetamol were transitory.

In summary, cefotaxime infusion reduced death and all sequelae in pneumococcal meningitis. The combination of infusion and paracetamol reduced mortality during many days, although they were admnistered for only 24 and 48 hours, respectively. Our view is that we ended our infusion + paracetamol regimen too early.

9.3 Hearing tests in childhood bacterial meningitis

BM is one of the most important causes of acquired sensorineural hearing loss in children.[196] Hearing impairment after BM has been reported in up to half the survivors and is common in industrialized countries, as well.[2, 192, 197] However, hearing screening is not a practice in many developing countries and not even for all BM children in the industrialized world.[192, 203] Before our prospective study, measurements of hearing were not available in the Paediatric Hospital of Luanda. A child whose hearing impairment remains undiagnosed and therefore goes without any special support measures can be left in total isolation in society and without opportunities for the future.

Comparison of the different study results is difficult, because their methods and auditory threshold levels vary. In many studies, hearing was tested only once with no follow-up. Because hearing loss in BM may be progressive or may resolve, repeated testing is recommended.[200, 201] We showed that hearing screening is possible even in a developing country.

We used brain-stem auditory evoked potentials and oto-acoustic emissions. The latter seemed to be very sensitive, as almost all children showed abnormal results. However, since it is quick and easy to perform, and the result is obtained immediately, perhaps it could serve as a screening test. The children who have absent otoacoustic emissions need the more complicated and time-consuming BERA which requires a specialist for interpretation.

In summary, all children should undergo a hearing test after BM, and the test should be repeated, especially if the first test is abnormal. The testing should be done before hospital discharge so that all children would be tested, and should be repeated after a month to allow possible middle ear secretion to disappear. Researchers should all use the same standards, so that comparisons between studies are possible.

9.4 Outcomes of childhood bacterial meningitis in Luanda

The outcomes of the children with BM in Luanda were miserable. Before our interventive study, half the children died. In our retrospective study of 2004 [I], the in-ward mortality was 35%, but if we add deaths in the emergency department (17%), no less than 46% of the children succumbed. In our prospective study [IV], the in-ward mortality was 38%, and almost no deaths occurred in the emergency department, thanks to the swift transfer to the ward.

Neurological sequelae have not been defined in many studies, and if they have, the definitions have varied. Therefore, comparison of different studies is difficult. In our retrospective study [I], 24% of children with confirmed or probable BM were left with SeNeSe, 9% with moderate sequelae. In the prospective study (IV), 15% of children developed SeNeSe, which is notably less than in 2004. We believe that this is due to glycerol, which in a large study in South America reduced SeNeSe significantly,[11] and which here was administered to all children. In 2004, 52% of children encountered death or SeNeSe; in 2005-2008, 47%. However, in 2004, less severe neurological sequelae such as ataxia went unreported. In our prospective study, 56% of children died or developed SeNeSe or deafness; 80% died or showed any sequelae.

We should aim for more extensive prevention and search for better treatments for this devastating disease. Studies should use comparable definitions for neurological sequelae.

9.5 Prognostic and risk factors for unfavourable outcomes in childhood bacterial meningitis

Identification of the risk factors on admission or during illness may provide clinicians with valuable information, because this helps to identify the patients at greatest risk. Thus—resources permitting—efforts could be maximized.

Our finding of the association between delayed presentation and poor prognosis agrees with earlier findings from developing countries.[221, 222, 224, 234] Lowered consciousness was the most important prognostic factor, as shown in other studies as well.[221, 224] The risk of SeNeSe increased with prolonged unconsciousness, and convulsions were also a warning sign.[220, 221, 224] In India, focal neurological signs (Figure 12) were associated with neurological sequelae.[219] In our study this was the case only in univariate analysis, where, in addition, a concomitant focus of infection (mostly pneumonia) also correlated with poor outcome.[263] Malnutrition, which in Latin America elevated the probability of death and of SeNeSe,[80] showed this association here only in univariate analysis. However, 70% of children with severe malnutrition died. Unfortunately, slow capillary filling and low blood pressure,

found to be signs of poor prognosis,[221, 224, 264] were not recorded in our retrospective study. In the prospective study, low blood pressure predicted death in univariate analysis, but in multivariate analysis showed only a trend towards it. Prevention and treatment of malnutrition, increased awareness of BM to aid in avoiding delay in presentation, and intensive treatment of convulsions and shock are among the measures to improve BM prognosis.

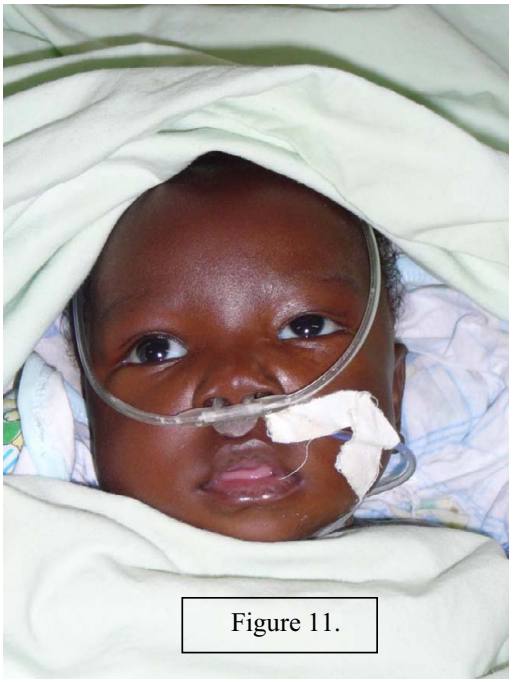


Figure 11.

Except for identification of the causative agent, laboratory analyses were, in our study, not very useful in predicting outcome. The risk of death and SeNeSe was reduced in meningococcal meningitis, and the risk of death increased in meningitides caused by other, mainly Gram-negative enteric bacteria. Low CSF glucose predicted SeNeSe, as in earlier studies,[264] but only in univariate analysis. In the prospective study [V], low or high blood glucose associated with unfavourable outcomes. An association with low blood glucose was reported earlier,[27] but, to our knowledge, an association with high blood glucose has been evident only in experimental pneumococcal meningitis.[265] However, a link between hyperglycaemia and unfavourable outcome in sepsis and other severe disorders has gained attention in the past few years.[266] Normal fasting blood glucose concentrations achieved with insulin treatment have improved the short-term outcome in a paediatric intensive care unit.[267] Therefore, also meningitis patients require intensive blood glucose monitoring, and their hypoglycaemia should be corrected immediately. Hyperglycaemia should be avoided, and if necessary, treated with insulin infusions.

9.6 Value of prognostic scales for unfavourable outcomes in childhood bacterial meningitis

Our study is the first to compare the value of the Glasgow Coma Scale, Blantyre Coma Scale, and Herson-Todd Scale in bacterial meningitis. Based on our data, we created two new scales which showed the best predictive accuracy for all major outcomes. However, the Coma Scales were almost as accurate, which reflects the

importance of status of consciousness in this CNS disease. GCS is used worldwide, but inter-observer variations occur. BCS comprises fewer points, and is easier to use.

HTS, which is probably the most common scale used in childhood BM, did not perform equally well. Our results agreed with the following risk factors of HTS: "severe coma, seizures, shock, and symptoms for more than 3 days", but not with: "hypothermia, age <12 months, haemoglobin <11 g/dL, CSF leukocytes <1000/mm^3, and CSF glucose <20 mg/dL".[234]

Some other scales have also been published,[222, 233, 238] but have not been accepted into common use. The complex scales of the paediatric intensive care units in the industrialized world are of little use in developing countries. Interestingly, BLS, which included all the five parameters of SLS, but added blood glucose, did only a little better than SLS. It is quite surprising, how little laboratory results improved prognostic accuracy. Simple, easy to use, quick scoring systems are needed. We created two, but they must be validated in other populations, as well.

9.7 Methodological aspects

Our studies have some limitations. In our retrospective study [I, II] it was impossible to locate the hospital charts of the patients who died in the emergency department, and the children could not be analysed at all. Nor were the data complete from patients, especially if they had died soon after arrival. In 2004, hearing went untested; neither did we have any information on the follow-up visits.

The prospective study [III, IV, V] had to exclude many children because of reasons unknown in industrialized countries; their parents were unaware of the treatment the child had received before admission. Some laboratory analyses such as HIV-antibodies, a sickle cell screening test, and a tuberculin test were performed only on the working day following admission. Patients who died quickly thus went untested. Because of problems with transport to Lisbon, Portugal, the PCR of the culture-negative CSF was done only in the beginning of our prospective study. Only one doctor, when present, performed head ultrasound examinations, only when there was suspicion of a complication. Some parents described the child´s condition fulfilling the exclusion criteria only after their inclusion in the study. Finally, some children received study medication dosage incompletely, some doses of oral medication being missed because of gastric retention or haemorrhage.

Questions have risen as to the ethics of studies conducted by groups from industrialized countries in developing countries.[268] Clearly, the clinical trials in developing countries should meet the same ethical standards as studies in industrialized countries, respecting the local conditions, customs, and culture. An ethics committee approved our study, and children were included only after informed consent was obtained. If the guardian was illiterate, a finger-print was acceptable. Our research addressed BM, which is an important health problem in

Angola, and tried to find simple and applicable solutions to improve its poor prognosis.

10. Summary and Conclusions

Worldwide, acute BM still remains among the major causes of infection-related death and in survivors, causes permanent neurological disability. In developing countries, BM is ten times as common as in industrialized countries, and in resource-poor countries the risk of mortality and sequelae is much higher. As new antibiotics have not improved BM prognosis, aid has been sought from adjuvant medications. In earlier studies, dexamethasone has reduced hearing loss in industrialized countries, whereas glycerol reduces severe neurological sequelae.

We launched a study in Angola where the burden of BM is grave and sought ways to improve its prognosis. The studies showed that children in Luanda have many additional diseases, such as anaemia, sickle-cell disease, and HIV infection, as well as malnutrition, all of which complicate their management. Most children present late in the disease, in a poor general condition with impaired consciousness and seizures. Public awareness of the symptoms and signs of BM should be promoted, and health care workers trained in the diagnosis of BM to prevent delays in treatment.

Early prediction of a poor outcome can help the physician to determine which children require more intensive management and follow-up. We identified the most important prognostic factors for adverse outcomes: absence of electricity at home, delay in presentation, impaired consciousness, seizures, dyspnoea, and low or high blood glucose concentration. Our two new prognostic scales: the Bayesian Luanda Scale (BLS), and Simple Luanda Scale (SLS), performed better than the Glasgow or Blantyre Coma Scales. The Herson-Todd Scale proved the weakest of all these scales. The level of consciousness was the most important prognostic factor and by adding some clinical parameters and (where possible) one laboratory test (blood glucose), we delivered a scale which predicted the outcome of BM quite reliably. However, our scales require validation in other populations.

Many children were dehydrated on admission, and even more children in the ward. In the treatment, emphasis should be put on fluid management: correction of dehydration and normal, not restricted, maintenance fluids. The finding of reduced mortality in blood transfusion recipients deserves another study. Low or high blood glucose was associated with unfavourable outcomes. Meningitis patients require intensive blood glucose monitoring. Hypoglycaemia should be corrected immediately, and hyperglycaemic BM patients may benefit from insulin infusions. In our trial, no specific treatment alternative (none of the combinations: infusion or bolus plus paracetamol or placebo) finally affected the primary or secondary outcomes, but initial mortality in the infusion – paracetamol group fell more than in any other study since the advent of chloramphenicol and ampicillin some 50 years ago. In pneumococcal meningitis, the risk of death or any sequelae was reduced in

children who received cefotaxime infusion. We are planning a new study with longer treatment periods.

After Hib vaccinations began in Angola in 2006, the numbers of Hib meningitis cases have rapidly decreased. Improving the coverage of Hib vaccination and the introduction of pneumococcal and meningococcal vaccinations pose a major challenge to the health authorities; also much political will and good funding are required. While awaiting these, better treatments for BM should be sought.

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“Who, then, can separate us from the love of Christ? For I am certain that nothing can separate us from his love: neither death nor life, neither angels nor other heavenly rulers or powers, neither the present nor the future, neither the world above nor the world below – there is nothing in all creation that will ever be able to separate us from the love of God which is ours through Christ Jesus our Lord.” Romans 8:35, 38-39

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