TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

BACTERIAL MENINGITIS – INCIDENCE, ETIOLOGY, PREDISPOSING FACTORS AND OUTCOME

Sakke Niemelä

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1810 | MEDICA – ODONTOLOGICA | TURKU 2024

University of Turku

Faculty of Medicine
Department of Clinical Medicine
Otorhinolaryngology – Head and Neck Surgery, and Infectious Diseases
Doctoral Programme in Clinical Research

Supervised by

Professor Jarmo Oksi, M.D., Ph.D.
Department of Infectious Diseases
University of Turku
Turku, Finland

Professor Jussi Jero, M.D., Ph.D.
Department of Otorhinolaryngology
University of Helsinki
Helsinki, Finland

Reviewed by

Docent Olli-Pekka Kämäräinen, M.D., Ph.D.
Institute of Clinical Medicine
Neurocenter/Neurosurgery
University of Eastern Finland and
Kuopio University Hospital
Kuopio, Finland

Docent Merja Helminen, M.D., Ph.D.
Tampere Center for Child, Adolescent
and Maternal Health Research
Department of Pediatrics
Tampere University Hospital
Tampere, Finland

Opponent

Docent Kirsi Skogberg, M.D., Ph.D.
Division of Infectious Diseases
University of Helsinki
Helsinki, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin Originality Check service.

ISBN 978-951-29-9847-0 (PRINT)
ISBN 978-951-29-9848-7 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2024

To my loved ones

UNIVERSITY OF TURKU
Faculty of Medicine, Department of Otorhinolaryngology – Head and neck surgery, and Infectious Diseases
SAKKE NIEMELÄ: Bacterial Meningitis – Incidence, Etiology, Predisposing Factors and Outcome
Doctoral Dissertation, 125 pp.
Doctoral Programme in Clinical Research, September 2024

ABSTRACT

Bacterial meningitis (BM) is a severe infectious disease, which causes significant morbidity and mortality up to 30%. BM can be classified into community-acquired or nosocomial form. Post-neurosurgical meningitis (PNM), a subtype of nosocomial BM, can occur after neurosurgical operations. PNM prolongs treatment periods and causes significantly more costs. BM causes a substantial health economic burden. The implementation of vaccinations have caused a decrease in the incidence of BM worldwide.

The aim of this thesis was to describe the incidence, characterize the clinical picture, identify the causative bacteria, study the predisposing factors, and define the indicators of unfavorable outcome in pediatric and adult populations with BM.

This thesis consists of three different studies. In the first two studies the medical records of 185 patients diagnosed with BM and in the third 345 patients undergoing glioma surgery in Turku University Hospital, were retrospectively studied between 2011–2018. The included patients had either a cerebrospinal fluid (CSF) culture positive- or negative BM. The outcome was evaluated with Glasgow Outcome Scale, and unfavorable outcome was defined as a score from one to four.

The incidence of BM was slightly higher than previously reported. *Streptococcus pneumoniae* was the most frequent causative pathogen in children and adults, while *Streptococcus agalactiae* and *Escherichia coli* dominated the etiology in infants. *Staphylococcus epidermidis* was the most frequently found pathogen in PNM patients. The proportion of nosocomial BM was high, and so was the frequency of pre-diagnostic antibiotic use. Headache and administration of pre-diagnostic antibiotics were associated with unfavorable outcome in adult population, and pretermity and nosocomial BM with pediatric population. Repetitive surgeries were risk factors for PNM, and the rate of PNM was higher among low-grade glioma patients compared to patients with high-grade glioma. The frequency of unfavorable outcome of patients was either compatible with previous studies or lower. The management of BM patients is at good international class in Southwestern Finland.

KEYWORDS: Bacterial meningitis, post-neurosurgical meningitis, etiology, risk factors, outcome

TURUN YLIOPISTO
Lääketieteellinen tiedekunta, Korva-, nenä- ja kurkkutaudit ja infektiosairaudet
SAKKE NIEMELÄ: Bakteerimeningiitit – insidenssi, etiologia, altistavat tekijät ja ennuste
Väitöskirja, 125 s.
Turun kliininen tohtoriohjelma, Syyskuu 2024

TIIVISTELMÄ

Bakteeriperäinen aivokalvontulehdus eli meningiitti (BM) on vakava infektiotauti, joka aiheuttaa merkittävää sairastavuutta ja jopa 30 % kuolleisuutta. BM voidaan jaotella yhteisöstä tai sairaalasta saatuun muotoon. Post-neurokirurginen meningiitti (PNM), sairaalasta saadun meningiitin alatyyppi, voi ilmaantua neurokirurgisten toimenpiteiden jälkeen. PNM pidentää hoitojaksoja ja aiheuttaa merkittäviä lisäkustannuksia. BM aiheuttaa yleisesti merkittävää terveysekonomista taakkaa. Rokotteiden käyttöönotto on kuitenkin alentanut sairauden ilmaantuvuutta maailmanlaajuisesti.

Tämän väitöskirjatutkimuksen tarkoitus oli selvittää ilmaantuvuutta, määritellä kliinistä kuvaa, tunnistaa aiheuttavia bakteereja, tutkia altistavia tekijöitä ja epäsuotuisaan lopputulemaan vaikuttavia tekijöitä lapsi- ja aikuispotilailla.

Tämä väitöskirja koostuu kolmesta osajulkaisusta. Kahdessa ensimmäisessä sairauskertomukset käytiin läpi takautuvasti 185 BM potilaalta, ja kolmannessa 345 potilaalta, jotka olivat olleet glioomaleikkauksessa Turun yliopistollisessa keskussairaalassa vuosien 2011–2018 välillä. Potilailla oli joko aivo-selkäydinneste positiivinen tai -negatiivinen BM. Lopputulema määriteltiin Glasgow Outcome Scalen avulla, jossa pisteet yhdestä neljään määriteltiin huonoksi lopputulemaksi.

Bakteerimeningiitin ilmaantuvuus oli hieman korkeampi aiempiin tutkimuksiin nähden. *Streptococcus pneumoniae* oli yleisin bakteeri lapsilla ja aikuisilla, ja ryhmän B streptokokki ja *Escherichia coli* olivat imeväisten yleisimmät patogeenit. *Staphylococcus epidermidis* oli yleisin aiheuttajabakteeri PNM ryhmässä. Sairaalasyntyisten meningiittien osuus oli korkea, kuten myös edeltävien antibioottihoitojen määrä. Päänsärky, sekä edeltävät antibiootit, olivat yhteydessä epäsuotuisaan ennusteeseen aikuispotilailla, ja ennenaikaisuus ja sairaalaperäinen BM lapsipotilailla. Toistuvat leikkaukset olivat riskitekijä PNM:n kehittymiseen. Epäsuotuisan ennusteen ilmaantuvuus oli vastaava tai vähäisempi kuin aiemmin on todettu. Hoitotulokset BM potilailla Varsinais-Suomessa ovat hyvää kansainvälistä tasoa.

AVAINSANAT: Bakteeriperäinen meningiitti, post-neurokirurginen meningiitti, etiologia, riskitekijät, ennuste

Table of Contents

Abbreviations **8**

List of Original Publications **9**

1 Introduction **10**

2 Review of the Literature **13**
2.1 Anatomy 13
2.2 General pathogenesis of bacterial meningitis 13
2.2.1 Pathogen-specific pathogenesis 15
2.2.1.1 *Escherichia coli* 15
2.2.1.2 *Streptococcus pneumoniae* 17
2.2.1.3 *Neisseria meningitidis* 17
2.2.1.4 Group B Streptococcus 18
2.2.1.5 *Acinetobacter baumannii* 18
2.2.1.6 *Listeria monocytogenes* 19
2.2.1.7 *Staphylococcus epidermidis* 19
2.2.2 Mediators of neuronal injury in bacterial meningitis 19
2.3 Community-acquired bacterial meningitis 20
2.4 Nosocomial bacterial meningitis 23
2.5 Bacterial meningitis in infants and children 26
2.6 Prevention 27
2.7 Treatment 29
2.8 Complications and outcome 32
2.9 Risk factors of bacterial meningitis and predictors of unfavorable outcome 34

3 Aims **36**

4 Materials and Methods **37**
4.1 Patient selection 37
4.1.1 Studies I-II 37
4.1.2 Study III 37
4.2 Definitions 38
4.2.1 Study I 38
4.2.2 Study II 38
4.2.3 Study III 38
4.3 Diagnostic inclusion criteria 39
4.3.1 Study I 39
4.3.2 Study II 39

4.3.3 Study III 39
4.4 Laboratory methods 39
4.5 Statistical analysis 41
4.5.1 Study I 41
4.5.2 Study II 41
4.5.3 Study III 41
4.6 Evaluation of outcome 42
4.7 Ethics 42

5 Results 43
5.1 Study I 43
5.1.1 Background information 43
5.1.2 Clinical characteristics 46
5.1.3 Causative pathogens 47
5.1.4 Antibiotic resistance 49
5.1.5 Laboratory results 49
5.1.6 Imaging 50
5.1.7 Treatment 50
5.1.8 Outcome 52
5.2 Study II 54
5.2.1 Background information 54
5.2.2 Clinical characteristics 56
5.2.3 Outcome 57
5.3 Study III 60
5.3.1 Background information 60
5.3.2 Causative bacteria 60
5.3.3 Statistical analysis 60

6 Discussion 62
6.1 Bacterial meningitis in adults (study I) 62
6.2 Pediatric bacterial meningitis (study II) 65
6.3 Post-neurosurgical meningitis (study III) 67
6.4 Strengths and limitations 69
6.5 General discussion and future aspects 70

7 Conclusions 74

Acknowledgements 75

References 77

Original Publications 93

Abbreviations

ASA	American Society of Anesthesiologists
BBB	Blood-brain barrier
BM	Bacterial meningitis
BMI	Body mass index
CD	Cluster of differentiation
CI	Confidence interval
CNF1	Cytotoxic necrotizing factor 1
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
DNA	Deoxyribonucleic acid
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
FAA	Fastidious anaerobe agar
FAB	Fastidious anaerobe broth
GBS	Group B streptococcus; *Streptococcus agalactiae*
GOS	Glasgow Outcome Scale
HBMEC	Human brain microvascular endothelial cell
Hib	*Haemophilus influenzae* type b
HBP	Heparin binding protein
ICD-10	International Classification of Diseases 10th Revision
MALDI-TOF	Matrix-assisted laser-desorption-ionization time-of-flight
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
OmpA	Outer membrane protein A
OR	Odds ratio
PCR	Polymerase chain reaction
PCT	Procalcitonin
PNM	Post-neurosurgical meningitis
Q1	Lower quartile
Q3	Upper quartile
TNF-α	Tumour necrosis factor α

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Niemelä S, Lempinen L, Löyttyniemi E, Oksi J, Jero J. Bacterial meningitis in adults: a retrospective study among 148 patients in an 8-year period in a university hospital, Finland. BMC Infect Dis. 2023 Jan 23;23(1):45.

II Niemelä S, Lempinen L, Löyttyniemi E, Grönroos JO, Luoto R, Peltola V, Jero J. Finnish paediatric study found a low incidence of bacterial meningitis from 2011 to 2018 but a substantial proportion of nosocomial meningitis. Acta Paediatr. 2024 Feb;113(2):327–335.

III Niemelä S, Oksi J, Jero J, Löyttyniemi E, Rahi M, Rinne J, Posti JP, Laukka D. Glioma grade and post-neurosurgical meningitis risk. Acta Neurochir (Wien). 2024 Jul 18;166(1):300.

1 Introduction

Bacterial meningitis (BM) is a notorius and severe infection, which causes substantial morbidity and mortality (van de Beek et al., 2004, A). The infection is the tenth most common cause of death in children below five years of age (Mijovic et al., 2019). Worldwide, the infection may exceed 16 million cases annually (Global Burden of Disease Study, 2015) and mortality of 30% in adults and children (Klinger et al., 2000; Lovera et al., 2022). BM can be classified to either nosocomial or community-acquired form (Davis, 2018). Post-neurosurgical meningitis (PNM) can develop after craniectomies, craniotomies or after implementation of ventricular or lumbar instruments (Hussein et al., 2017). PNM prolongs treatment periods, causing significantly more costs (Hussein et al., 2017; Reichert et al., 2002). BM causes a significant health economic burden (Kiyani et al., 2021).

The implementation of conjugate vaccinations during childhood against *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type B (Hib) has significantly reduced the overall incidence of BM worldwide among patients of all ages (Koelman et al., 2021; McIntyre et al., 2012; Mijovic et al., 2019; Whitney et al., 2003). In the Netherlands, the implementation of Hib vaccination has diminished the incidence of BM caused by Hib from 1.44 to 0.04 episodes per 100 000 population per year (Koelman et al., 2021). In the United States, the 7-valent pneumococcal conjugate vaccine was associated with a 59% decrease in pneumococcal BM in children (Whitney et al., 2003). Also, the implementation of meningococcal group C vaccination has been effective, as it decreased the incidence of *N. meningitidis* BM from 2.87 to 0.20 per 100 000 population between 1989–1993 and 2014–2019 (Koelman et al., 2021). The 10-valent pneumococcal conjugate vaccine caused 54–64% decrease in the incidence of pneumococcal meningitis in Finland after its implementation in 2010 (Polkowska et al., 2021). Additionally, the implementation of Hib conjugate vaccination in 1989 caused the decrease of Hib infections of even 90–100% (Eskola et al., 1991).

The geographical location affects substantially to the incidence of BM; in developed countries the incidence has been reported to be 0.5–3.4/100 000/year (Johansson Kostenniemi et al., 2019; Kurtaran et al., 2018; Robinson et al., 2019; Valdoleiros et al., 2022) in patients of all ages, and in developing countries with even

1000/100 000 cases due to local epidemics (Erdem et al., 2017; Gessner et al., 2010; Hasun et al., 2017; Koelman et al., 2021).

The typical symptoms of BM consist of headache, fever, and neck stiffness (Davis, 2018). However, especially with neonates and infants, the clinical presentation may be quite different: sleepiness, hypotonia, lethargy and irritability are very often present (Ku et al., 2015; Swanson, 2015). The diagnosis of BM needs to be confirmed with cerebrospinal fluid (CSF) culture or polymerase chain reaction (PCR) of the CSF specimen (Davis, 2018).

S. pneumoniae has been reported recently to be the most common pathogen causing BM in all age groups (Bijlsma et al., 2016; Polkowska et al., 2017; Thigpen et al., 2011). *N. meningitidis* is also a notorious and common pathogen causing BM (Oordt-Speets et al., 2018), and vaccinations against it have been reported effective in children (Pascucci et al., 2014). However, the vaccines have not been implemented widely in low-income countries, which suggests that the proportion of the pathogen causing serious diseases could be lower in developing countries. Group B streptococcus (GBS; *Streptococcus agalactiae*) and *Escherichia coli* are the most predominant pathogens among infants (Koelman et al., 2021; Mijovic et al., 2019). Prevention of neonatal BM is proven to be a challenge because maternal intrapartum antibiotic prophylaxis does not protect children from late-onset GBS disease (Delara et al., 2023). *Staphylococcus epidermidis* and *Staphylococcus aureus* used to be the main gram-positive cocci causing nosocomial meningitis (van Soest et al., 2022), but recently the proportion of gram-negative bacteria such as *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *E. coli* has been rising (Hasanuzzaman et al., 2021; Welinder-Olsson et al., 2007).

The research on risk factors of BM has been a major interest in recent years. Immunosuppression, human immunodeficiency virus -infection (Paireau et al., 2016), indoor air pollution (Wall et al., 2014), overcrowded houses (Mazamay et al., 2020) and malnutrition (Miller et al., 2014) have been reported as risk factors. Re-operation, ventricular shunts and male gender have been reported as risk factors of PNM (Korinek et al., 2008; Reichert et al., 2002). With infants and children, prematurity and male gender have been reported as risk factors of BM (Haffner et al., 2021).

The survivors of BM often suffer from wide variety of neurological deficits afterwards, such as cognitive impairment, motor difficulties, seizures, and paralysis (Kohli-Lynch et al., 2017). Additionally, with infants and children, hearing loss and cerebral palsy may be the long-term deficits after BM (Kim, 2010).

The knowledge of current epidemiology of BM in Finland is not up to date, which was one of the inspirations of this thesis. The differences in clinical picture in neonates, children, and adults, or with patients with PNM varies widely, and may change during the constant development of vaccinations and treatments. Also, the

significance of certain predisposing factors remained of our utmost interest as well as the indicators of unfavorable outcome.

2 Review of the Literature

2.1 Anatomy

Brain and spinal cord are surrounded by a triple-layered membrane, defined as the meninges. The meninges consist of dura mater and thin layers of tissue covering the central nervous system (CNS), called leptomeninges, which consists of arachnoid mater and pia mater. Dura mater lays closest to the skull, and it contains blood vessels, lymphatic vessels, and immune cells. Arachnoid mater lays in the middle layer, and it is composed of multilayer cells combined with tight junctions, and it regulates the transport of compounds. CSF fills the area of subarachnoid space between arachnoid mater and pia mater. Pia mater follows closely the outlines of the brain parenchyma and spinal cord, and it is highly vascularized and semipermeable to the CSF. CSF is mostly produced in the choroid plexus of the brain ventricles, and it pours towards the subarachnoid space. Lymphatic vessels may be playing an essential role in clearance of CSF (Tavares et al., 2022).

2.2 General pathogenesis of bacterial meningitis

BM causes inflammation of pia mater, arachnoid mater, and the subarachnoid space of the brain (**Figure 1**). The pathogens may travel to CNS from upper respiratory tract, gastrointestinal tract or by hematogenous spread. Spread from ear-nose-throat areas happen also from sinusitis, mastoiditis, or otitis media (Durand et al., 1993). A passage of pathogens to CNS may also be a consequence of a skull fracture or an invasive, often neurosurgical operation (Valdoleiros et al., 2022). In most cases the spread is hematogenous (Kim, 2003). In neonates, bacterial shift into mucosal surfaces during or prior to parturition can be a pathway to BM (Edwards et al., 2016).

Certain pathogens are shown to account for the most cases of bacterial meningitis, and to cause meningeal infections they first need to cross the blood-brain barrier (BBB) and the blood-CSF barrier (Mastorakos & McGavern, 2019). BBB is supposed to protect the brain from circulating pathogens and harmful compounds. BBB consists of human brain microvascular endothelial cells (HBMEC), and they regulate the entry and exit of the compounds and molecules to the brain. HBMECs are also responsible for optimal neural microenvironment. The blood-CSF barrier

consists of the choroid plexus and the leptomeningeal vasculature, and it acts similarly as a controlled channel, which enables immunosurveillance (Mastorakos & McGavern, 2019). The blood vessels there lack tight junctions and are fenestrated, allowing the transversal of blood cells and various molecules into the stroma (Wolburg & Paulus, 2010). An additional layer of ependymal cells and arachnoid mater provides a barrier between the fenestrated vessels and the CSF (Mastorakos & McGavern, 2019). Post-capillary veins and venules around the perivascular areas and subarachnoid space may be the areas bacteria uses for entry primarily into CNS (Iovino et al., 2013, B; Ridpath et al., 2014).

Crossing of the BBB may be done transcellularly, paracellularly, or also by infected phagocytes with so-called Trojan horse mechanism (Kim, 2008). Transcellular drifting through the BBB has been the way to penetrate the CNS by *E. coli*, GBS and *S. pneumoniae* (Kim, 2003; Kim, 2008). Next, the bacteria invade the meninges, relying on high concentration of bacteremia. After that, pathogen causes modifications to host-cell cytoskeleton in order to be engulfed and protected from host-cell attacks. When the pathogen has access to the CSF, the proliferation of the affecting pathogen causes increasing permeability of the BBB by releasing proinflammatory compounds. All these reactions cause increased intracranial pressure, cell toxicity and edema, which eventually causes neuronal injury (Kim, 2003).

Normally, the levels of complement are too low in CSF, even 100–1000-fold lower than in blood, to sustain necessary antibacterial activity. BBB prevents the complement proteins from blood to enter the CSF, and even in the case of increased permeability of BBB such as BM, the levels of complement remains often substantially lower than in blood. Hence, bacteria can grow effectively in the CSF and achieve dense population in hours (Mook-Kanamori et al., 2011; Pachter et al., 2003; van de Beek et al., 2016, A). The complement system has two main goals here; to kill bacteria directly or by marking them for phagocytosis and to boost the inflammatory response in several ways (Morgan et al., 2015).

The glial-lymphatic or glymphatic system is a clearance system of the brain, and it functions mainly during sleep (Jessen et al., 2015). This system is responsible for disposing waste among other tasks, and BM interferes with this essential function. The malfunction of the glymphatic system leads to the accumulation of bacterial parts in the CSF, which is shown to cause cell damage to the neurons, neuroinflammation and unfavorable neurological outcomes (Oggioni & Koedel, 2022).

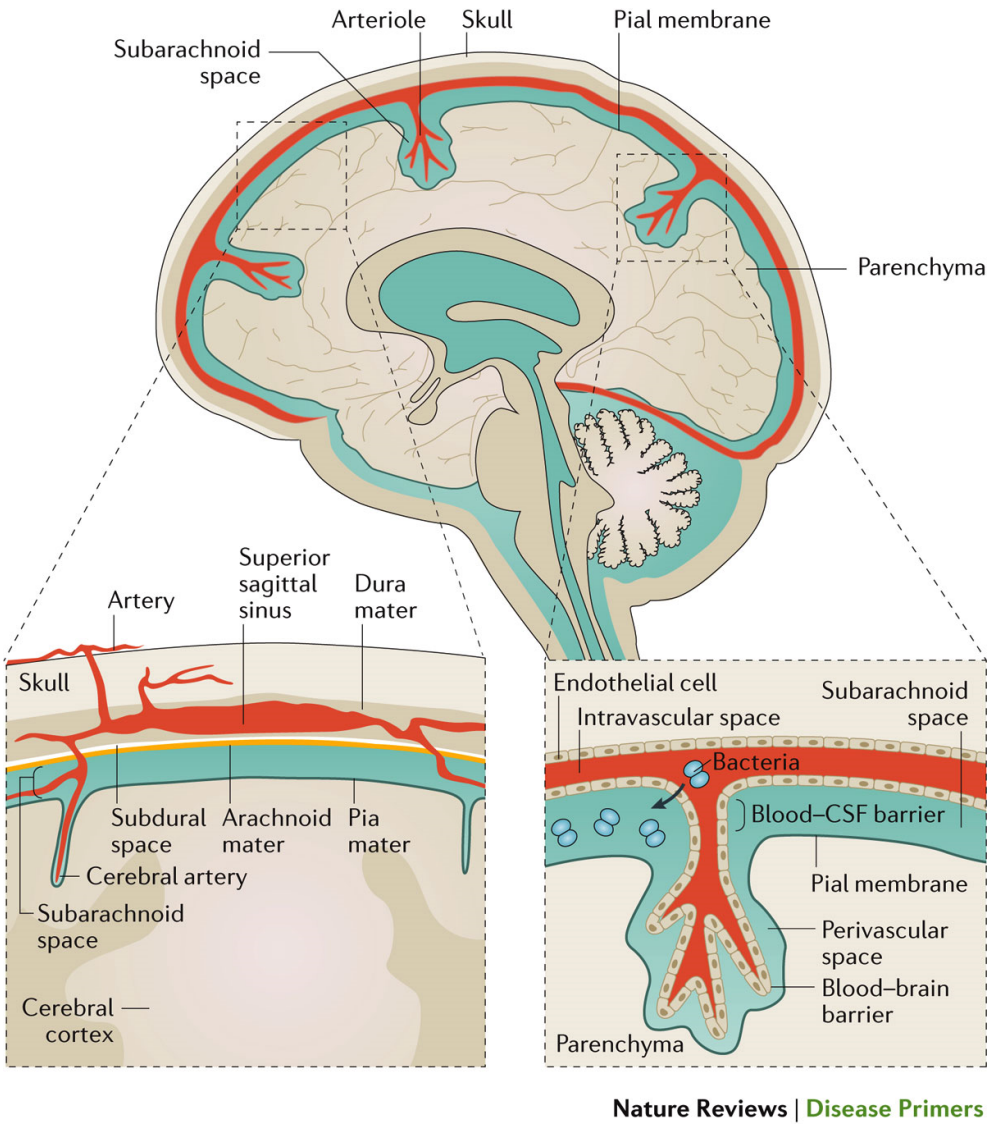


Figure 1. Anatomical structures regarding bacterial meningitis. Reproduced with permission from van de Beek et al. Community-acquired bacterial meningitis. Nat Rev Dis Primers. 2016 Nov 3;2:16074 and *Springer Nature* ©.

2.2.1 Pathogen-specific pathogenesis

2.2.1.1 *Escherichia coli*

E. coli has been the subject of most studies to understand the pathogenesis of BM better, one of most prominent causative pathogens in neonates and children (Kim,

2003). The association with this pathogen and BM relies on the pathogens' ability to escape from host defence reactions and the ability to reach necessary state of bacteremia to invade the meninges. Especially the pathogenesis of *E. coli* serotype K1 has been studied deeply, which accounts for most cases of neonatal BM (Robbins et al., 1974). This pathogen colonizes the surface of epithelial cells in genital or gastrointestinal tract and enters the bloodstream afterwards (Vila et al., 2016). In the bloodstream a capsule made of polysaccharides inhibits the attacks of immune response thus protecting *E. coli* (Koedel et al., 2010).

E. coli binds to HBMEC through adhesion protein FimH and outer membrane protein A (OmpA) and interacts with cluster of differentiation (CD) 48 and endoplasmin, which exists in the surface of HBMEC, and then the pathogen invades the HBMEC through cytotoxic necrotizing factor 1 (CNF1) and protein Ibe. CNF1 has an interaction with 40S ribosomal protein subunit A on HBMEC (Kim et al., 2004). This compound is a 37-kilodalton laminin receptor protein, and it is presented on the surface of the cells, and it has an essential function regarding adhesion. This protein has been proven to be a target of many microorganisms, such as *N. meningitidis*, *S. pneumoniae*, Hib, multiple viruses and even prion protein (Kim, 2010). CNF1 and Ibe interacts with actin cytoskeleton and causes rearrangements in the host cell structures and activates multiple molecular signalling pathways (Kim, 2003). As an additional defensive mechanism, OmpA binds to complement C4 binding protein, which inhibits the lectin and classical pathways of the immune system and therefore is a mechanism to avoid demolition (Mittal et al., 2011).

The invasion also includes the activation of focal adhesion kinase and its associated cytoskeletal protein paxillin, phosphatidylinositol 3-kinase. Activation and associations of these compounds are the requirements for the invasion of HBMEC by *E. coli* K1 (Kim, 2003). The Ras homolog gene family member A activation is also required for the invasion of HBMEC, and here CNF1 plays a key role (Doran et al., 2016). Finally, *E. coli* traverses as a live pathogen through the K1 capsule and penetrates across the BBB, which seem to be done by both transcellular and paracellular ways (Kim, 2003, van de Beek et al., 2016, A).

After crossing the BBB, the pathogen multiplies in the subarachnoid space and causes host inflammatory responses in the meninges. Traversing of *E. coli* K1 through HBMEC as a live bacterium is associated with its ability to prevent lysosomal fusion and avoidance of lysosomal enzymes (Kim, 2003). Next, these reactions lead to pleocytosis, and increased permeability of the BBB affected by several mediators, such as cytokines, tumour necrosis factor α (TNF-α) -converting enzyme, platelet activating factor and caspases (Braun et al., 1999; Scheld et al., 2002; van Furth et al., 1996). Interference with these mediators could be a target for supplemental therapy for BM. However, previous studies have indicated that CSF

pleocytosis and BBB permeability increase can occur independently, inducing bacterial invasion of the meninges and neuronal injury (Kim, 2003).

2.2.1.2 *Streptococcus pneumoniae*

S. pneumoniae colonizes the surface of epithelial cells in respiratory tract and advances to bloodstream afterwards (Boegart et al., 2004). While in the bloodstream, it survives partly because of polysaccharide capsules, which makes the bacteria anti-phagocytic and the capsule acts as a shield defending the bacterial from complement factors (Doran et al., 2016; Koedel et al., 2010). Additionally, pneumococcal surface proteins and toxin called pneumolysin are involved in the inhibition of activation of the complement. Bacterial autolysis releases pneumolysin, and it can activate multiple complement pathways and confuse the complement aside from bacterial surface (Ali et al., 2013). Pneumococci can also interact with factor H and thus inhibit the activation of complement pathways. Pneumococcal surface protein A plays an essential role in adhesion, which is essential for the pathogen to invade CSF. This protein initially binds to laminin receptor, and when binding to wall of vessels and travelling through BBB, interactions between cell-wall phosphorylcholine and platelet-activating factor receptor happen, and it enables the internalization of pneumococcus through intracellular invasion (Iovino et al., 2013, A).

2.2.1.3 *Neisseria meningitidis*

N. meningitidis enters the bloodstream through colonization of respiratory epithelium. There are six serogroups which are identified as causative agents in BM: A, B, C, W-135, X and Y (Rouphael & Stephens, 2012). Similarly to *S. pneumoniae*, also *N. meningitidis* has a protective polysaccharide capsule which shields the pathogen from attacks of the immune system (Doran et al., 2016; Koedel et al., 2010). Additionally, this pathogen can bind to factor H, which plays a key role in alternative complement activation, resulting in decreased efficacy of immune response (Lewis et al., 2013). OmpA plays a key role in adhesion of *N. meningitidis* to HBMEC, and especially the interaction to laminin receptors (Orihuela et al., 2009). Meningococcal pilus components pilin protein E and V mediate adhesion with immunoglobulin CD147 on host cells (Bernard et al., 2014). After primary adhesion, type IV pilus activates the β2-adrenoceptor which triggers the organization of certain molecular compounds called cortical plaques in the underlying cells cytoplasm, and this plaque formation is followed by actin polymerization, leading to protrusions in membrane structures, which protects the bacteria from complement-mediated lysis and opsonophagocytosis. These plaques also trigger the inter-endothelial junctions to open which eventually leads to *N. meningitidis* traversal to

CSF through paracellular route (Coureuil et al., 2010; Coureuil et al., 2014). Outer membrane protein Opc, bonding to fibronectin is a key mediator with *N. meningitidis* invading HBMECs, anchoring the pathogen to integrin receptor on the surface of the cell (Unkmeir et al., 2002). Furthermore, meningococcal pili binds to CD46 molecule on the surface of HBMEC (Johansson et al., 2003).

2.2.1.4 Group B Streptococcus

S. agalactiae, or GBS, engulfs itself also to polysaccharide capsules to ensure its survival in the bloodstream (Doran et al., 2016; Koedel et al., 2010). This pathogen possesses wide variety of virulence factors which causes interaction with brain endothelium, such as hypervirulent GBS adhesin laminin-binding protein, bacterial surface adhesin of GBS, streptococcal fibronectin-binding protein A and pilus protein A (Doran et al., 2016; Doran et al. 2005; Tazi et al., 2010). Pilus protein A can form bonds with collagen, which causes interactions with endothelial integrins, and eventually leads to activation of focal adhesion kinase and other signalling cascades which causes rearrangements of actin and bacterial uptake through paracellular way (Banerjee et al., 2011).

This pathogen can also display sialic acid on its surface and therefore mimic human cells, and eventually it can protect itself from complement attacks this way (Carlin et al., 2009). Sialic acid can also decrease complement deposition, inhibit complement component C5a, and interact with inhibitory immunoglobulin-like lectins, which may damp platelet activation and endorse survival of the bacteria in the bloodstream (Tavares et al., 2022). Clustered regularly interspaced short palindromic repeats -associated protein 9 is a key regulator in the virulence of GBS, as it regulates part of GBS genome including genes that code many virulence factors. The protein also promotes interactions with host cells and plays a role in penetration to the brain (Tavares et al., 2022). A serotype III GBS clone is almost solely associated with meningitis and late-onset disease among infants because it possesses hypervirulent characteristics (Joubrel et al., 2015; Tazi et al., 2010).

2.2.1.5 *Acinetobacter baumannii*

A. baumannii colonizes epithelial cells and internalizes via zipper-like mechanism, and the pathogen resides in vacuoles in the host cell cytoplasm (Choi et al., 2008). This pathogen possesses protein OmpA, which lays in the outer membrane of the bacteria, and it is essential for bacterial adhesion to host cells, forming biofilms and defending itself from complement attacks (Schweppe et al., 2015). OmpA also targets mitochondria of host cells, which leads to release of mitochondrial protein cytochrome C, and this compound eventually induces apoptotic cell death (Tiku,

2022). OmpA is also most likely essential for developing multidrug resistance features, because OmpA loss lowered minimal inhibitory concentrations of multiple antibiotics (Smani et al., 2014).

2.2.1.6 *Listeria monocytogenes*

HBMEC invasion by *L. monocytogenes* happens via internalin B (Greiffenberg et al., 1998), and crossover into the CNS through BBB is mediated with monocytes and myeloid cells infected with *L. monocytogenes* (Greiffenberg et al., 1998; Join-Lambert et al., 2005). Endoplasmin acts as a cellular receptor for *L. monocytogenes* gene Vip, which have a role in the infection of brain tissue in mice (Cabanes et al., 2005).

2.2.1.7 *Staphylococcus epidermidis*

S. epidermidis is an opportunistic pathogen and a common causative bacteria in nosocomial meningitis, related especially to neurosurgical devices such as ventriculoperitoneal shunts (Noguchi et al., 2018). The pathogen enters the CNS usually directly from the patient's skin or the hands of the health care professionals (Noguchi et al., 2018). *S. epidermidis* has multiple virulence factors, such as cysteine proteinases and lipases and it can also produce delta toxin and form biofilms on the surfaces of foreign devices (Azimi et al., 2020). This pathogen can express multiple resistance genes and therefore it often causes antibiotic-resistant infections, which has made this pathogen difficult to eradicate and an increasing problem (Azimi et al., 2020). The continuing challenge is to distinguish if *S. epidermidis* is a causative pathogen in BM or just a contamination (Zheng et al., 2020).

2.2.2 Mediators of neuronal injury in bacterial meningitis

Necrotic cortical injury and apoptotic hippocampal injury are the two types of neuronal injury predominant in patients with BM (Braun et al., 1999; Nau et al., 1999). In experimental models, apoptosis is considered to happen through caspase-dependant or mitochondrial cytochrome C -induced signalling events, and the scope of these reactions depend on the causative bacteria and the time after infection (Gerber et al., 2010; Weber et al., 2007). The mechanisms explain partly the quite common neurological sequelae after BM, such as memory difficulties and learning problems. Multiple different reactive oxygen species seem to act as key mediators to neuronal injury, but the exact mechanisms may vary between different bacteria causing BM (Kim, 2003). The higher the concentration of bacterial products are present in CSF, the poorer the neurological outcome seem to be in BM caused by *E.*

coli, *S. pneumoniae* and Hib, and elevated levels of inflammatory markers such as interleukin 1-beta have been associated with unfavorable outcome in children with BM (McCracken et al., 1974; McCracken et al., 1989; Mertsola et al., 1991; Mustafa et al., 1989; Schneider et al., 1999).

Matrix metalloproteinases (MMPs) are compounds which contribute to reactions resulting increased permeability of BBB. Especially increased amount of MMP9 have been reported in CSF with patients suffering from BM (Paul et al., 1998). These compounds are responsible for degradation of compounds in the extracellular matrix. MMP inhibitor batimastat had an effect of significant reduction of BBB disruption in rats with meningococcal meningitis but did not reduce the levels of pleocytosis in the CSF (Paul et al., 1998).

Excitatory amino acids are molecules, which take part in neuronal injury in BM. One of them, glutamate, has been shown to be indicator of unfavorable clinical outcome after BM and glutamate has also been shown to be present in animal models (Perry et al., 1993; Spranger et al., 1996).

Certain types of vasoconstrictors, endothelins, are found in different sized arteries. Increased amount of endothelins have been detected in CSF during BM and are proposed to be an essential factor in cerebral hypoperfusion associating with BM (Koedel et al., 1997). Brain injury seems to be partly mediated by vasculitis and other types of pathological modifications of the vascular structures (Schaper et al., 2002; Vergouwen et al., 2010).

It is required that pathogens also intake iron to ensure replication of deoxyribonucleic acid (DNA), generate energy, and enable efficient metabolism and transcription, which is essential to survive in the extracellular environment (Sheldon et al., 2016).

2.3 Community-acquired bacterial meningitis

BM can be obtained spontaneously from community and out of hospital, and that form of BM is called community-acquired BM. The incidence of community-acquired BM in adults is estimated to be between 0.6–4/100 000/year in developed countries and 1.3/100 000/year in Finland in 2017 (Matulyte et al., 2020; Polkowska et al., 2017). However, in developing countries the incidence can rise to 1000/100 000 cases due to local epidemics (Erdem et al., 2017; Gessner et al., 2010; Hasun et al., 2017; Koelman et al., 2021). In Sweden between 1964–2014, community-acquired BM was the most common form with percentage of 86% of all BM detected (Block et al., 2022). Almost similar rate of 84% were found in a recent study from United States of America (Kiyani et al., 2021).

One of the most important aspects on the diagnosis of BM is to differentiate aseptic or viral meningitis from BM. Many algorithms has been proposed, but the

golden-standard method, analysis of CSF via bacterial culture is essential in differentiating BM from other forms of meningeal infections (Brouwer et al., 2012; Nigrovic et al., 2007; van de Beek et al., 2016, A). Gram staining of CSF is also a validated and fast method to identify bacteria in the CSF (Brouwer et al., 2010). CSF culture is positive in approximately 43–85% of patients with BM (Hasanuzzaman et al., 2021; Heckenberg et al., 2014). Latex agglutination testing of CSF is also an option to detect pathogens in CSF, but with rather uncertain sensitivities varying 59–100% and 22–93% regarding whether there is pneumococcal or meningococcal meningitis, respectively (Brouwer et al., 2010). Immunochromatographic testing of antigens in CSF has been shown sensitivities and specifities of near 100% in studies with pediatric BM caused by *S. pneumoniae*, but false-positive results has presented problems due to other species of streptococcus (Brouwer et al., 2010; Saha et al., 2005; van de Beek et al., 2016, B).

The most typical symptoms of BM in adults are headache, fever, decreased level of consciousness and neck stiffness (Bijlsma et al., 2014, A). The proportion of the "classical triad" (fever, altered consciousness and neck stiffness) is reported to be present in 41%, minority of patients (van de Beek et al., 2004, B). Many neurological symptoms such as seizures, paresis and aphasia are also possible symptoms of BM (Bijlsma et al., 2016). Petechial rash is often associated with meningococcal or pneumococcal BM (Nigrovic et al., 2008; Vasilopoulou et al., 2011).

Neck stiffness, Brudzinski sign, and Kernig sign are possible clinical manifestations of BM, however the sensitivity is not very high (Thomas et al., 2002). Kernig sign is positive when there is pain in knee extension when simultaneously the hip and knee are at 90 degree angles, and Brudzinski sign is positive when knees reactively flex when neck is flexed (Fitch et al., 2007). Neck stiffness, however, may occur with many other benign conditions, and it is important to recognize that there are substantial neck stiffness only when neck flexion causes considerable pain and the chin cannot touch the chest (Fitch et al., 2007; van de Beek et al., 2016, A).

The pre-diagnostic administering of antibiotics may decrease the identification of causative bacteria by at least 30% (Corless et al., 2001). Sterilization of CSF may happen only hours after administration of antibiotic therapy. *N. meningitidis* may be sterilized from CSF in two hours and *S. pneumoniae* after four hours after parenteral antibiotic therapy is initiated (Kanegaye et al., 2001). However, in urgent medical situations such as treating patients with suspected BM or in suspected case of sepsis, the immediate administration of antibiotics remains essential, sometimes before the necessary diagnostic tests, until the yield of CSF culture is negative (Brouwer et al., 2010; Sherwin et al., 2017).

Multiplex and quantitative PCR of CSF has been shown to be faster, more sensitive and more specific for diagnosing BM compared to culture method, thus its use has been rapidly increasing (Brouwer et al., 2012; Hasanuzzaman et al., 2021).

Multiplex PCR has a specificity of 95–100% when simultaneously detecting DNA of *N. meningitidis*, *H. influenzae* and *S. pneumoniae* according to a study by Corless et al. in 2001. PCR tests may detect the pathogen when CSF cultures are negative, being a valuable asset in diagnosing BM (van de Beek et al., 2016, A). However, PCR tests does not provide information on bacterial antimicrobial susceptibility characteristics. Blood cultures can also be used to identify bacteria causing BM, and even in 50–80% of cases the cultures are positive in blood while simultaneously causing inflammation in the meninges (Brouwer et al., 2010).

In order to obtain CSF, a lumbar puncture is needed. Suspected elevated intracranial pressure is often needed to be ruled out before the puncture, because of the risk of possible cerebral herniation, and the exclusion of this condition may require computed tomography (CT) scan (Fitch et al., 2007). Additionally, significant thrombocytopenia and other coagulation deficiencies are contraindications for this procedure (van de Beek et al., 2006, A).

Typical presentation of a CSF sample in BM includes pleocytosis with high percentage of polymorphonuclear leukocytes, elevated levels of protein and low concentration of glucose, and at least one of these three markers are presented in 96% of the patients with community-acquired BM (Bijlsma et al., 2016; Brouwer et al., 2012). Increased level of lactate in CSF are often presented in BM, and this test provides additional information on differential diagnosis between BM and other forms of meningitis (Brouwer et al., 2012; Hussein et al., 2017).

Procalcitonin (PCT) and C-reactive protein (CRP) are both inflammatory acute-phase proteins, which play an important role in BM and serum testing of both of these markers have proven to be of a strong diagnostic value in differentiating BM from viral meningitis, where elevated PCT and CRP values prefer the diagnosis of BM (Brouwer et al., 2012; van de Beek et al., 2016, A)

Most common causative pathogens of community-acquired BM are *S. pneumoniae* and *N. meningitidis*, the first being most found in patients below five years of age and over 65 years of age and the latter in adolescents and adults (Bijlsma et al., 2014, A; Brouwer et al., 2010; Thigpen et al., 2011).

The meningitis belt – a sub-Saharan region from Senegal to Ethiopia – is known for meningococcal epidemics with almost 1% of the population suffering from the disease in the most unfortunate outbreaks for over a century (McIntyre et al., 2012). Outbreaks occur normally in the beginning of dry season in January and ends in May or June when the rainy seasons begin (Sridhar et al., 2015). Fortunately, the success of meningococcal vaccinations has reduced the incidence in the recent years (Daugla et al., 2014).

Thirteen different subgroups of *N. meningitidis* have been identified, and the most virulent groups are serotypes A-C and W-Y (van de Beek et al., 2016, A). *N. meningitidis* serotype C seems to be the most common type of meningococci causing

BM in both adults and children (Bijlsma et al., 2014, A). Serogroups considering *S. pneumoniae* have reached the number of at least 94, and latest vaccinations cover the most important serotypes worldwide (Johnson et al., 2010). However, serotype replacement has been seen lately in the countries where the pneumococcal conjugate vaccination is implemented, where new non-vaccinable serotypes emerge, which remains a continuous problem (Polkowska et al., 2021).

Hib was previously a prominent causative pathogen of community-acquired BM, but efficient vaccinations caused a rapid and notable decline in the incidence (Koelman et al., 2021; Schlech et al., 1985). In Netherlands, incidence of BM caused by Hib was declined from 1.44 to 0.04 episodes per 100 000 population per year (Koelman et al., 2021).

GBS and *E. coli* are the main causative agents of BM in infants and children (Lingani et al., 2015; Mijovic et al., 2019). GBS also include multiple serotypes, of which serotype III is reported to be the most common to cause BM in newborns (Lingani et al., 2015).

E. coli causes BM most commonly in newborns and elderly patients (Brouwer et al., 2010). There are also dozens of different serogroups of *E. coli*, but serotype K1 has been the most predominant form causing even 80% of BM in newborns (Kim, 2003).

L. monocytogenes is a food-borne pathogen causing sepsis or BM usually with individuals who have impaired immune systems, for example, after treatments of cancer (Brouwer et al., 2010; Costerus et al., 2016). This pathogen is usually found in patients over 60 years of age (van de Beek et al., 2016, B).

Several prediction models of BM have been in development, especially in pediatric patients. None of these models have provided 100% sensitivity in cohorts, and a key limitation of these models are that they focus on differentiating between bacterial and viral meningitis, but in clinical setting many other diagnoses need to be considered (van de Beek et al., 2016, B). According to European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines from 2016, clinical judgement is essential when considering whether to treat suspected BM patients, not diagnostic algorithms.

2.4 Nosocomial bacterial meningitis

Nosocomial BM consists of BM acquired during hospital stay or after discharge from hospital, as a complication of a neurosurgical or surgical procedure, or head trauma, and the incidence has been reported to vary between 14–73% of all BM detected (Block et al., 2022; Davis, 2018; Durand et al., 1993; Kiyani et al., 2021; van de Beek et al., 2016, A). The proportions of nosocomial BM has been rising due to conjugate-vaccinations (Block et al., 2022; Durand et al., 1993; Sunwoo et al., 2021).

PNM is a subtype of nosocomial BM, and it is a major complication after neurosurgical procedure. PNM causes notable morbidity and mortality, potentially unfavorable impacts on patient survival, and prolongs treatment periods, causes more costs, and delays postoperative treatments, for example chemotherapy or radiotherapy (Hussein et al., 2017; Reichert et al., 2002; Salle et al., 2021). The incidence of PNM has been estimated to be 2–9% (Hussein et al., 2017; Kourbeti et al., 2015; Reichert et al., 2002). PNM can occur after craniectomy, craniotomy, or after insertation of lumbar or ventricular catheters (Hussein et al., 2017). Administering prophylactic antibiotics have been proven to decrease superficial and deep infections during neurosurgery, and the antibiotics are mainly targeted against gram-positive pathogens (Jackson et al., 2016; Robinson & Busl, 2019). In neurosurgical units in Finland this practise is applied in intensive care where patients receive prophylactic antibiotics constantly when ventriculostomy is in place in the brain, which is proved to be effective in prevention of infections (Sonabend et al., 2011).

Magnetic resonance imaging (MRI) of suspected patients with PNM is often needed to exclude complications, such as hydrocephalus, brain abscess or empyemas (Hussein et al., 2017). However, cranial imaging has shown to delay the antibiotic therapy, and is thus associated with unfavorable outcomes (Proulx et al., 2005). Therefore the following criteria for the imaging with brain CT of BM patients are suggested to implement in clinical practise: focal neurological deficits excluding cranial nerve palsies, seizures, Glasgow Coma Scale below 10 points or severely immunosuppressed patients (van de Beek et al., 2016, B).

In a case of PNM associated with catheter or other intracranial devices, the removal of the item is recommended along with appropriate antibiotic therapy, although careful consideration of possible risks associated with reoperative neurosurgery should be performed (van de Beek et al., 2010, B). According to a recent study, the mortality associated with nosocomial meningitis was approximately 10%, but with studies performed with critically ill patients, the mortality rate was even 37% (Sunwoo et al., 2021; Valdoleiros et al., 2022).

The pathogens causing PNM usually enters CNS directly via CSF during a neurosurgical operation, and the likelihood of an infection to occur is increased if there is a CSF leakage from the wound (Kourbeti et al., 2015). The causative pathogens differ significantly from those of community-acquired BM. *S. aureus* and *S. epidermidis* have been the predominant pathogens causing nosocomial meningitis previously, but recently the proportions of *A. baumannii*, *K. pneumoniae* and *E. coli* has been rising (Kurtanan et al., 2018; Robinson & Busl, 2019; Valdoleiros et al., 2022). In 2022, Panic et al. found that *A. baumannii,* with resistance to carbapenem, was the most common pathogen of nosocomial CNS infections. Pathogens causing nosocomial BM often possess multidrug resistance characteristics and are thus more

challenging to overcome (Ippolito et al., 2022). Nosocomial meningitis, caused by multidrug resistant gram negative pathogens, causes more complications and are associated with higher rate of mortality compared to non-resistant pathogens (Sari et al., 2021).

A. baumannii is often highly resistant to many antibiotics, and it causes often serious nosocomial infections, and the proportions of this pathogen have been rising (Tiku, 2022). This notorious bacteria is known to endure disinfection and it forms sturdy biofilms within the host and hospital surfaces (Hassan et al., 2013; Tiku, 2022).

CSF culture is also a gold-standard method for diagnosing nosocomial meningitis, but in this case the culture needs at least 10 days to be comprehensively informative on pathogens' growth. Additionally, it is recommended, if possible, to culture the surface of neurosurgical intracranial items, such as shunts or drains, to gain additional knowledge of a possible pathogen. If there is a positive CSF culture in the absence of symptoms or other CSF inflammatory markers, a contamination should be suspected (Ippolito et al., 2022).

With almost all neurosurgical patients receiving antibiotics pre-diagnosticly, there have been reports that the CSF culture positivity rate in PNM could vary between 10–30% (Chen et al., 2014; Valdoleiros et al., 2022). Patients are often sedated or unresponsive after neurosurgical procedure, so the clinical assessment is difficult considering whether a patient has BM symptoms or not. Fever and decreased mental status are found to be common signs of patients with PNM (Valdoleiros et al., 2022; van de Beek et al., 2010, A). In addition, laboratory markers which are used for indicating BM are often, at least minorly, elevated due to neurosurgical operation itself, which makes the diagnosis of PNM difficult (Valdoleiros et al., 2022). PCR methods are valuable assets for more rapid and efficient detection of pathogens causing nosocomial meningitis (Ippolito et al., 2022).

Aseptic meningitis presents a challenge to differentiate from bacterial nosocomial meningitis. CSF lactate level over four millimoles per liter favors meningitis of a bacterial origin, and it has been shown to be a useful tool in this regard according to a recent study by Stephani et al. in 2021. However, CSF lactate levels are elevated also by brain ischemia, trauma, or seizures, which should be noted (Ippolito et al., 2022). PCT levels in CSF are also elevated in nosocomial meningitis, and it may be useful for differentiating between PNM and surgical operations only (Ippolito et al., 2022). A longitudinal study from the United States found that costs related to treatments and hospital stays in nosocomial BM were two times higher two years after the diagnosis compared to community-acquired BM, but this economical difference was not seen at early stage after 90 days after BM (Adil et al., 2021).

2.5 Bacterial meningitis in infants and children

BM is the tenth most common cause of mortality in children below five years of age worldwide (Koelman et al., 2021). The incidence of BM among infants and children in Finland is reported to vary between 0.8–11/100 000/year, the lowest incidence among children 5–17 years of age and the highest among infants below two months of age (Polkowska et al., 2017). In Sweden, the incidence has been reported to be 1.9–3.4/100 000 in infants and children (Johansson Kostenniemi et al., 2019). The highest incidence rate was reported among infants and lowest among older children. The incidence of neonatal BM has been around 0.3/1000 live births in developed countries and 3–6/1000 in developing countries (Ku et al., 2015). GBS and *E. coli* have been identified as the most common causative pathogens causing BM in infants from 0 days to 89 days of age, and *S. pneumoniae* and *N. meningitidis* have dominated the bacterial etiology in children aged over 90 days and adolescents (Koelman et al., 2021; Mijovic et al., 2019).

Early-onset BM is defined to occur between 0–6 days of life and late-onset between 7–89 days of age (Delara et al., 2023). In early-onset BM the infection is mainly occurring through vertical transmission from mother to neonate through birth canal, and in late-onset BM it is usually horizontal from person to person or through activation of previously colonized bacteria such as GBS (Berardi et al., 2021; van de Beek et al., 2016, B). Newborn infants are susceptible to serious bacterial infections due to their immature and undeveloped innate and adaptive immune systems. Additionally, the innate cytokine response against bacteria may be insufficient or even overwhelming in this group of patients, and this phenomenon has been associated with a more serious clinical presentation of disease (Yu et al., 2018).

The clinical presentation of BM in neonates is quite nonspecific and therefore presents challenges. The symptoms include irritability, hypotonia, problems in feeding, lethargy, decreased mental status, diarrhea, bulging fontanelle and troubles in breathing (Brouwer et al., 2010; Swanson, 2015; Tavares et al., 2022). More inflammation-specific symptoms such as fever and seizures may also occur, and with older children the more typical clinical symptoms such as neck stiffness, headache, vomiting, and photophobia (Kim, 2010; van de Beek et al., 2016, B). Petechial rash can be also present in meningococcal or pneumococcal BM in children (Nigrovic et al., 2008; Vasilopoulou et al., 2011).

The diagnosis of BM in newborns presents challenges, because it cannot be ruled out by clinical examination only, and therefore a low threshold to perform lumbar puncture should be preferred (van de Beek et al., 2016, B). Additionally, CSF may present normal number of leukocytes (Garges et al., 2006). Blood culture and culture of CSF are the fundamental diagnostic methods to detect BM, but even with negative cultures there may be ongoing infection of the meninges, because prediagnostic antibiotic administration may decrease the amount of bacteria below the detection

radar, causing a false-negative culture result (Tavares et al., 2022). BM is often associated with sepsis in neonates (Grandgirard & Leib, 2010).

Cranial ultrasound has been proven to be a useful tool to rule out complications of BM among infants, and it proves an additional asset also in diagnosing BM, where abnormal ultrasound identifications were observed in 65% of infants with BM (Yikilmaz & Taylor, 2008). Cranial ultrasound can detect widening of brain sulci and meningeal thickening, which are signs of inflammatory exudate accumulating in the brain (Yikilmaz & Taylor, 2008). MRI is also an efficient way to detect meningitis-related changes, such as pachymeningeal or leptomeningeal intensifications, because Oliveira et al. found in 2014 that 81% of patients with culture-confirmed BM presented these changes. MRI is used also to rule out complications, but the method can also be costly, time-consuming and often requires anesthesia of an infant (Tavares et al., 2022).

The gastrointestinal tract colonization of causative bacteria, such as *E. coli*, GBS and *L. monocytogenes*, most likely plays a role in late-onset meningitis, and additionally, GBS is usually transmitted from mother to newborn (Doran et al., 2016; Edwards et al., 2016). Asymptomatic bacteriuria of mothers may be another possible site of colonization of the infant (Whiteside et al., 2015). Nosocomial transmission, nonmaternal caretakers and even infected milk has also been suggested as a transmission pathway of the infection in newborns (MacFarquhar et al., 2010; Salamat et al., 2014; Ueda et al., 2018).

E. coli is a common pathogen causing neonatal BM, and the mortality is reported to be 20–29%, and incidence among live births 0.1/1000 (Bonacorsi & Bingen, 2005). Most of these infections happen earlier than 28 days of life, and around 10% develop between one and three months of age (Okike et al., 2014; Unhanand et al., 1993).

According to Vila et al. in 2016, *E. coli* has surpassed GBS as the most common causative pathogen of neonatal sepsis and meningitis, especially in countries where GBS prophylactic guidelines have been implemented. However, even more recent review by Tavares et al. 2022 stated that GBS remains the most frequent causative pathogen of BM in neonatal period.

S. pneumoniae has also been reported as a common causative pathogen of BM in childhood, and according to some studies it may cover over a third of all BM in infants and children (Thigpen et al., 2011).

2.6 Prevention

BM is partly a disease which can be prevented by different measures, and vaccines play the most important role here (McIntyre et al., 2012). Hib conjugate vaccines has reduced significantly the incidence of BM caused by Hib from 1.44 to 0.04 episodes

per 100 000 population per year, with even 97% reduction rate according to Koelman et al. in 2021. Pneumococcal conjugate vaccines target several different serotypes that are most likely to cause severe pneumococcal infections (van de Beek et al., 2016, A). Implementation of the 7-valent pneumococcal conjugate vaccine in the United States caused a 59% reduction in the incidence of pneumococcal BM in children from 96/100 000 to 40/100 000/ year (Whitney et al., 2003). Also, the 13-valent pneumococcal vaccine was efficient in preventing severe pneumococcal disease in elderly adults (Bonten et al., 2015). In Finland, the implementation of a 10-valent pneumococcal conjugate vaccine has decreased the incidence of pneumococcal meningitis efficiently: 0.19 to 0.09 episodes per 100 000 population per year (54%) among 5–17 aged children and 2.35 to 0.84 episodes per 100 000 population per year (64%) in children between ages 0–4 (Polkowska et al., 2021). The wide usage of pneumococcal vaccinations has led to serotype replacement, where non-vaccine serotypes have been emerging as a causative agents of BM (Polkowska et al., 2021). After pneumococcal BM or with surgical patients with CSF leakage with the dural barrier reformations, it is recommended for the individual to be administered with pneumococcal conjugate vaccine (van de Beek et al., 2016, B).

Meningococcal vaccinations are used for the prevention of meningococcal diseases, but the policy varies regarding the country (van de Beek et al., 2016, A). Meningococcal group C vaccination has significantly decreased the incidence of *N. meningitidis* BM with 93% decrease between 1989–1993 and 2014–2019 (Koelman et al., 2021). The vaccinations against *N. meningitidis* are recommended by the World Health Organization for especially to inhabitants in meningitis belt countries (van de Beek et al., 2016, A).

Many guidelines recommend general screening for colonization of GBS from recto-vaginal areas during pregnancy at 35–37 weeks of gestation, and intrapartum antibiotic prophylaxis is administered for patients with positive tests. Antibiotics, usually penicillin G or ampicillin, are most effective if administered approximately four hours before labour (ACOG committee members, 2020). This procedure has shown to diminish the incidence of neonatal early-onset GBS meningitis in the United States (Simonsen et al., 2014). However, this measure could lead to a possible increase of other pathogens such as *E. coli* and an increase in antimicrobial resistance (Lin et al., 2011; Sgro et al., 2011). Additionally, vaccinations against GBS are in development, and are urgently needed for use in pregnant women to protect infants from late-onset GBS disease through transplacental antibody transfer (Delara et al., 2023; van de Beek et al., 2016, A). Neonatal BM has proven to be a challenge in terms of prevention, because maternal intrapartum antibiotic prophylaxis has not been shown to be effective in prevention of late-onset GBS disease (Delara et al., 2023).

It is recommended that individuals who have been in close interaction with a patient suffering from meningococcal meningitis are administered prophylactic antibiotics, because the risk of transmission is 400–800 fold increased (van de Beek et al., 2016, B; Zalmanovici et al., 2013). In these cases, ceftriaxone, rifampicin or ciprofloxacin should be administered to risk contacts (van de Beek et al., 2016, B). Prophylactic antibiotics have also been shown to significantly decrease the incidence of superficial and deep infections, administered at the beginning of neurosurgery (Jackson et al., 2016). Prophylactic antibiotics are also used in intensive care units while ventriculostomy is present in the brain (Sonabend et al., 2011). In addition, antimicrobial-impregnated devices are recommended in neurosurgery to prevent PNM (Atkinson et al., 2016).

Patients ongoing glioma surgery in Turku University Hospital receive routinely cefuroxime 3 grams intravenously in the operation room before the start of surgery. The skin is cleaned with chlorhexidine. Patients who do not tolerate or have suspected allergy towards cefuroxime, intravenous clindamycin 600mg is used as a prophylaxis instead. The skin is closed with antibacterial sutures and hooks.

Neonatal nosocomial infections may be prevented, to some extent, by probiotics, breastfeeding and standardized infection prevention protocols in neonatal departments (Deshmukh & Patole, 2021).

The Finnish national vaccination programme has provided children the 10-valent pneumococcal conjugate vaccine at the ages of three, five and 12 months, since 2010. This vaccine covers *S. pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Hib vaccines have been given at the similar ages since 1993. Meningococcal vaccines are not part of the Finnish national vaccination programme for children.

13-valent pneumococcal conjugate vaccination has been recommended to adults with stem cell transplants since 2014, and the recommendations expanded in 2022 to cover adults with severe kidney disease, and severely immunosupprimed patients under 75-years of age and additionally asthma and chronic pulmonary obstructive disease - patients over 65 years of age in 2023. The vaccine covers *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (Finnish institute for health and welfare, https://thl.fi/en/topics/infectious-diseases-and-vaccinations/vaccines-a-to-z/pneumococcal-vaccines/pneumococcal-conjugate-vaccine-pcv).

2.7 Treatment

Considering the severity and mortality related to BM, treatments should be administered at the time of suspicion, before the diagnosis can be confirmed, and the time period between the diagnosis and antibiotic administration should not exceed one hour (van de Beek et al. 2016, B). Numerous tests should be done in a swift manner; blood tests relating to infection, blood cultures, CSF samples as CSF

leukocytes, protein, glucose, lactate, and CSF culture, and if possible PCR for bacterial nucleic acid detection in CSF (Brouwer et al., 2012; Hasanuzzaman et al., 2021; van de Beek et al., 2016, B). Antibiotic treatment should be started if necessary even before imaging, because delays may have unfavorable impacts regarding the outcome (McMillan et al., 2001).

The choice of the primary antibiotic regimen to treat BM should consider the knowledge of local epidemiology, especially the resistance patterns of *S. pneumoniae*, and age, status of immunosuppression and allergies of an individual being treated for BM (van de Beek et al., 2012; van de Beek et al., 2016, A). Administering antibiotics via constant infusion or bolus have not been yet studied profoundly to give recommendations (van de Beek et al., 2016, B).

ESCMID recommends a third-generation cephalosporin, ceftriaxone or cefotaxime, with simultaneous vancomycin primarily for the treatment of BM; however, in certain countries where the prevalence of cephalosporin-resistant *S. pneumoniae* is below 1%, treatment with ceftriaxone only is sufficient (Tunkel et al., 2004; van de Beek et al., 2016, B). There has also been growing number of penicillin resistant *S. pneumoniae* strains recently in Europe (van de Beek et al., 2016, B).

L. monocytogenes presents resistance to cephalosporins, and therefore ampicillin or amoxicillin should be administered usually along with other antibiotics to all suspected immunosuppressed patients with BM, for example neonates, patients over 50 years and pregnant women (van de Beek et al., 2012; van de Beek et al., 2016, A). The role of gentamicin remains controversial, as a study from 1998 by Mylonakis et al. presented that gentamicin may reduce the mortality of listerial meningitis, but a more recent study from 2011 by Mitja et al., showed that gentamicin may, on the contrary, increase mortality and the rate of kidney injury.

When treating an infant for neonatal BM, the treatment should cover especially GBS and *E. coli* (Brouwer et al., 2012). Considering infants, combination of ampicillin and gentamicin or cefotaxime should be used until further findings from CSF or blood and the possible susceptibility results (Nelson, 2019). Ceftriaxone should be chosen when suspecting meningococcal meningitis (Harcourt et al., 2015). When, and if, the causative bacteria with its antimicrobial susceptibility patterns have been detected, should the antibiotic therapy be optimized accordingly (van de Beek et al., 2016, A).

Duration of antibiotic therapy is recommended to be 7–10 days for meningococcal meningitis or *H. influenzae* meningitis, 10–14 days for pneumococcal meningitis and 21 days for listerial meningitis (Tunkel et al., 2004; van de Beek et al., 2016, B; van de Beek et al., 2012). Interestingly, there were no statistically significant differences regarding efficacy and safety between 5-day versus 10-day ceftriaxone treatments with children (Molyneux et al., 2011). When treating an infant with BM, the duration of antibiotic therapy should be 14–21 days

(Tavares et al., 2022). When treating nosocomial meningitis, duration of antibiotic therapy up to 21 days is recommended in case of gram-negative bacilli. When treating BM caused by *S. aureus*, flucloxacillin or oxacillin or a combination therapy including rifampicin is recommended, and vancomycin with methicillin-resistant *S. aureus*, and if the pathogen is vancomycin-resistant, linezolid may be effective (Ippolito et al., 2022; van de Beek et al., 2016, B). Rifampicin is recommended in combination with other antibiotics to patients with intracranial devices and staphylococcal infections (Ippolito et al., 2022). Endocarditis or spinal abscesses should be suspected when staphylococcal meningitis is detected (Brouwer et al., 2009).

Intraventricular or intrathecal administration of antibiotics are methods to treat BM in cases where the patient is not responding adequately to intravenous therapy, and especially in CNS infections by *Acinetobacter* species, which are often nosocomial (Nau et al., 2020; Tunkel et al., 2017). In these occasions, the concentrations of antibiotics should be monitored and titrated closely to maintain adequate levels to efficiently treat the infection (Tunkel et al., 2017). Intraventricular or intrathecal colistin may be the only suitable choice of treatment for multidrug resistant bacteria, despite its possible adverse effects, such as seizures (Perez-Alba et al., 2020; Tsimogianni et al., 2017). Intrathecal vancomycin may also be used (Tsimogianni et al., 2017). According to a study by Kizilates et al. in 2021, intrathecal administration of antibiotics such as amikacin, colistin or gentamicin, in case of carbapenem-resistant gram-negative bacteria, was found to be beneficial. Although the administration of antibiotics via these methods may present risks, the systemic side effects compared to intravenous antibiotic therapy is usually reduced (Sari et al., 2021). According to a recent meta-analysis, the morbidity related to intraventricular or intrathecal antibiotic usage was 13%, consisting of mainly aseptic meningitis and seizures (Brotis et al., 2021).

The severity and remaining significant mortality of BM, regardless of antibiotic therapies, has led to studies investigating possible adjunctive therapies to treat BM. Therapeutic hypothermia, paracetamol and glycerol, for example, have been studied for this purpose but with inconclusive or even adverse results (Molyneux et al., 2014; Mourvillier et al., 2013; Pelkonen et al., 2011).

Dexamethasone, in addition to antibiotic treatment, has been shown to reduce adverse outcomes and mortality in children and adults, especially in cases of pneumococcal meningitis (Brouwer et al., 2015, de Gans & van de Beek, 2002). Dexamethasone should be provided before or with the first dosage of antibiotics in order to inhibit the inflammatory response resulting from bacteriolysis by antibiotics (de Gans & van de Beek, 2002; Nguyen et al., 2007). A comprehensive study found that dexamethasone mainly decreased mortality in pneumococcal meningitis by preventing systemic complications (van de Beek & de Gans, 2004). Furthermore,

some studies have found that corticosteroids may reduce the rate of hearing loss and neurological sequelae, but not mortality (Brouwer et al., 2015; van de Beek et al., 2010, B; van de Beek et al,. 2004). Interestingly, corticosteroid administration had no favorable effects with individuals from low-income countries, possibly because of late administration of corticosteroids (van de Beek et al., 2010, B). After all, dexamethasone is the only approved adjunctive therapy for BM according to ESCMID and Infectious Diseases Society of America guidelines for adults and children but not for neonates (Tunkel et al., 2004; van de Beek et al., 2016, B). The recommended doses are 10 mg four times a day with adults and 0.15 mg per kilogram four times a day with children (van de Beek et al., 2016, B).

Adjunctive dexamethasone therapy should be administered along or even before antibiotic therapy and continued for four days with children and adults, and especially if patients suffer from sepsis or septic shock (van de Beek et al., 2006, B; van de Beek et al., 2016, B; van de Beek et al., 2012). However, if the diagnosis of BM is unsure or the causative bacteria is other than *S. pneumoniae* or *H. influenzae*, dexamethasone treatment may be beneficial to suspend (van de Beek et al., 2016, B).

2.8 Complications and outcome

Seizures, brain infarctations and hydrocephalus are possible complications of BM among all ages (Tavares et al., 2022; van de Beek et al., 2006, A). A study by Lindvall et al. in 2004 presented that an eye should be kept on intracranial pressure with head CT scans and if necessary to administer corticosteroids, osmotic diuretics and ventriculostomy if hydrocephalus is detected, decompressive craniectomy is needed when there is a need to lower uncontrollable intracranial pressure. However a more recent paper stated that these treatments may be unbeneficial or even harmful to patients (Brouwer et al., 2016). With meticulous patient selection, it is nevertheless recommended to implement intracranial pressure monitoring if there is a suspicion of brain herniation and elevated intracranial pressure, and if necessary, to apply osmotic therapy, repeat lumbar punctures or implement an external lumbar drain to decrease intracranial pressure (van de Beek et al., 2006, B; van de Beek et al., 2016, A). The rate of hydrocephalus was reported to be around 5% , but more recently a pediatric study found that the rate of this complication may be even 20–28% (Adil et al., 2021; Kasanmoentalib et al., 2010).

Sinovenous thrombosis presents another dangerous complication of BM (Tibussek et al., 2015). If a patient is not starting to recover via appropriate antibiotic therapies and the parameters of infection increases or does not decrease, imaging of the brain and the head should be considered to rule out brain abscess, which had an incidence of 9% in pediatric population after BM (Adil et al., 2021). Neonatal encephalopathy, often related to GBS meningitis, is a clinical presentation associated

with significant mortality and long-term impairment of the child, which can be detected using brain imaging methods (Gunn & Thoresen, 2019; Tann et al., 2017).

There is evidence that even in seemingly poor state of a patient the treatments should be continued if an individual presents with preserved brainstem reflexes, because the possibility of survival and recovering is notable (Muralidharan et al., 2014). Even 20% of totally unresponsive patients with a Glasgow Coma Scale score of three are reported to make a full recovery, highlighting the need for continued supportive treatment (Lucas et al., 2014).

Risk of neurological sequelae, such as epilepsy, cerebral palsy, hearing loss and cognitive impairment, is reported in about half of the survivors of BM and especially with individuals suffering from pneumococcal meningitis (Edmond et al., 2010; Kim, 2010; Portnoy et al., 2015; Sridhar et al., 2015; van de Beek et al., 2002; Watt et al., 2009). BM is reported to be a common cause of acquired sensorineural hearing loss in children (Fortnum & Davis, 1993). The rate of hearing loss has been reported to be around 22–30%, and 4% of patients are reported to suffer from bilateral hearing loss (Arditi et al., 1998; van de Beek et al., 2016, B). According to Worsoe et al. in 2010, the rate of hearing loss could be even 55% after pneumococcal meningitis. Hearing loss has been shown to be reversible in some cases, but approximately 30% of patients suffer from permanent hearing loss after BM caused by *S. pneumoniae* (Arditi et al., 1998; Lucas et al., 2016). Hearing loss may not be present at admission and may develop later, so meticulous caution should be taken and hearing tests, otoacoustic emissions or brainstem auditory evoked responses with children, or audiometry with adults, should be performed with a very low threshold, and follow-up testing may be needed (van de Beek et al., 2016, B). Early detection of hearing deficiencies is crucial, because obliteration of the cochlear lumen might be a consequence of BM and has been associated with unfavorable outcomes in cochlear implant surgery, so therefore the screening of hearing levels can be recommended in these circumstances (van Loon et al., 2013). In children, hearing loss may cause impairments in speech development, and cochlear implant may be needed to prevent this process (van de Beek et al., 2016, B).

In high-income countries the rate of major neurological deficits are 50% lower compared to those in low-income countries (Edmond et al., 2010). Around 33% of patients suffer from reduced processing speed as a form of cognitive impairment after BM caused by *S. pneumoniae* or *N. meningitidis* (Hoogman et al., 2007; van de Beek et al., 2002). Neuropsychological sequelae may cause difficulties in social relationships, language developments and general ability to learn (Saha et al., 2009). Childhood BM has been shown to have adverse effects on educational level in Denmark (Roed et al., 2013). Patients with unfavorable outcomes after BM burden the healthcare systems (Watt et al., 2009).

There has been many proposed scales to determine the patients´ outcome after neurological diseases. Glasgow Outcome Scale (GOS) has been shown to be a valid choice both in children and adults (Beers et al., 2012; Matulyte et al., 2020). The rate of unfavorable outcome among infants and children after BM has been reported to be 10–18%, and around 16–38% among adults (Baraff et al., 1993; Bijlsma et al., 2016; Matulyte et al., 2020; Svendsen et al., 2020). The mortality of BM has been reported to range from 2% to 33% among infants and children and 6–17% among adults (Bijlsma et al., 2016; Jung, 2022; Lovera et al., 2022; Matulyte et al., 2020; Polkowska et al., 2017).

2.9 Risk factors of bacterial meningitis and predictors of unfavorable outcome

Otitis media is shown to be a key risk factor for BM (Worsoe et al., 2010). Additionally, human immunodeficiency virus -infection, indoor air pollution, overcrowded houses, malnutrition, and genetic deficiencies in immune systems such as asplenia, complement system deficiencies and antibody deficiencies along with smoking and sickle cell anemia has been reported as risk factors for BM (Baker et al., 2000; Battersby et al., 2010; Hodgson et al., 2001; Miller et al., 2014; Mook-Kanamori et al., 2011; Müller & Krawinkel, 2005; van de Beek et al., 2016, A). Furthermore, poverty has been identified as a strong risk factor for BM (Global Burden of Diseases, 2018).

Considering newborns, low birth weight, low birth length, prolonged time of rupture of membranes over 18 hours, intrapartum maternal fever and use of invasive measures during parturition have been recognized as risk factors for GBS disease (Ku et al., 2015; Puopolo et al., 2019; Verani et al., 2010; Zaleznik et al., 2000).

Considering PNM, reoperations, insertion of postoperative ventricular shunts, and male sex have been identified to be risk factors after craniotomy (Korinek et al., 2008; Reichert et al., 2002). In addition, diabetes mellitus, administration of corticosteroids, CSF leakage, and increased duration of surgery have been found to elevate the risk of PNM (Jackson et al., 2016; Kourbeti et al., 2015). Interestingly, glioblastoma patients with tumour maintaining chromosome 10q was found to have increased rates of infections (Aghi et al., 2009).

Several clinical symptoms have been identified as predictors of unfavorable outcome after BM. The role of headache has been unclear, as according to the study by Bijlsma et al. in 2016, headache was not a predictor of unfavorable outcome, but more recently Matulyte et al. in 2020 found that headache was a predictor of unfavorable outcome. Neurological symptoms and confusion have also been reported to be predictors of unfavorable outcome (van de Beek et al., 2016, B). Prematurity (<37 weeks of pregnancy), seizures and male gender have been

identified as predictors of unfavorable outcome in newborns (Haffner et al., 2021). Patients over 65 years of age with PNM had significantly higher risk of mortality according to a recent study by Valdoleiros et al. in 2022.

3 Aims

The objective of this doctoral thesis was to characterize the epidemiology of BM among patients of all backgrounds in Southwestern Finland and the significance of potential predisposing factors and the indicators of unfavorable outcome. The specific aims of the studies were:

1. To characterize the current clinical picture of BM, to identify the causative pathogens, to determine the predisposing factors and indicators of unfavorable outcome of community-acquired and nosocomial BM in adult population.
2. To describe the incidence, epidemiology, and clinical presentation of BM, to identify the causative bacteria, and to study the predisposing factors and indicators of unfavorable outcome of community-acquired and nosocomial BM in infants and children.
3. To investigate the incidence of PNM after glioma surgery, characterize the causative pathogens, to study the predisposing factors and to determine the risk factors for developing PNM.

4 Materials and Methods

4.1 Patient selection

4.1.1 Studies I-II

The medical records of adult patients over 16 years of age and infants and children under 16 years of age treated for BM at Turku University Hospital, Turku, Finland, between 2011 and 2018, were retrospectively investigated. Our hospital is a tertiary referral centre in the Hospital District of Southwest Finland, which can receive patients also from elsewhere Western Finland. At the time of these studies, our hospitals catchment area was approximately 480 000 inhabitants, of which 75 000 infants and children below 16 years of age, and 4000 live births per year.

A database search with the following International Classification of Diseases 10th Revision (ICD-10) codes were performed: A87.9, B94.80, G00.9, G01*A32.1, G01*A39.0, G01*A69.2, G05.2*B83.2, A17.0, A32.1, A87, B01.0, B02.1, B05.1, B37.5, B38.4, B45.1, B94.80, G00, G01, G02, G03, G05.

From a total of 896 patients with an ICD-10 code for meningitis, all meningitis caused by non-bacterial pathogens, such as viruses, fungi, parasites, or probable aseptic meningitis cases were excluded, and so were all neuroborreliosis cases. The ICD-10 codes included meningitis of all causes, and the patients who were excluded from these studies had a confirmed or probable excluded type of meningitis, or they did not fill the laboratory inclusion criteria for BM. The patient data was investigated further by going through all the previous patients including clinical findings, laboratory results on blood and CSF, and imaging results one by one.

Finally, 148 adults and 37 infants and children were included with either community-acquired or nosocomial BM. The pediatric patients were further classified into two age groups: infants from 0 to 89 days of age and children from 90 days to 15 years of age.

4.1.2 Study III

After the surprisingly high proportion of nosocomial meningitis, especially PNM from studies I and II, a meeting was set up with neurosurgeons to plan further

investigations. We decided to border the cases of PNM with only glioma patients, the group with highest amount of PNM according to study I to make the patient selection more uniform, because in studies I and II all kinds of neurosurgical operations before PNM were included.

We systematically analyzed the patient records of a consecutive cohort comprising 1 161 patients undergoing craniotomy for intracranial tumors between 2011 and 2018. Next, a database search for World Health Organization grade 1–4 glioma patients treated with craniotomies between 2011–2018 in Turku University Hospital, Finland, was carried out. ICD-10 codes C71.*, The Nordic Medico-Statistical Committee codes AAB00, AAB10 and AW*** were used to identify suitable patients. Out of this cohort, 345 patients received a glioma diagnosis and were subsequently included in this study.

4.2 Definitions

4.2.1 Study I

BM was defined as nosocomial, if the individual was already admitted to hospital when developing BM or, if there was a history of surgery in the previous 54 days. BM was defined as community-acquired if the individual had no history of surgery or hospitalization during the previous 54 days.

4.2.2 Study II

Nosocomial BM was defined as an early-onset meningitis (0–6 days of age), meningitis acquired during the patient's hospital stay or meningitis after a neurosurgical procedure, which occurred before 30 days after discharge. All other individuals were defined as having a community-acquired BM.

4.2.3 Study III

Revision surgery was defined as a reoperation occurring before 100 days after primary surgery, and reoperation was defined as a repetitive glioma surgery in the history of patient without specific time limits. Reoperations and revision surgeries were executed from the same area as the index surgery. Recurring or residive gliomas were the motives for reoperations, while CSF leakage, surgical site infections, hydrocephalus or intracranial infections were the reasons for revisions. Classical signs of infection in the area of surgery such as redness, tenderness, swelling, or pus rose the suspicion of a wound infection. Low-grade gliomas were defined as grades 1–2 while grades 3–4 were defined as high-grade.

4.3 Diagnostic inclusion criteria

4.3.1 Study I

This study included culture- or PCR positive BM cases but also CSF culture negative cases with symptomatology of BM with neutrophilic pleocytosis and at least one of the following: decreased CSF glucose levels (< 2.2 mmol/L), high protein levels (> 1000 mg/L) or high CSF lactate levels (> 3.0 mmol/L), and those with meningitis-related findings interpret by radiologists in imaging examinations. All methods of data collection remained uniform through 2011–2018.

When found in CSF, *S. epidermidis* was considered to be a causative agent of BM if the patient was having BM symptoms and simultaneous CSF pleocytosis to rule out contamination.

4.3.2 Study II

This study included patients with positive CSF culture or PCR but also CSF culture negative patients with clinical symptoms of BM and CSF pleocytosis (>30 × 10^6/L). Additionally, patients had to have at least one of the following laboratory findings: a positive blood bacterial culture, a high CSF protein level (>1000 mg/L) or elevated plasma CRP levels (>50 mg/L). The inclusion criteria for neonatal early-onset BM cases were clinical symptoms of BM and a CSF leukocyte count over 30 × 10^6/L.

When found in CSF, *S. epidermidis* was considered to be a causative agent of BM if the patient was having BM symptoms and simultaneous CSF pleocytosis to rule out contamination.

4.3.3 Study III

Patients enrolled had at least one of the possible symptoms of PNM: fever, headache, decreased mental status, seizures, or neck stiffness. To identify the appropriate PNM patients and rule out aseptic meningitis cases, the following inclusion criteria to define PNM were implemented: 1. CSF culture positivity, 2. CSF leukocyte count ≥ 250x10^6/L with granulocyte percentage ≥50% or 3. CSF lactate ≥4mmol/L (Hussein et al., 2017). Eventually, 25 patients with PNM were identified.

4.4 Laboratory methods

This chapter characterizes the standard laboratory methods used in this thesis, not all methods. During the study period, the laboratory methods of BM were as following: A minimum of two ml of CSF was gathered from adult patients with suspected BM,

and even lower volume of CSF from neonates and children. Gram staining was performed to screen the potential bacterial pathogens. A drop of sediment was spread over culture media, chocolate agar plates (BD Diagnostic Systems) and trypticase soy sheep blood agar plates (TSA-S, BD Diagnostic Systems). Additionally, a drop of sediment was added into fastidious anaerobe broth (FAB, in-house) and if postoperative BM was suspected, a fastidious anaerobe agar (FAA, in-house) plate was cultured.

The aerobic plates were read on the first and second day after the inoculation. If no growth was detected, negative result was given to clinician. The anaerobic FAA and FAB plates were read on the second and fourth day after the inoculation, after which the negative result was given if no growth was noticed. The media were further incubated until total of seven days, and if growth was detected at that point, the clinician was informed.

When growth was noticed on any media, the pathogens were identified with matrix-assisted laser-desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry (MALDI Biotyper® System, Bruker Daltonics, Bremen, Germany).

Species-specific PCR-methods were not available for bacteria in our institute. When requested by a clinician, general PCR for bacteria with 16S ribosomal ribonucleic acid -sequencing method was performed to identify bacterial pathogens from CSF. Bacterial DNA was isolated in our laboratory and sent for sequencing to Eurofins Genomics laboratory (Ebersberg, Germany) and the resulting DNA sequence was compared with Basic Local Alignment Search Tool- software (https://blast.ncbi.nlm.nih.gov) to GeneBank database.

Blood culture samples from adults were harvested into Bactec™ Plus Aerobic/F and Bactec™ Plus anaerobic/F bottles (BD Diagnostic Systems, Sparks, Maryland, USA). With pediatric patients, blood culture samples were collected to Bactec™ Peds Plus™/F vials (BD Diagnostic Systems, Sparks, Maryland, USA).

The samples were incubated for maximum of 120 hours or until signalled positive. The positive samples were placed on chocolate agar and FAA plates and the bacteria were identified by MALDI Biotyper® System (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility tests were performed with disk diffusion (Oxoid, Cambridge, UK), minimal inhibitory concentration gradient -tests (Etest, bioMérieux, Marcy I'Etoile, France) or VITEK® 2 Compact automated ID/AST system (bioMérieux). The results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing guidelines.

4.5 Statistical analysis

4.5.1 Study I

The incidence of BM in adults was calculated by dividing the number of patients in the Hospital District of Southwestern Finland by the number of years studied and the population over 16 years of age. The categorical variables are summarized with counts and percentages (%), and the continuous variables are presented with ranges, means for normally distributed variables or medians.

To discover factors affecting to unfavorable outcome (GOS scores 1–4), log binomial model was performed separately for each factor with univariate approach and reported with relative risk and it's 95% confidence intervals (CI) together with *p*-value. *P*-values of <0.05 were interpreted as statistically significant.

Association with two categorical variables was tested with Fisher's exact test. The data analysis was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). All statistical analyses were performed by Master of Science, biostatistician Eliisa Löyttyniemi.

4.5.2 Study II

The incidence of BM in pediatric patients was calculated by dividing the number of patients in the Hospital District of Southwestern Finland by the number of study years and the population below 16 years of age. The incidence in infants was reached by dividing the annual number of infant BM cases by the number of live births.

The two age groups were compared with the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Statistical associations between two categorical variables were tested with Fisher's exact test. Additionally, a separate log-binomial model was performed with unfavorable outcomes, defined as GOS scores 1–4, for each factor as univariate approach.

We were not able to perform a multivariate analysis because of the low number of children with an unfavorable outcome. Two- tailed *p* values of <0.05 were interpreted as statistically significant. The data analysis was generated using SAS for Windows, Version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical analyses were performed by Master of Science, biostatistician Eliisa Löyttyniemi.

4.5.3 Study III

Continuous data of patients were summarized with median and lower (Q1) and upper (Q3) quartiles and comparisons between patients with PNM and without PNM with Wilcoxon rank sum test. Associations between two categorical variables was

primarily evaluated with Fisher's exact test. Additionally, logistic regression analysis was performed to reoperation and revision surgery, separately for each explanatory variable with univariate approach, and reported with odds ratio (OR) and its 95% CIs. After univariate modelling, multivariable model was constructed based on univariate results. Two-tailed p values of <0.05 were regarded as statistically significant. The data analysis was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). All statistical analyses were performed by Master of Science, biostatistician Eliisa Löyttyniemi and Doctor of Medicine, Doctor of Philosophy Dan Laukka.

4.6 Evaluation of outcome

In studies I and II, the clinical outcomes after BM were evaluated. The outcomes were defined with the five-point GOS scale based on the information in the patient's medical records (Beers et al., 2012; Matulyte et al., 2020). The scale comprises of death (one point), vegetative state (two points), severe disability (three points), moderate disability (four points) and mild or no disability (five points).

The outcomes of adult patients in study I were evaluated at discharge. The outcomes of pediatric patients in study II were evaluated at discharge and eight months after discharge. An unfavorable outcome was defined in both studies as a score from 1 to 4. Considering adults, the scores 2–4 were interpreted as following: 2= patient is unable to interact with the environment, 3=patient is unable to live independently, 4=patient can live independently but is unable to return to previous work. Considering pediatric patients when interpreting the GOS scores, we considered the age of the patient, and the disability was assessed in relation to their age-appropriate behaviour.

Hearing was evaluated with an appropriate method, either a brainstem auditory evoked response, an audiogram, otoacoustic emissions or mechanical source of voice, depending on the age and status of the patient. Hearing deficiency was defined by a better ear hearing level of 20 decibels or above.

4.7 Ethics

This was a retrospective single centre study from Turku University Hospital, Turku, Hospital District of Southwest Finland, Finland. This study received an institutional approval and was not subject to the Ethics Committee approval, but all separate studies received research permit.

5 Results

5.1 Study I

5.1.1 Background information

The medical information of 148 adults with BM were included in study I. We identified 72 (49%) males and 76 (51%) females. Median age of patients was 57 years (range 16–95). The most common age groups with BM were patients between 46–65 years of age (n=64, 43%), followed by individuals aged 66 years or older (n=40, 27%), 26–45 years (n=29, 20%), and young adults 16–25 years of age (n=15, 10%). Almost all (145, 98%) patients had Finnish nationality. Individual characteristics, underlying conditions, associated background infections, and signs and symptoms of patients on admission are presented in **Table 1**. The age distribution of patients is presented in **Figures 2** and **3**.

Most patients contacted the hospital emergency department primarily (120, 81%) and some local health center (24, 16%) and a few with private medical clinics (4, 3%). Majority of individuals had nosocomial BM (82, 55%) and the rest (66, 45%) community-acquired BM. Neurosurgical procedure or acute cerebral incident prior BM were documented in 74 patients (50%). Forty-nine patients (33%) had no previous infection or operation prior BM. Nine patients (6%) had otogenic, another nine patients (6%) odontogenic, and seven patients (5%) sinonasal etiology of BM. Seven individuals (5%) had recurrent BM. Majority of BM cases were diagnosed in the Hospital District of Southwest Finland (139, 94%), and the rest (9, 6%) were transferred to our hospital from regional hospitals elsewhere. The total adult population in our district during the study years was approximately 405 000, and thus the total yearly incidence was approximately 4.3/100 000. Vaccination status of patients was poorly mentioned in the medical records, as only one (1%) was reported to having received all vaccinations in the Finnish national vaccination programme.
Active cancer, diabetes, lower and upper respiratory tract infections, excessive alcohol use, smoking, and skin infections were relatively common among patients (**Table 1**.) Sixty-seven patients (45%) had previous surgery prior BM and two (1%) of them were ear- related.

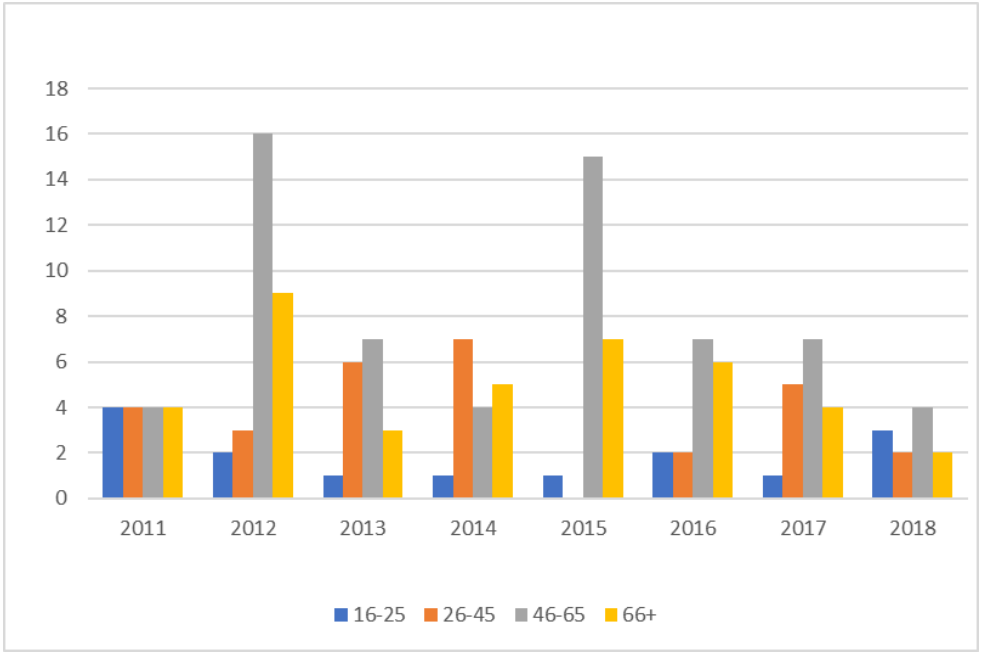


Figure 2. Incidence of bacterial meningitis in age groups per year. Reprinted with permission from the copyright holders from original publication I. The y-axis shows the number of patients.

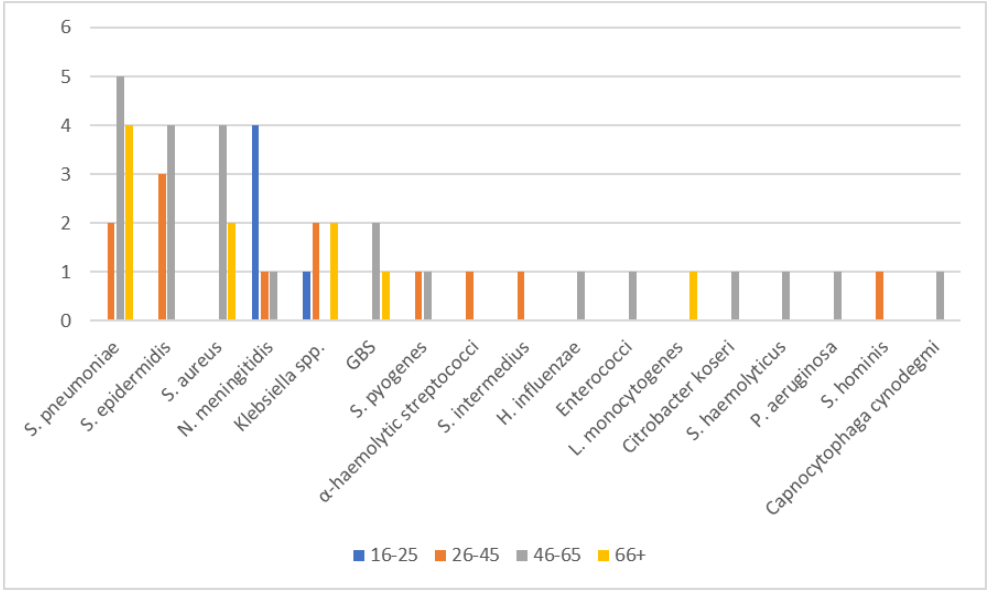


Figure 3. Number of bacteria detected in the cerebrospinal fluid by age groups. Modified and reprinted with the permission from the copyright holders from original publication I. The y-axis shows the number of bacteria.

Table 1. Individual characteristics, underlying conditions, associated background infections, and signs and symptoms of adult patients with bacterial meningitis. Modified and reprinted with the permission from the copyright holders from original publication I.

Variable	BM patients (n=148)
Demographics	
Age (years)	57 (median)
Men	72 (49%)
Finnish nationality	145 (98%)
Predisposing conditions	
Sinusitis	7 (5%)
Otitis	9 (6%)
Dental infection	9 (6%)
Post-neurosurgical infection	74 (50%)
Brain abscess	6 (4%)
Urinary tract infection	3 (2%)
Recurrent meningitis	7 (5%)
Smoking	21 (14%)
Alcohol overuse	18 (12%)
Sepsis	42 (28%)
Cancer	22 (15%)
Diabetes (type I and II)	17 (12%)
Hypertension	44 (30%)
Asthma	7 (5%)
Previous operative treatment	67 (45%)
Mental disability	1 (1%)
Respiratory infections	
Pneumonia	15 (10%)
Bronchitis	1 (1%)
Aspergillosis	1 (1%)
Upper respiratory infection	15 (10%)
Tonsillitis	1 (1%)
Skin infections	
Head area	11 (7%)
Other	11 (7%)
History of acute illness	
Seizures	8 (5%)
Pre-diagnostic antibiotic use	85 (57%)
Pre-diagnostic corticosteroids	33 (22%)
Clinical findings on admission	
Decreased general condition	90 (61%)

Variable	BM patients (n=148)
Decreased consciousness	62 (42%)
Fever	123 (83%)
Headache	83 (56%)
Neck stiffness	73 (49%)
Triad of fever, headache, and neck stiffness	39 (26%)
Triad of fever, neck stiffness and decreased consciousness	20 (14%)
Vomiting	36 (24%)
Skin color change	12 (8%)
Confusion	58 (39%)
Aphasia or dysphasia	13 (9%)
Visual deviation	3 (2%)
Psychic retardation	3 (2%)
Pupil-asymmetry	3 (2%)
Babinski sign	2 (1%)
Nystagmus	2 (1%)
Eyes-fixed-gaze	2 (1%)
Hearing loss	1 (1%)
Dysarthria	1 (1%)
Vertigo	1 (1%)
Double vision	1 (1%)
Strabismus	1 (1%)

5.1.2 Clinical characteristics

The median duration of symptoms before admission to hospital was one day (range 0–30 days). Eight individuals (5%) had seizures (three generalized, one focal, four undefined) prior admission to hospital. In the emergency department eight (5%) patients had seizures. Decreased level of consciousness was noticed in 62 (42%) patients, four of them being in coma—one in a ventilator and three sedated due to severe clinical condition. Eighteen patients (12%) had two or three neurological symptoms at the same time. One (1%) monoparesis and two (1%) hemiparesis were reported, but those were most likely related to acute ischemic brain attack prior to BM. Changes in skin color were observed in 12 (8%) patients: petechiae in nine, marble skin in two patients, and yellowish skin in one patient. All clinical symptoms are presented in **Table 1**.

5.1.3 Causative pathogens

Blood culture detected bacteria in 42 (28%) patients. CSF culture for bacteria was conducted in 146 (99%) patients showing positivity in 50 (34%) cases. PCR of CSF specimen was performed with 46 individuals (31%) presenting positivity in 10 (20%) cases. Same bacteria were detected in CSF and blood in 17 (12%) patients. The most frequent pathogens were *S. pneumoniae* (11, 7%), *S. epidermidis* (7, 5%), *S. aureus* (6, 4%), *N. meningitidis* (6, 4%) and *Klebsiella* species (5, 3%). CSF culture was used to identify seven *S. epidermidis* cases and PCR was used for one. There were nine (6%) Gram stain negative rods cultured from CSF in study I: Five *Klebsiella* species, one each of the following bacteria: *H. influenzae, Citrobacter koseri, Pseudomonas aeruginosa* and *Capnocytophaga cynodegmi. Pasteurella multocida* was observed once with PCR. All causative bacteria cultured from CSF are presented in **Figures 3** and **4**.

Besides from CSF, pathogens were cultured from other sources as well. Most common pathogens detected from blood were *S. pneumoniae* (12, 29%), *S. aureus* (7, 17%), *Streptococcus pyogenes* (5, 12%), *N. meningitidis* (4, 10%), *S. epidermidis* and GBS (both 3, 7%). All detected pathogens are shown in **Figure 5.**

Bacteria most frequently cultured from pus from different origins (ear, sinuses, neurosurgical wound, or abscess) were *S. aureus* (3, 18%) and *S. pyogenes* (2, 12%). *S. epidermidis* (4, 67%) accounted for most cultured bacteria from intracranial material, such as cannula, shunt, or suture. **Figure 5** presents all detected pathogens from study I.

In seven (5%) cases the bacterium was detected by PCR from a CSF specimen when CSF culture was negative, and the pathogens were *N. meningitidis* (3), *S. epidermidis* (1), *P. multocida* (1), *Cellulosimicrobium* (1) and *Bacillus cereus* (1). In three (2%) cases two different bacteria were simultaneously detected in the CSF.

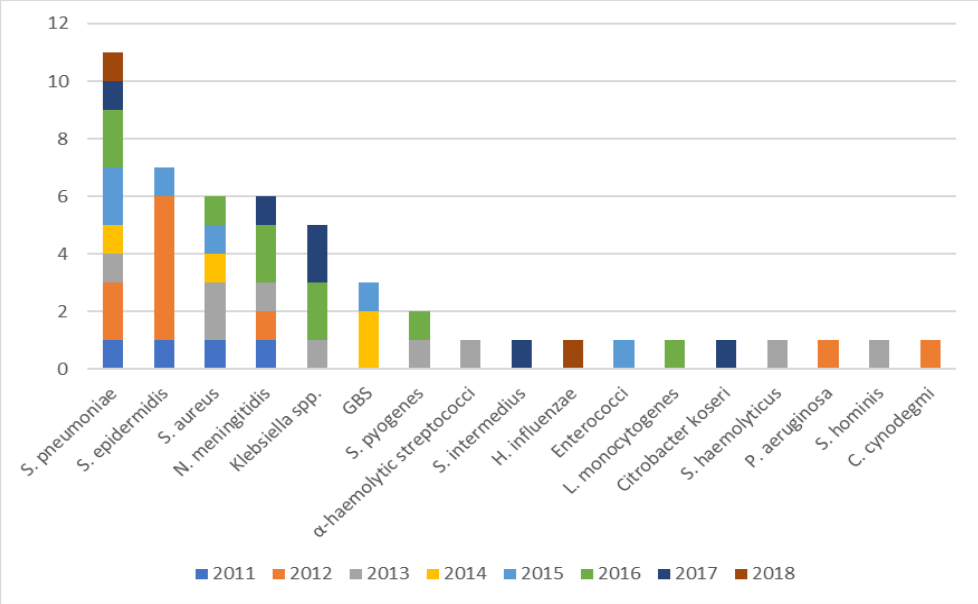


Figure 4. Bacteria cultured from CSF by year of bacterial meningitis. Modified and reprinted with the permission from the copyright holders from original publication I. The y-axis shows the number of bacteria.

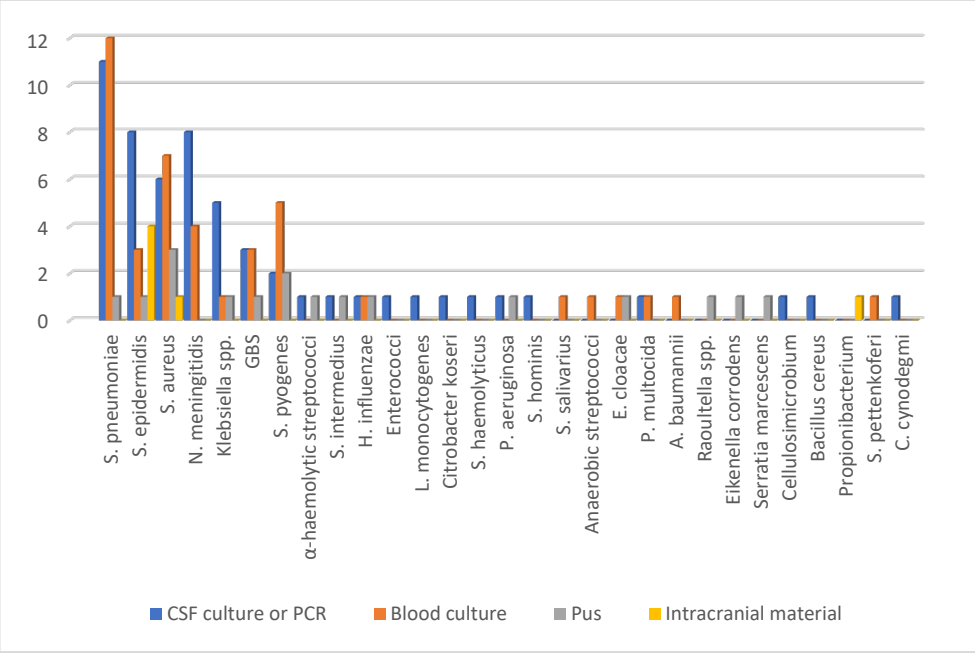


Figure 5. All bacteria detected in study I. Own drawing. The y-axis shows the number of bacteria.

5.1.4 Antibiotic resistance

Bacteria detected from CSF were most likely resistant to cefuroxime (10, 7%), ampicillin (9, 6%) and tetracycline (9, 6%). All CSF bacterial culture resistance profiles are shown in **Figure 6**. Seven (5%) bacteria cultured from CSF were resistant to one antibiotic, three (2%) to two different antibiotics, one (1%) to three different antibiotics, five (3%) to four different antibiotics, two (1%) to six different antibiotics, three (2%) to eight different antibiotics, three (2%) to 11 different antibiotics and one (1%) to 12 different antibiotics. It is worth noticing that there were no species of bacteria with acquired resistance to vancomycin or ceftriaxone. Multi-drug resistance, defined here as a resistance to three or more antibiotics, was seen in 13 (9%) patients, mostly patients with nosocomial BM (8, 5%). In other bacterial cultures from blood, pus, or intracranial material, 30 (20%) cases presented resistance to at least one antibiotic. Multi-drug resistance was seen in 14 (9%) patients. There were six (4%) simultaneous fungal infections.

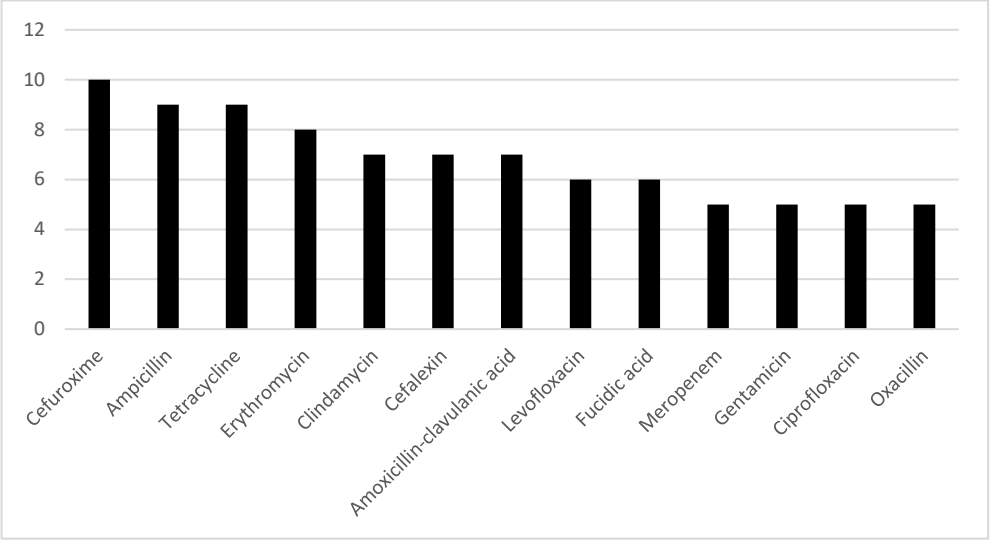


Figure 6. Antibiotic resistance profiles from all bacteria cultured from cerebrospinal fluid. Reprinted with permission from the copyright holders from original publication I. The y-axis shows the number of antibiotics used.

5.1.5 Laboratory results

Laboratory results from blood, plasma and CSF are presented in **Table 2**.

Table 2. Values of fundamental laboratory tests on admission. Reprinted with permission from the copyright holders from original publication I.

Laboratory results	Median	Normal values
C-reactive protein (mg/L)	61	<10
Leukocyte count in blood (x10^9/L)	12.2	3.4–8.2
Plasma glucose (mmol/l)	6.0	<6.0
Leukocyte count in CSF (x10^6/L)	566	0–5
Granulocyte percentage in CSF (%)	75	0
Glucose levels in CSF (mmol/L)	1.5	2.2–4.2
Lactate levels in CSF (mmol/L)	5.7	1.1–2.2
Protein levels in CSF (mg/L)	1563	150–650

5.1.6 Imaging

On admission, CT scan of the head was performed to most patients (119, 80%) and MRI to 26 (18%) patients. In 14 (10%) cases imaging findings were found to present leptomeningeal or pachymeningeal intensifications as a sign of meningitis, most frequently seen with MRI (8, 57%), but also with CT (6, 43%). The imaging methods presented specific BM related findings in 31% and 5% of cases, respectively by MRI and CT. In 15 (10%) patients imaging found findings consistent with elevated intracranial pressure. Imaging controls, when appropriate, were performed most frequently with MRI (62, 42%) and CT controls were performed to 43 (29%) individuals. Fifty (34%) patients had at least one imaging control executed from one month to two years after discharge from the hospital.

5.1.7 Treatment

Pre-diagnostic antibiotics, including perioperative ones, were administered to 85 (57%) patients. Of them, 49 (58%) were diagnosed with postoperative meningitis.

Pre-diagnostic corticosteroids were given to 33 (22%) patients: tablets, intravenous products, inhalators, and nasal sprays in 19, 10, three, and one patient, respectively. The most common corticosteroid used was dexamethasone (12, 8%). Twenty-three (16%) patients received acyclovir treatment on admission along with antibiotics.

After the diagnosis of BM, ceftriaxone was the most common used antibiotic regimen (117, 79%), followed by meropenem and vancomycin with 11 (7%) cases each. The most frequent second antibiotic used in conjunction with the first one was vancomycin (93, 63%), meropenem (11, 7%), doxycycline (8, 5%), ampicillin and

clindamycin (both 5, 3%). Antibiotic monotherapy was administered to 13 (9%) patients. Eighteen patients received three-modal antibiotic treatment with the most common third antibiotic being ampicillin (8, 5%). The total number of intravenous antibiotics used are shown in **Figure 7**. Ceftriaxone and vancomycin were the most frequently used empiric antibiotics among all occasions and so were the case also after confirmed etiology.

The most common number of various antibiotics used in total during the treatment of BM were three (50, 34%), two (34, 23%), four (22, 15%), five (19, 13%), seven (8, 5%), six (6, 4%), eight and nine (both 3, 2%), one (2, 1%) and ten (1, 1%).

After the diagnosis of BM, corticosteroids were administered to 79 patients (53%). Operative treatment was required for 56 (38%) individuals with most cases being PNM. Mastoidectomy was operated to six (4%) patients of whom all had otogenic meningitis.

The median duration of intravenous antibiotic therapy was 18 days (range 2–125). At discharge, 29 (20%) patients were prescribed with oral antibiotics, while the duration ranged usually from five to 30 days, and in a few cases for 100–270 days as a suppressive antibiotic therapy for various reasons. Five most frequent oral antibiotics used were amoxicillin with clavulanic acid (5, 3%) followed by clindamycin, moxifloxacin, penicillin and cefalexin (all 4, 3%). Median number of the days on intravenous and oral antibiotics combined was 21 days.

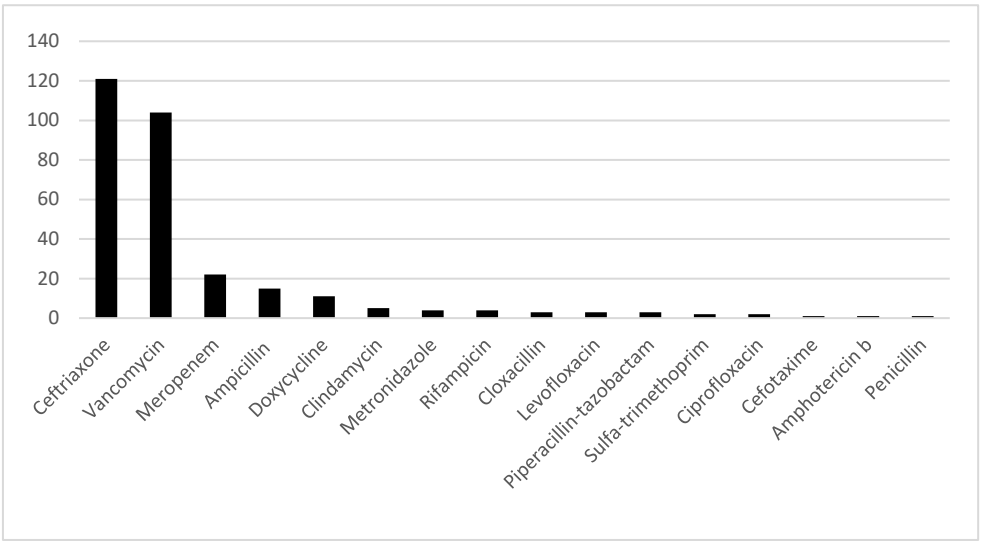


Figure 7. Number of patients with antibiotics used intravenously after the diagnosis of bacterial meningitis. Reprinted with permission from the copyright holders from original publication I. The y-axis shows the number of antibiotics used.

5.1.8 Outcome

The median duration of hospital stay was 20 days. A total of 49 patients (33%) had developed at least one neurological deficit at the time of discharge. Most frequent deficits were memory difficulties (15, 10%) and mental regression (13, 9%), followed by dysphasia or aphasia (9, 6%), visual disorders (9, 6%), vertigo and hydrocephalus (7, 5% each), decreased level of consciousness (5, 3%), hemiparesis and change in personality (4, 3%). Twelve (8%) patients had their hearing investigated with audiogram during their hospital stay. After discharge until one-year control, eight (5%) patients had developed permanent hearing impairment. There was no deafness documented in any patient.

Fourteen patients (9%) passed away (GOS score 1), all but one directly from BM. From the survivors of BM, five (3%), 18 (12%), 23 (16%) and 89 (60%) patients had the GOS scores 2, 3, 4, and 5, respectively. In total, 41% of the patients had an unfavorable outcome (GOS scores 1–4). 30-day overall mortality was 11% with one-year and two-year overall mortality being 14% and 20%, respectively.

Patients who were diagnosed with otogenic meningitis had unfavorable outcome likelihood of 22%, those from sinonasal meningitis 29%, from odontogenic meningitis 33%, from PNM 45% and patients with no specific source of BM 39%. CSF culture was most frequently negative with PNM with 16 (22%) individuals.

Headache (p=0.0001, 95% CI 0.16–0.35), decreased general condition (p=0.0001, 95% CI 0.23–0.67), head CT (p=0.0001, 95% CI 0.073–0.64) and MRI of the head (p=0.04, 95% CI 0.92–4.0), hypertension (p=0.0002, 95% CI 0.34– 0.70), altered mental status (p=0.0002, 95% CI 0.47– 0.73), confusion (p=0.0011, 95% CI 0.36–0.78), operative treatment (p=0.012, 95% CI 0.42–0.89), neurological symptoms (p=0.023, 95% CI 0.44–0.93), pre-diagnostic antibiotic administration (p =0.026, 95% Cl 0.40–0.97) and prescription of oral antibiotics on discharge (p=0.039, 95% CI 0.94–3.6) were statistically associated with unfavorable outcome. In other statistical analyses, pre-diagnostic antibiotic use was statistically associated with negative CSF culture (p=0.05), positive blood culture was statistically associated with positive CSF culture (p=0.0001) and pre-diagnostic antibiotic use was statistically associated with negative blood culture (p=0.01). Only age group of 46–65 years were statistically associated with positive blood cultures (p=0.008). CSF culture positivity was not statistically associated with age groups (p=0.69). Statistical analyses are presented in **Table 3**.

Table 3. Factors related to clinical outcome of patients. Modified and reprinted with the permission from the copyright holders from original publication I.

Variable	Correlation to unfavorable outcome (n=60)	P-value of univariable analysis
Headache	Yes	0.0001
Decreased general condition	Yes	0.0001
Head CT	Yes	0.0001
Hypertension	Yes	0.0002
Altered mental status	Yes	0.0002
Confusion	Yes	0.001
Operative treatment	Yes	0.01
Focal neurological symptoms	Yes	0.02
Prediagnostic antibiotic use	Yes	0.03
Oral antibiotics on discharge	Yes	0.04
Head MRI	Yes	0.04
Type 2 diabetes	No	0.06
Blood culture positivity	No	0.07
Prediagnostic corticosteroid	No	0.07
Bacteria cultured from other sources beside CSF	No	0.1
Nosocomial meningitis	No	0.11
Pulmonary infections	No	0.11
Signs of elevated intracranial pressure with imaging	No	0.11
Previous surgery	No	0.20
Tobacco use	No	0.24
Upper respiratory infection	No	0.24
Multi-drug resistance of CSF pathogens	No	0.31
Skin infections of the body	No	0.33
Acute otitis media	No	0.34
Gender	No	0.35
Asthma	No	0.36
CSF culture positivity	No	0.38
Alcohol overuse	No	0.39
Acyclovir use	No	0.44
Seizures prior admission to hospital	No	0.58
Dental infections	No	0.59
Fever	No	0.59
Cancer	No	0.61
Skin infections of the head	No	0.73
Corticosteroid use	No	0.74
First contacted healthcare provider	No	0.80
Vomiting	No	0.86
Skin color changes	No	0.87
Sinusitis	No	0.90
Neck stiffness	No	0.92
Signs of meningitis with imaging	No	1.00

5.2 Study II

5.2.1 Background information

Thirty-seven children (20, 54% male) were identified with BM treated at Turku University Hospital between 2011 and 2018. There were 22 infants aged 0– 89 days and 15 children or adolescents aged 90 days to 15 years (**Figure 8**).

Three children had been transferred from other hospitals in Finland. The incidence was approximately 5.7/100 000/year based on the 34 newborns and children living in the Hospital District of Southwest Finland. Incidence among infants was estimated to be 0.7/1000 live births. The median age of the 37 children was one month, with Q1 nine days and Q3 three years and nine months. Most (19, 51%) of the BM cases were nosocomial (**Table 6**).

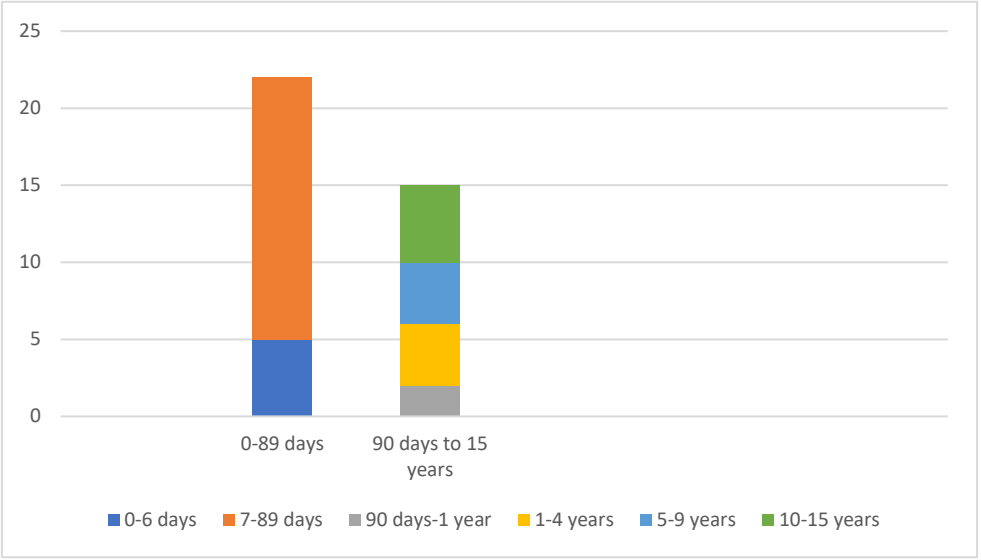


Figure 8. Age distribution of the 37 pediatric patients with bacterial meningitis. Reprinted with permission from the copyright holders from original publication II. The y-axis shows the number of patients.

Bacteria were detected in either the CSF or blood in 21 (57%) patients (**Table 5**). The CSF culture was positive for bacteria in 15 (41%) of cases and the PCR of the CSF was positive once when culture was negative (**Figure 9**). A blood culture detected bacteria in five (14%) cases when the CSF culture was negative. The most frequently detected pathogens in CSF culture were GBS (4, 11%), *S. pneumoniae* (3, 8%) and *E. coli* (2, 5%). All the detected causative bacteria are shown in **Figure 9**. The CSF culture was positive in three (15%) of the 20 patients who received pre-

diagnostic antibiotics before their lumbar puncture and in 12 (71%) of the 17 patients who only received antibiotic therapy after the lumbar puncture (p=0.001).

The majority (12, 55%) of the 22 infants aged 0–89 days of age were born preterm before 37+0 weeks of gestation: three (14%) before 28+0 and four (18%) between 28+0 and 31+6 weeks of pregnancy. Four (18%) of the infants' mothers were carrying GBS. The proportions of various patient groups are presented in **Table 4**.

Two (13%) of the 15 children aged 90 days to 15 years had both otitis media and mastoiditis. Various infections were detected prior or simultaneously with BM: pneumonia, pyelonephritis, brain abscess and dental infection were each detected in one patient.

Table 4. Proportions of subgroups by age groups with bacterial meningitis. Modified and reprinted with the permission from the copyright holders from original publication II.

Infants aged 0–89 days (n = 22)	**N (%)**
Early onset (0–6 days)	5 (23)
Late onset (7–89 days)	17 (77)
Late-onset community acquired	6 (27)
Late-onset nosocomial (not neurosurgical)	8 (36)
Post-neurosurgical meningitis	3 (14)
Children aged 90 days to 15 years (n = 15)	**N (%)**
Community acquired	9 (60)
Nosocomial (not neurosurgical)	2 (13)
Post-neurosurgical meningitis	4 (27)

Table 5. Pathogens detected in cerebrospinal fluid or blood culture by age groups. Modified and reprinted with the permission from the copyright holders from original publication II.

Pathogens in CSF or blood culture	**Infants aged 0–89 days n=22** N/n (%)	**Children aged 90 days to 15 years n=15** N/n (%)	**All children n=37** N/n (%)
E. coli	4 (18)	1 (7)	5 (14)
GBS	4 (18)	0	4 (11)
S. pneumoniae	0	3 (20)	3 (8)
S. aureus	2 (9)	0	2 (5)
N. meningitidis	0	1 (7)	1 (3)
S. epidermidis	1 (5)	0	1 (3)
S. capitis	0	1 (7)	1 (3)
Actinomyces sp.	0	1 (7)	1 (3)
S. hominis	1 (5)	0	1 (3)
Anaerobic gram-positive cocci	0	1 (7)	1 (3)

5.2.2 Clinical characteristics

The clinical characteristics of the infants 0–89 days of age are shown in **Table 6**. The most frequent symptoms included decreased general condition (19, 86%), irritability (18, 82%), decreased consciousness (11, 50%) and fever (9, 41%). The most frequent pathogens cultured from either CSF or blood were *E. coli* (4, 18%), GBS (4, 18%) and *S. aureus* (2, 9%). Two (9%) infants aged 0–6 days had GBS and so did two (9%) infants aged 7–89 days. All the detected bacteria are shown in **Figure 9**. Multi-drug resistance, which was defined as resistance to three or more relevant antibiotics, was seen in two (9%) bacterial species: *S. epidermidis* and *Staphylococcus hominis*. One CSF sample was PCR positive for *Sphingomonas* species when the CSF culture was negative.

The most frequently administered antibiotics were ampicillin (12, 55%), cefotaxime (9, 41%) and gentamicin (6, 27%). Multimodal antibiotic treatment was used to treat 17 (77%) of the patients with BM and the number ranged from three to seven different antibiotics. There were no cases detected where the cultured bacteria that caused BM had acquired resistance to the empirically initiated antimicrobial therapy. Two (9%) patients had a neurosurgical operation prior BM: one had a brain hemorrhage and one had hydrocephalus. Two (9%) neonates needed invasive respiratory support.

The clinical characteristics of the children aged 90 days to 15 years are shown in **Table 6**. The most frequent bacteria, cultured from either from CSF or blood, was *S. pneumoniae* (3, 20%). *E. coli*, *Staphylococcus capitis* and *N. meningitidis* were each detected once. There was one CSF specimen with two cultured bacteria. All the pathogens detected are shown in **Figure 9**.

Pre-diagnostic antibiotics were administered to five (33%) children. The most frequently administered antibiotics after the diagnosis of BM were ceftriaxone (13, 87%) and vancomycin (5, 33%). Multimodal antibiotic treatment was used to treat eight (53%) of the patients with BM and the number ranged from three to seven different antibiotics. Corticosteroid treatment was used with nine (60%) patients as well as antibiotics. Two children needed implantation of ventriculoperitoneal shunt and one mastoidectomy. Six (40%) patients were prescribed with oral antibiotics after discharge and the duration ranged from seven to 14 days.

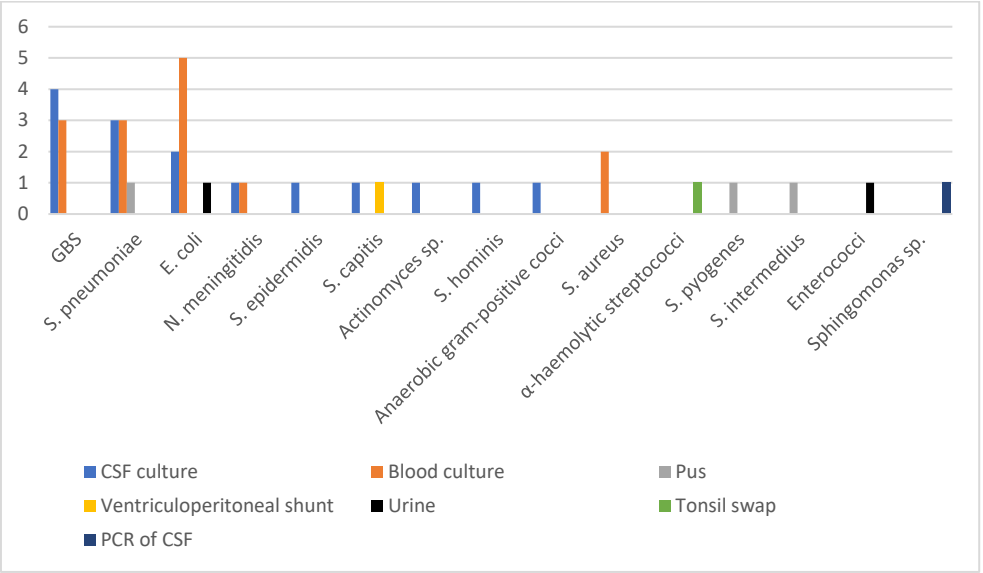


Figure 9. Numbers of bacterial detections by culture methods of cerebrospinal fluid (CSF), blood, pus, ventriculoperitoneal shunt, urine, or tonsil swap sample or by polymerase chain reaction of CSF. Modified and reprinted with the permission from the copyright holders from original publication II. The y-axis shows the number of bacteria.

5.2.3 Outcome

The majority (18, 82%) of the patients aged 0–89 days underwent hearing tests, using a brainstem auditory evoked response or otoacoustic emissions (16, 89%) and a mechanical source of voice (2, 11%). Permanent hearing deficiency was found in one patient. Two (9%) patients received a ventriculoperitoneal shunt. One infant was diagnosed with epilepsy. Six (27%) infants had an unfavorable outcome at discharge: four (18%) had a GOS score of three and two (9%) had a GOS score of four. Three (14%) infants with a GOS score of three had an unfavorable outcome eight months after discharge. There was no mortality among study population.

The majority (10, 67%) of the children aged 90 days to 15 years had hearing tests, mostly with an audiogram (7, 70%). A brainstem auditory evoked response was used with two (20%) patients and otoacoustic emissions with one patient. One child had a permanent hearing deficiency, and another received a ventriculoperitoneal shunt. Other adverse outcomes were visual difficulties in one patient and a change in personality in another. Three (20%) children had an unfavorable outcome at discharge: one had a GOS score of three and two (13%) had a GOS score of four. The two (13%) children with a GOS score of four had unfavorable outcomes eight months after discharge. There was no mortality among study population.

The univariate statistical analysis found that a positive CSF culture was associated with an unfavorable outcome at discharge ($p=0.02$), but not eight months

after discharge (p =0.1). Nosocomial meningitis (p=0.007) and preterm birth (p=0.04) were statistically associated with an unfavorable outcome eight months after discharge. All statistical analyses performed are presented in **Table 7**.

Table 6. Comparison of the clinical characteristics, laboratory values and outcomes of 37 children with bacterial meningitis by age. Modified and reprinted with the permission from the copyright holders from original publication II.

Variable	Infants aged 0–89 days N=22 N/n (%) or median	Children aged 90 days to 15 years N=15 N/n (%) or median	All children N=37 N/n (%) or median	*P* value	Proportion difference (%) and 95% confidence interval
Type of bacterial meningitis					
Community acquired	9 (41)	9 (60)	18 (49)	0.32	19 (-13 to 51)
Previous surgery	3 (14)	7 (47)	10 (27)	0.056	33 (4 to 62)
Neurosurgical	3 (14)	4 (27)	7 (19)	0.41	13 (-14 to 40)
Nosocomial	13 (59)	6 (40)	19 (51)	0.32	-19 (-51 to 13)
Clinical findings at presentation					
Pre-diagnostic antibiotics	15 (68)	5 (33)	20 (54)	0.050	-35 (-66 to -4)
Neurological symptoms#	3 (14)	5 (33)	8 (22)	0.41	13 (-14 to 40)
Decreased general condition	19 (86)	12 (80)	31 (84)	0.67	-6 (-31 to 18)
Irritability	18 (82)	6 (40)	24 (65)	0.015	-42 (-71 to -12)
Fever	9 (41)	14 (93)	23 (62)	0.002	52 (28 to 77)
Decreased consciousness	11 (50)	5 (33)	16 (43)	0.50	-17 (-48 to 15)
Vomiting	Not available	12 (80)	12 (32)	0.0001	Not available
Neck stiffness	0	9 (60)	9 (24)	0.0001	60 (35 to 85)
Headache	Not available	8 (53)	8 (22)	0.0001	Not available
Petechiae	0	3 (20)	3 (8)	0.059	20 (0 to 40)
Seizures	1 (5)	2 (13)	3 (8)	0.55	9 (-10 to 28)
Confusion	0	2 (13)	2 (5)	0.16	13 (-4 to 31)
Facial paresis	0	1 (7)	1 (3)	0.41	7 (-6 to 19)
Pupil-asymmetry	1 (5)	0	1 (3)	1.0	-5 (-13 to 4)
Bulging fontanel	1 (5)	0	1 (3)	1.0	-5 (-13 to 4)
Laboratory and imaging results (interquartile range)					
C-reactive protein (mg/L)	19.5 (4.8–75)	85 (28–133)	45 (5–86)	0.033	-61 (-124 to -31)
Leukocyte count in blood (x10^9/L)	9.2 (4.5–12.5)	14.9 (8.3–22)	9.6 (6.8–16.6)	0.016	-6 (-13 to 1)
Leukocyte count in CSF (x10^6/L)	360 (45–1848)	1600 (414–2430)	738 (92–2220)	0.052	1230 (-2102 to -10)
Granulocyte percentage in CSF (%)	44 (0–78)	79 (66–96)	75 (10–85)	0.016	-29 (-75 to -4)
Glucose levels in CSF (mmol/L)	2.1 (1.2–3)	3.2 (1–3.4)	2.3 (1.1–3.4)	0.22	-1 (-2 to 1)
Lactate levels in CSF (mmol/L)	3.4 (2.6–3.9)	6.3 (3.1–8.7)	3.5 (2.9–7.0)	0.040	-3 (-5 to 0)
Protein levels in CSF (mg/L)	1784 (1063–2645)	1105 (566–1791)	1277 (702–2569)	0.092	555 (119 to 1524)
Head magnetic resonance imaging performed	5 (23)	7 (47)	12 (32)	0.16	24 (-7 to 55)
Imaging findings consistent with BM	2 (9)	5 (33)	7 (19)	0.095	24 (-7 to 55)
CSF culture positive	7 (32)	8 (53)	15 (41)	0.31	22 (-10 to 53)

Variable	Infants aged 0–89 days N=22 N/n (%) or median	Children aged 90 days to 15 years N=15 N/n (%) or median	All children N=37 N/n (%) or median	*P* value	Proportion difference (%) and 95% confidence interval
Blood culture positive	10 (45)	4 (27)	14 (38)	0.31	-19 (-49 to 12)
Treatment and outcome					
Hospital stay in days (median): 1st to 3rd quartile	21 (14–51)	7 (5–14)	15 (7–33)	0.0015	14 (7 to 17)
Intravenous antibiotic therapy in days (median): 1st to 3rd quartile	14 (12–21)	11 (7–25)	14 (10–21)	0.50	3 (-3 to 8)
Unfavorable outcome at discharge	6 (27)	3 (20)	9 (24)	0.71	-7 (-35 to 20)
Unfavorable outcome at eight months control	3 (14)	2 (13)	5 (14)	1.0	0 (-23 to 22
Hearing tests performed	18 (82)	10 (67)	28 (76)	0.71	-11 (-40 to 19)
Permanent hearing deficiency	1 (5)	1 (7)	2 (5)	1.0	-2 (-17 to 13)

Neurological symptoms were defined as seizures, confusion, facial paresis, pupil-asymmetry and bulging fontanel.

Table 7. Variables associated with unfavorable outcome at eight months after discharge among children with bacterial meningitis. Modified and reprinted with the permission from the copyright holders from original publication II.

Variable	Correlation to unfavorable outcome at eight months after discharge (n=5)	p-value of univariate analysis
Nosocomial meningitis	Yes	0.007
Preterm birth (<37 weeks)	Yes	0.04
Previous surgery	No	0.09
Operative treatment	No	0.10
CSF culture positivity	No	0.14
Altered mental status	No	0.15
Premature rupture of membranes	No	0.17
Performed ultrasound exam of brain	No	0.22
Pre-diagnostic antibiotic	No	0.25
Skin color changes	No	0.31
Decreased general condition	No	0.31
Performed head CT	No	0.35
Seizures	No	0.36
Irritability	No	0.43
Performed head MRI	No	0.51
Fever	No	0.59
Positive blood culture	No	0.63
Neck stiffness	No	0.81
Vomiting	No	0.82
Headache	No	0.91
Signs of meningitis with imaging	No	1.00
Corticosteroid treatment	No	1.00

5.3 Study III

5.3.1 Background information

The median age of the 345 patients who underwent glioma surgery was 60 years (Q1–Q3: 44–68 years) with majority (186, 54%) being male. High-grade glioma was diagnosed in 262 (76%) patients, while low-grade glioma was observed in 83 (24%) individuals. Sixty-nine (20%) of the surgeries were reoperations for recurrent glioma. The rate of PNM was 7% (n=25) after glioma surgery. The median time interval between glioma surgery and the diagnosis of PNM was 12 days (Q1–Q3: 7–20 days).

5.3.2 Causative bacteria

Positive CSF cultures were detected in seven (28%) of the PNM cases. The bacteria acquired from CSF cultures were *S. epidermidis* (3, 43%), *S. aureus* (2, 29%), and *E. cloacae* and *P. aeruginosa* were each detected once. There were 40 (12%) individuals with suspected wound infection, of which 19 (6%) presented bacteria in bacterial culture causing the local infection. Five (1%) individuals with culture confirmed local wound infection also had CSF culture confirmed PNM. Blood cultures were harvested from 58 (17%) of the patients with only one blood culture positive discovery. All bacteria detected are shown in **Figure 10**.

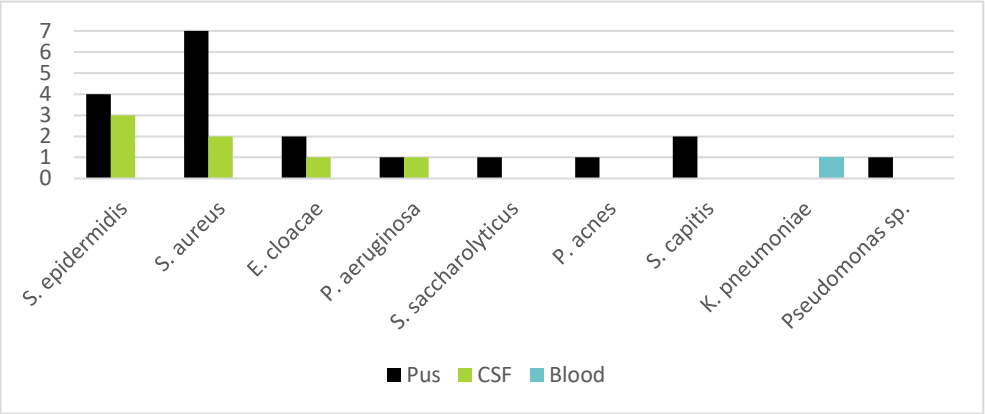


Figure 10. All bacteria detected from 345 patients after glioma surgery. Reprinted with the permission from the copyright holders from original publication III. The y-axis shows the number of bacteria.

5.3.3 Statistical analysis

Patients who were diagnosed with PNM were significantly younger, with a median age of 49 years (Q1–Q3: 32–62 years) compared to 60 years (Q1–Q3: 46–68 years)

in those without PNM (p=0.013). Furthermore, patients with PNM had a higher proportion of low-grade gliomas (44% vs. 23%, p=0.027) and a higher frequency of reoperations (52% vs. 18%, p<0.001) and revision surgeries (40% vs. 6%, p<0.001) compared to glioma patients without PNM.

There were no statistically significant differences between patients with PNM and those without PNM in regards of sex (female) (56% vs. 45%, p=0.31), body mass index (BMI) (28 [Q1–Q3: 23–31] vs. 26 [Q1–Q3: 24–30], p=0.576), American Society of Anesthesiologists (ASA) classification (p=0.97), or the length of the surgery (202 minutes [Q1–Q3: 165–301 minutes] vs. 207 minutes [Q1–Q3: 156–251 minutes], p=0.216). All comparisons are presented in **Table 8**.

Multivariable analysis discovered that reoperation (OR 2.63, 95% CI 1.04–6.67, p=0.042) and revision surgery (OR 7.08, 95% CI 2.55–19.70, p=0.001) were significantly associated with PNM, while age (OR 0.98, 95% CI 0.95–1.01, p=0.11) and glioma grade (high-grade vs. low-grade, OR 0.81, 95% CI 0.30–2.22, p=0.69) presented no statistically significant associations.

Table 8. Background characteristics of patients with or without post-neurosurgical meningitis (PNM). Reprinted with the permission from the copyright holders from original publication III.

Variable	PNM (n=25)	No PNM (n=320)	p-value
Age, median (Q1–Q3)	49 (32–62)	60 (46–68)	0.01
Sex (female)	14 (56%)	145 (45%)	0.31
BMI, median (Q1–Q3)	28 (23–31)	26 (24–30)	0.54
ASA classification			0.97
ASA 1	0 (0%)	4 (1%)	
ASA 2	2 (8%)	27 (8%)	
ASA 3	15 (60%)	197 (62%)	
ASA 4	8 (32%)	87 (27%)	
ASA 5	0 (0%)	1 (0%)	
Glioma grade			0.03
Grade 1	4 (16%)	13 (4%)	
Grade 2	7 (28%)	60 (19%)	
Grade 3	3 (12%)	41 (13%)	
Grade 4	11 (44%)	206 (64%)	
High-grade vs. Low-grade glioma			0.027
Low-grade (grade 1–2)	11 (44%)	73 (23%)	
High-grade (grade 3–4)	14 (56%)	247 (77%)	
Reoperation	13 (52%)	57 (18%)	0.001
Revision surgery	10 (40%)	18 (6%)	0.001
Emergency surgery	3 (12%)	11 (3%)	0.07
Operation time (min), median (Q1–Q3)	202 (165–301)	207 (156–251)	0.22
CSF sample available	25 (100%)	24 (8%)	0.001
CSF leukocyte count (cells/mm^3), median (Q1–Q3)	425 (86–1140)	7 (1–35)	0.001
CSF neutrophil count (%), median (Q1–Q3)	79 (55–92)	2 (0–9)	0.001

6 Discussion

6.1 Bacterial meningitis in adults (study I)

Study I presented extensively the variety of clinical characteristics, causative bacteria, and outcome of BM with various etiologies of BM in Southwestern Finland among adult population. This study included culture positive and -negative cases of BM, covering larger entities than if only culture positive BM cases were included (Baspinar et al., 2017). Due to severity of the disease, it is necessary to regularly assess and determine possible predictors of unfavorable outcome.

The incidence of BM was approximately 4.3/100 000 per year, which was higher than previously reported (Bijlsma et al., 2016; Koelman et al., 2021). However, our study also included culture negative BM cases as well as nosocomial BM. *S. pneumoniae* was the most common (11, 7%) detected bacteria confirming the results of previous studies (Bijlsma et al., 2016; Polkowska et al., 2017). In addition to *S. pneumoniae*, *N. meningitidis* is a frequent causative bacterium of BM among individuals of all ages (Oordt-Speets et al., 2018), but in our study the *N. meningitidis* cases were most frequently seen with young adults between 16–25 years of age. Unexpectedly there were only one *L. monocytogenes* and *H. influenzae* BM although it is estimated that these bacteria cause around 9% and 7% of BM worldwide, respectively (Davis, 2018). Nevertheless, it is possible that patients with septicemia and concomitant BM had an ICD-10 code of only sepsis in their patient records and were therefore excluded from inclusion.

Median CSF leukocyte count was 566 × 10^6/L among BM patients and median protein levels were 1563 mg/L. However, BM can occur even with normal count of CSF leukocytes, especially with simultaneous high protein levels in CSF. In those cases, the outcome can be even worse than usually, with incidence of unfavorable outcome 59% and mortality 31% according to van Soest et al. in 2022.

During the study period seven patients were identified with culture negative CSF samples but positive PCR of CSF specimen for bacteria, a technique proven to be more sensitive than CSF culture (Baspinar et al., 2017). CSF culture has demonstrated varying sensitivities between 43–85%, and specificity up to 97%, at least in patients without the administration of pre-diagnostic antibiotics (Hasanuzzaman et al., 2021; Heckenberg et al., 2014; Welinder-Olsson et al., 2007).

The use of antibiotics before the collection of CSF specimen reduces the identification of bacteria by culture with at least 30% (Corless et al., 2001). Multiplex or quantitative PCR of CSF specimen has shown up to two-fold better sensitivities than CSF culture and specificities up to 100% (Corless et al., 2001; Hasanuzzaman et al., 2021). Our result of CSF culture positivity rate of 34% is compatible with earlier studies, especially considering the rate of frequently used pre-diagnostic antibiotics (57%). Our 16S ribosomal ribonucleic acid -sequencing based PCR technique was clearly inferior compared to newer methods.

Earlier studies have found that CSF sterilization may occur in hours after parenteral antibiotic administration. *N. meningitidis* may be sterilized within two hours and *S. pneumoniae* within four hours after administering parenteral antibiotic treatment (Kanegaye et al., 2001). Our results demonstrated that pre-diagnostic antibiotic administration was statistically associated with both negative blood- and CSF cultures. Positive blood cultures were statistically associated with positive CSF cultures. Hence, pre-diagnostic antibiotic therapy before lumbar puncture may cause unsuccessful detection of bacteria in BM patients. However, in urgent medical situations such as sepsis and suspicion of BM the quick administration of antibiotics is crucial (Sherwin et al., 2017).

Triad of fever, neck stiffness and altered mental status has been reported to be present in 41–59% of BM patients (Matulyte et al., 2020; van de Beek et al., 2016, B). Study I found that the prevalence of this triad was much lower (14%). However, triad of fever, neck stiffness and headache were more common (26%). Therefore, the absence of these triads cannot be used to rule out the possibility of BM. Neurological symptoms and confusion were associated with unfavorable outcome, as discovered previously (Sunwoo et al., 2021). In an older study headache was found not to be associated with unfavorable outcome, but with a more recent study headache was found to be associated with unfavorable outcome, as was the case also in our study (Bijlsma et al., 2016; Matulyte et al., 2020). Physicians should pay even more attention to BM patients experiencing headache and not only to altered mental status, which may be a symptom of a more advanced disease.

Head CT scan was performed to most patients (80%) and head MRI with only 18% of patients. The lower percentage of head MRI usage may be due to the lack of resources to use MRI-equipment and the need for faster results, which is essential to avoid unfavorable outcomes (Proulx et al., 2005). Our results found 31% and 5% specificities for MRI- and CT scans of the head, respectively, on identifying meningitis-related findings. Our finding indicated MRI being more specific than previously reported by Bineshfar et al. in 2022 with 16% specificity.

The treatment administered after the diagnosis of BM was effective with mostly ceftriaxone and vancomycin due to lower mortality than previously reported (Bijlsma et al., 2016). The efficacy was also highlighted by the fact that there were

no bacterial acquired resistance to these antibiotics, as shown earlier with ceftriaxone (Matulyte et al., 2020).

Community-acquired BM has been found to count for most BM cases with even 86% proportion, with *S. pneumoniae* being the most dominant pathogen in adults (Block et al., 2022). Nosocomial BM, on the other hand, has been found to cover varying proportions of all BM detected with 14–73% rate, most cases being dominated by staphylococci. Proportions of nosocomial BM has been increasing during the conjugate-vaccine era (Block et al., 2022; Kiyani et al., 2021; Sunwoo et al., 2021). Insufficiency in antibiotic prophylaxis or perioperative aseptic measures during neurosurgery may explain the current considerable proportion of patients with nosocomial BM (Kiyani et al., 2021).

The proportion of patients with nosocomial BM (55%) was relatively high. Pre-diagnostic antibiotic therapy was associated with unfavorable outcome. Explanation of this finding could be that preoperative antibiotics are almost always administered to patients ongoing neurosurgery, and they may suffer from adverse events related to neurosurgery alone. Imaging with either MRI or CT of the head was associated with unfavorable outcome, as severe symptoms on admission require more frequently imaging to exclude other conditions or diseases. Prescription of oral antibiotics at discharge was also associated with unfavorable outcome, perhaps due to the more severe clinical presentation and the need for longer duration of antibiotic therapy.

The frequency of an unfavorable outcome was 41% after BM and it was compatible with previous study presenting the frequency of unfavorable outcome of 38%, but this previous European study excluded all cases of nosocomial BM (Bijlsma et al., 2016). Previous research has reported mortality of BM to be 10–17%, but in our study the mortality was only 9% (Bijlsma et al., 2016; Polkowska et al., 2017). A recent study from Lithuania found the likelihood of unfavorable outcome (GOS 1–3 in their study) to be 16% and mortality of 6% (Matulyte et al., 2020). The respective proportion for GOS 1–3 unfavorable outcomes in our study was 24%. However, straight comparisons cannot be made, since the Lithuanian study excluded patients with nosocomial BM. Additionally, Finland has mandatory military service for most men, where has been reports of BM outbreaks during the past decades, but in this study, there were not any reported cases related to military (Hannila-Handelberg et al., 2015).

The proportion of nosocomial BM was high, and nosocomial BM requires often surgical procedures with notable risks. To conclude, our results regarding unfavorable outcome are compatible with previous studies (Gudina et al., 2018; Matulyte et al., 2020; Sunwoo et al., 2021).

The global disease burden of BM is substantial especially in developing countries. Prevention of BM with vaccines falls behind many other vaccine-

preventable infectious diseases. Despite improvements of vaccine development against pathogens of BM, corresponding figures of measles (93%) and tetanus (91%) vaccination coverage, for example, suggests that this could be better also against BM (Global Burden of Diseases, 2017).

6.2 Pediatric bacterial meningitis (study II)

Study II found a low incidence of pediatric BM in Southwestern Finland. Community acquired BM was uncommon in children 90 days to 15 years of age, but the proportion of infants 0– 89 days of age with nosocomial BM was substantial. Many individuals had a negative CSF and blood bacterial cultures. The outcomes in both age groups were mostly good.

The incidence rates of BM among infants and children in Northern Sweden between 2010–2015 were 1.9– 3.4/100 000 (Johansson Kostenniemi et al., 2019). The incidence was highest in infants and lowest in adolescents in the previous study, and it was slightly lower compared to our results in study II with incidence of 5.7/100 000/ year. The global incidence of pediatric BM has decreased since the early 1990s and a crucial factor for this development has been the increased use of vaccines against the predominant bacterium. Differences in the diagnostic techniques, recording and definitions of BM have hampered the estimations of the true incidence of BM and comparisons between studies. The pre-diagnostic use of antibiotics was common in our study population and bacterial PCR tests on CSF specimens were infrequently performed.

S. pneumoniae is a common bacterium causing BM in childhood. This was investigated by a study from the United States that covered years from 1998 to 2007, which found that *S. pneumoniae* is responsible for over a third of all BM in infants and children (Thigpen et al., 2011). However, we found only three cases of BM caused by *S. pneumoniae* in children aged 90 days to 15 years. The 10-valent pneumococcal conjugate vaccine was introduced to the Finnish national vaccination programme in 2010. This was followed by a swift decrease in the incidence of pneumococcal meningitis in children in Finland: 54% in children 5–17 years of age and 64% in children aged 0–4 years (Polkowska et al., 2021). Replacement by serotypes not covered by the vaccine has been found mainly in older adults (Polkowska et al., 2021). Although vaccines against *N. meningitidis* are not included in the Finnish national vaccination programme for infants and children, only one case of meningococcal BM was found in study II. Other studies have pointed that meningococcal diseases may be more common in other European countries than in Southwestern Finland. For instance, a study from Iceland reported that *N. meningitidis* was the most frequent causative pathogen of BM (Snaebjarnardóttir

et al., 2013). No case of BM caused by Hib was found in study II, as it has disappeared due to the wide coverage of vaccinations (Peltola et al., 1992).

Our study found that the incidence of BM in infants aged 0–89 days was high compared to infants 0–60 days of age in another study (Thigpen et al., 2011). Our incidence rate of 0.7 per 1000 live births was compatible with the estimated incidences of neonatal BM of 0.3 per 1000 live births in high-income countries and up to 3–6 per 1000 live births in low- and middle-income countries (Ku et al., 2015). GBS and *E. coli* were the most frequent pathogens in infants. Noticeably, no BM cases caused by *L. monocytogenes* were observed. Maternal GBS antibiotic prophylaxis has been reported to be effective against early-onset disease, but not against late-onset disease (Nusman et al., 2023). GBS vaccines are urgently needed for mothers to prevent late-onset GBS disease (Delara et al., 2023).

Neonatal nosocomial infections can partly be prevented by breastfeeding, probiotics, and strict infection prevention routines in neonatal units (Deshmukh & Patole, 2021). The rapid initiation of antibiotic therapy for any suspicion of sepsis may prevent the infection from developing into BM (Shane et al., 2017). Newborn infants, especially those born prematurely, are regardless susceptible to invasive bacterial infections, due to their immature and inexperienced innate and adaptive immune systems. Preterm infants have also insufficient protection against infectious pathogens through maternal immunity. Our findings demonstrated this, as 55% of the infants were born prematurely and 14% of them before 28+0 and 18% between 28+0 and 31+6 weeks of pregnancy. Furthermore, in newborns, the innate cytokine response against bacteria can be inadequate or, conversely, overwhelming and has been associated with increased severity of the disease (Yu et al., 2018).

We discovered that 41% of the CSF cultures were positive for bacteria, and negative cultures of CSF were associated with pre-diagnostic administering of antibiotics before a lumbar puncture. Pre-diagnostic antibiotics were administered to 54% of the patients, compared to 35–46% rate in previous studies (Peltola et al., 2022). Certain pathogens can be completely sterilized from CSF within two hours of parenteral antibiotics and an interval of over six hours between administering antibiotics and a lumbar puncture can decrease CSF culture positivity from 100% to 40% (Kim, 2010; Stevens et al., 2022). Using PCR techniques as well as culturing bacteria from CSF has resulted in a more sensitive and rapid yield, compared to the culture method alone (Leber et al., 2016). PCR of the CSF sample was not routinely performed during our study period, but this data supports its use.

The rate of permanent hearing deficiency was 5%, which was lower than previously documented (22–30%) by Arditi et al. in 1998. The reason for this finding may have been the success of pneumococcal vaccines by decreasing the proportion of pneumococcal BM, as *S. pneumoniae* is a key bacterium causing hearing loss after BM (Arditi et al., 1998). The overall outcome was unfavorable in 14% of the

pediatric population, and the result was compatible with previous studies with rates between 10–18% (Baraff et al., 1993; Svendsen et al., 2020). We found that nosocomial BM and preterm birth were associated with unfavorable outcomes eight months after discharge. However, these results should be interpreted carefully, because unfavorable outcomes only occurred in a small number of patients and the results were based on univariate statistical analyses. Nevertheless, study II highlighted the increased role of nosocomial BM and its potential to induce significant long-term morbidity. Additionally, these findings supported previous evidence that prematurity can predict unfavorable outcomes (Ouchenir et al., 2017). There was no mortality in our study, but a larger study cohort would have provided a more reliable estimate of the mortality rate. Worldwide, the mortality due to pediatric BM has been reported to vary from 2% to 33% (Jung, 2022; Lovera et al., 2022).

6.3 Post-neurosurgical meningitis (study III)

Study III enlightens the characteristics of PNM occurring after glioma surgery among 345 patients. The incidence of PNM in this setting was 7%. Glioma grade was not an independent risk factor for PNM, but low-grade gliomas had higher incidence of PNM because of the higher proportion of reoperations. Reoperation and revision surgery were independent risk factors for PNM.

Typically, individuals with high-grade gliomas are older and thus have more comorbidities than younger patients (Natukka et al., 2019). Hence, it would be probable that patients with high-grade gliomas would be more prone to PNM than patients with low-grade gliomas.

Study III found that the rate of PNM was higher in low-grade gliomas when compared to high-grade gliomas. Multivariable analysis revealed, however, that the glioma grade was not an independent risk factor for PNM. PNM rate was in the upper proportion when compared to earlier reported incidences of 0.5–8.9% (Dashti et al., 2008; Korinek et al., 2008; Reichert et al., 2002). The perioperative procedures to prevent infections during craniotomy need constant assessments and improvements. The administration of prophylactic antibiotics at the beginning of the surgery has been shown to be effective in prevention of postoperative superficial and deep infections (Jackson et al., 2016). On the other hand, the usage of pre-diagnostic antibiotics reduces the positivity rate of CSF culture, but the strategy would nevertheless be supported (Corless et al., 2001). Cao et al. found in 2017 that the role of prophylactic antibiotic administration was ineffective in prevention of postoperative infections in cases of clean neurosurgery, and on the contrary the use increased the proportions of multidrug-resistant bacteria and negative CSF cultures. The previous study preferred the precise sewing techniques over prophylactic

antibiotics, for example to prevent leakage of CSF, which may cause PNM (Cao et al., 2017). The role of precise suturing should be kept in high regard. Combined prophylactic antibiotic usage with vancomycin and cephalosporins seems to lower the risk of surgical site infections (Corsini et al., 2022). Interestingly, the administration of vancomycin powder has been shown to reduce postoperative infections (Ravikumar et al., 2017). Furthermore, routine CSF sampling with asymptomatic patients should be avoided (Hussein et al., 2017).

Bohman et al. published in 2009 a study, which found that there was no statistically significant difference regarding survival between patients with or without postoperative infections after glioma surgery. Two years later in 2011, De Bonis et al. presented rather contradictory findings that postoperative infections may in fact prolong the survival of patients after glioblastoma surgery, with medians of 16 months versus 30 months, maybe by activating the immune system. Another study with a population of 3784 individuals found that there was no statistically significant difference on survival between patients with or without postoperative infections, with medians five months versus six months (Chen et al., 2017). After all, the most recent study found that glioma patients with postoperative infections tend to have 30% decreased overall survival (Salle et al., 2021). PNM after glioma surgery frequently leads to delays in postoperative treatments such as radiotherapy or chemotherapy, which is unfavorable (Salle et al., 2021). PNM also induces prolongations of hospital stays and causes thus more costs (Hussein et al., 2017; Kuwano et al., 2023).

Reoperations are a substantial risk factor for developing PNM after glioma surgery (Chen et al., 2016; Korinek et al., 2008; Kuwano et al., 2023; Reichert et al., 2002). Risks of reoperations should be noted and carefully considered individually. Frailty has been recognized as an indicator of adverse outcome, post-operative complications, and mortality in patients with glioblastoma, but unfortunately, we were not capable to implement frailty-index in our study (Krenzlin et al., 2021; Zhu et al., 2023). There were no statistically significant differences on developing PNM with ASA classification or length of the surgery in our study, as previously reported (Jackson et al., 2016). A more recent study found that ASA classification or glioma grade were not statistically associated with increased risk of developing PNM (Kuwano et al., 2023). It appears that glioma grade is not associated with postoperative complications in general, which was the conclusion of a recent publication as well (Morshed et al., 2022).

The demographic data of patients with and without PNM were rather similar, which is important to pay attention to in clinical work. Study III showed that PNM is a compartmentalized infection of the CNS, because even 98% of the blood cultures remained negative.

The rate of CSF culture positivity was 28%, which was slightly lower than previously reported, 32% (Reichert et al., 2002). Lately the incidence of CSF culture positive PNM has been decreasing according to a study performed in China in 2014, where only 10% of individuals had a CSF culture positive PNM after craniotomy (Chen et al., 2014). The use of multiplex or quantitative PCR techniques has been shown to be more sensitive and specific methods detecting bacteria compared to CSF culture, and these methods should be used more frequently in the future among PNM patients (Corless et al., 2001).

Emergency surgeries were relatively rare (4%) in individuals undergoing craniotomy for gliomas. The rate of PNM was higher in patients undergoing emergency surgery, but there was no statistically significant difference compared to individuals undergoing elective surgery (p=0.07). Old age and emergency surgeries have been recognized as risk factors for PNM in earlier studies (Chen et al., 2016; Tian et al., 2015). Surprisingly, we found that younger age of patients seemed to controversially be a risk factor for PNM. The reason for this discovery may be that younger patients undergo revision surgeries or reoperations more frequently, and consequently they are at higher risk of developing PNM. Lastly, the incidence of PNM has been reported highest during autumn and winter, which should be further investigated in the future to determine the optimal time for surgeries (Tian et al., 2015).

6.4 Strengths and limitations

This thesis has several strengths, including the massive number of variables collected from study population in studies I and II. Additionally, study II has a follow-up period of eight months to demonstrate the partly reversible condition regarding possible neurological sequelae after BM. The number of variables from study III was lower compared to studies I and II, but the number of patients included were superior. Furthermore, multivariable analysis was possible to perform in study III. The strict definition of PNM in study III was a strength, and it probably ruled out all aseptic meningitis cases.

This thesis has also limitations. Retrospective approach of this thesis may have caused inaccuracies in data collection, and incorrectly reported clinical data is also possible. Being a single-centre study is also a limitation, but the design enabled uniform and detailed data collection and solid transfer to statistical analyses. The number of subjects in study II was rather small and heterogenic and there were consequently small subgroups of children with BM, but our results do provide a comprehensive overview of BM in infants and children in Southwestern Finland.

Using the GOS method with small infants and children may be difficult, and it can also be challenging to differentiate moderate disability from mild disability using

only medical data. Still, we believe that our main discovery of generally good outcomes after BM was reliably determined by using the GOS method in pediatric population. Unfortunately, we were not able to perform a follow-up assessment on adult patients in study I. Additionally, we had no long-term follow-up data on pediatric patients in study II nor the information on quality of life.

The patients included in this thesis may not represent the whole population of infants, children, adults, and glioma patients in Finland. We were unable to exclude the possibility of neurosurgical operations itself being the cause of complications or unfavorable outcomes in some subjects during studies I and II.

6.5 General discussion and future aspects

The ultimate knowledge of pathogenesis of BM is essential to develop more efficient prevention and treatment options for this notorious disease. Continuous efforts and studies in animal models and human participants are needed to understand the pathogenesis better (Tavares et al., 2022). The urgent need to develop new and more specific treatment options for BM is obvious because of the increasing rate of antibiotic resistant pathogens and serotype and serogroup shifts (Mook-Kanamori et al., 2011; van de Beek et al., 2016, A). Even more broad-spectrum, protein-based vaccinations are needed (Black et al., 2012). Also, in the era of increasing antibiotic resistance, adjunctive therapy against BM with pharmacological compounds excluding antibiotics would be interesting issues to further explore. The blockage of complement cascade, especially complement C5, has been proposed to be one promising method (Kasanmoentalib et al., 2015). Daptomycin is investigated for pneumococcal meningitis along with ceftriaxone, because as a nonlytic antibiotic it may be associated with less inflammation of the CNS, and thus the outcome of a BM patient may be better (Grandgirard et al., 2007; Ribes et al., 2005; Wall et al., 2021). MMP-inhibitors, possible neuroprotective characteristics of metformin and adjunctive antipneumococcal therapy is being studied for possible therapies for BM (Liechti et al., 2014; Morton et al., 2016; Muri et al., 2019).

Herd protection regarding conjugate vaccines is also essential especially for infants and elderly, who cannot be completely immunized because of their young age or having inadequate immunological responses for vaccinations (Bijlsma et al., 2016; Bijlsma et al., 2014, B; Hsu et al., 2009; von Gottberg et al., 2014). Consistent surveillance systems are needed globally to detect the effects of conjugate vaccinations, and to detect emerging strains not affected by existing vaccinations (van de Beek et al., 2016, A).

Regardless of the progression in prevention, diagnosis, and treatments of BM, it remains a notorious and fatal infectious disease worldwide. Along with improved prevention and treatment options, the rapid and efficient diagnostic methods play a

key role in identification of this disease and enable rapid initiation of appropriate treatments.

Wider use of nucleic acid amplification testing seems promising, as it can detect a small number of pathogen DNA, especially in cases where antibiotic therapy is administered before diagnostic testing. Indeed, a study by Meehan et al. in 2015 found that in infant population with previous maternal antibiotic administration, the rate of PCR positivity was nearly 50%, while cultures remained negative. Another study of BM caused by GBS found that PCR method resulted in a positivity rate of 64% in patients with negative CSF cultures (Geteneh et al., 2020). Accordingly, clinicians cannot rule out BM with confidence based on solely CSF cultures (Geteneh et al., 2020). However, there seems to be a few concerns regarding multiplex PCR methods. Some studies have reported false positive and false negative results, which should be considered while implementing standard protocols for the diagnosis of BM (Fleischer & Aronson, 2020; Leber et al., 2016). While PCR methods provide swift and effective assessment of wide range of bacteria, the need for more comprehensive cohort studies regarding neonatal BM is needed to clinically validate this method.

The use of next-generation sequence method has been increasing recently, and it may prove to be the most accurate and rapid method yet to diagnose BM, as it is completely unbiased and it is not limited by a previous selection of suspected bacteria and it can detect potential pathogens in a single test, which is especially important when the volume of the sample is limited, especially in cases of neonatal BM (Ramchandar et al., 2021; Wilson et al., 2019). Whole-genome sequencing has been proven an asset to tract the virulence, emergence, and pathophysiology of bacterial species (Chewapreecha et al., 2014; Croucher et al., 2015). However, as good as this method seems, it is time-consuming, costly, and requires notable expertise to employ.

Differential diagnosis between aseptic meningitis, viral meningitis and BM remains a continuing challenge. Numerous molecular markers have been proposed to differentiate the diagnosis of BM, such as TNF-α and multiple interleukins. A study with pediatric population found that the levels of TNF-α, interleukins 6 and 8 in CSF were remarkably higher compared to those with viral meningitis or control population (Prasad et al., 2014), and TNF-α levels were found to be higher in BM compared to aseptic meningitis in another study (Mukai et al., 2006). Additionally, CSF heparin binding protein (HBP) seem a valuable candidate in diagnosing BM and especially nosocomial meningitis, as it was found to have sensitivity of 97% and specificity of 95%, and a positive prediction value of 93%. Furthermore, HBP levels were not affected by previous antibiotic therapy, which has been problematic with previous markers of BM, and this characteristic of HBP highlights its potential for wider use in the future (Kong et al., 2022).

The number of BM caused by *L. monocytogenes* detected in our studies was lower than previously reported, as we reported only one case. Previous research has found that listerial meningitis may cause even 9% of all BM worldwide (Davis, 2018). This decrease may be the consequence of GBS intrapartum prophylaxis because the antibiotics used for prophylaxis are effective also against *L. monocytogenes* (Lee et al., 2016).

The prevention of GBS disease remains a constant challenge. Despite the success of prophylactic intrapartum antibiotics, maternal GBS vaccinations seem as the most promising and effective strategy to prevent serious GBS disease (Tavares et al., 2022). A commercial vaccination to prevent GBS disease is not yet available, but research considering possible candidates against different types of GBS is in process (Carreras-Abad et al., 2020; Vekemans et al., 2019).

Although the hematogenous spread of bacteria to the meninges is the most common pathway of meningeal infections, there are often no detected bacteria in bloodstream. An intriguing explanation of this phenomenon could be that some bacteria may reach the meninges via lymphatic network, and this possibility has not received much value. For example, group A streptococcus and *S. aureus* have been found to exploit lymphatic tropism (Bogoslowski et al., 2018; Bogolowski & Kubes, 2018; Lynskey et al., 2015).

As BM is associated with drier seasons worldwide, it is estimated that climate change may impact the incidence of BM (Mazamay et al., 2020; Wall et al., 2014). Severe acute respiratory syndrome coronavirus 2 -pandemic is estimated to lead in a significant decrease in meningitis incidence due to recommended social distancing protocols and more intense hygiene measures (Luciani et al., 2021; Wall et al., 2021).

The role of corticosteroids for treatment of BM remains an important subject of studies. Valdoleiros et al. reported in 2022 that the use of steroids did not decrease the rate of death, and they proposed that the decreased inflammatory reaction induced by dexamethasone could reduce the penetration of vancomycin to CSF, which was associated with higher rate of complications. If there seems to be a brain abscess along with BM, corticosteroid treatment should be administered immediately to decrease edema in the brain (Brouwer et al., 2014). Implementation of vancomycin powder in neurosurgical operations would be interesting to study in the future, as it has been shown to reduce postoperative infections (Ravikumar et al., 2017).

In cases with multidrug resistant gram-negative bacteria, especially after neurosurgical procedure, intraventricular antibiotic therapy along with intravenous treatment were found to be more effective than intravenous treatment alone on pathogen eradication and mortality, and this method should be further studied and possibly implemented in standard guidelines in the future (Karvouniaris et al., 2018).

In the future, comprehensive prospective studies are needed to better understand and determine factors associated with outcomes after BM in pediatric population as well as in adults and patients undergoing neurosurgery. Continuous research of the clinical characteristics and causative pathogens of BM are needed to prevent, identify and treat this constantly evolving notorious disease most efficiently. Comparisons on the efficacy of various perioperative measures should also be investigated in double blinded clinical trials. Long-term follow-up should be implemented, and standardized questionnaires on quality of life should be performed. Also, it would be beneficial to perform a multi-centre, international study on BM patients with large number of patients.

7 Conclusions

This thesis revealed that the incidence of BM was slightly higher in infants, children and adults than previously reported. The incidence of PNM after glioma surgery was in the upper proportion of previously reported incidences. This thesis updated the etiology of BM in Finland by discovering that *S. pneumoniae* was the most frequent causative bacteria among adult population and children over 90 days of age. GBS and *E. coli* were the most common causative bacteria in infants 0–89 days of age, while *S. epidermidis* and *S. aureus* were most frequently detected in patients with PNM.

The proportions of nosocomial BM were higher than previously reported both in pediatric and adult populations, and the administration of pre-diagnostic antibiotics was frequent among all patients. Antibiotics were administered according to recommendations, and there was no acquired resistance to ceftriaxone or vancomycin, the most frequently used antibiotics in children and adults. Headache was associated with unfavorable outcome in adult population, and pre-diagnostic antibiotic administration predicted unfavorable outcomes, but the reasons may be diverse. Physicians should pay attention to BM patients experiencing headache which may be a symptom of a more advanced and serious disease. Pretermity and nosocomial BM were statistically associated with unfavorable outcomes in pediatric population. Reoperations and revision surgeries were independent risk factors for PNM, and the rate of PNM was higher among low-grade gliomas.

The frequency of unfavorable outcome in adults was compatible with previous research but considering pediatric subjects the frequency was lower than previously reported. Mortality was lower compared to most previous studies among pediatric and adult subjects. PCR of the CSF specimen should be routinely performed along with culture method in the future, while the tests improve, become faster and cheaper.

The overall management of BM patients is well performed according to relevant guidelines and the treatment is effective in Southwestern Finland.

Acknowledgements

This thesis and the studies involved were performed in Departments of Otorhinolaryngology and Infectious Diseases, Turku University Hospital, and University of Turku, Finland, during the years 2018–2024.

This thesis was financially supported by Rauno and Anne Puolimatka Foundation, Centre of Excellence in Infections and Microbiomes of the Turku University Hospital -organization, and Western Finland Collaborative area research committee.

First, I would like to thank both my supervisors, professor Jarmo Oksi, M.D, Ph.D, Department of Infectious Diseases, Turku University Hospital and University of Turku, and professor Jussi Jero, M.D., Ph.D, Department of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Hospital. Jussi was present at the beginning of my studies and this thesis, and I'm very grateful for all the guidance and support in the early phase of my research. Jarmo, I'm forever thankful for your constant and invaluable help, support and guidance during the past few years, and especially for accepting me as your Ph.D student en route. I appreciate your patience, expertise and swiftness in all research-related comments, recommendations, and emails.

I want to thank also docent Kirsi Skogberg, M.D, Ph.D, from Division of Infectious Diseases, Helsinki University Hospital, and University of Helsinki, Finland, for accepting the invitation to be my opponent at my academic dissertation. Additionally, docents Olli-Pekka Kämäräinen and Merja Helminen deserves my gratitude for their experienced and valuable comments, which made this thesis much more improved.

Next, my sincere thanks go to biostatician Eliisa Löyttyniemi. I'm forever grateful for your will to participate in this research, and your invaluable statistical reports. Thank you also for your patience in explaining statistical methods and results for me whenever I needed.

I have had a great opportunity to work with numerous talented researchers during this thesis. I warmly acknowledge my co-authors Laura Lempinen, Raakel Luoto, Juha O. Grönroos, Melissa Rahi, Jaakko Rinne and Jussi Posti in the original publications for their valuable help in gathering data, conceptualization,

methodology, validation, visualization, writing, reviewing, and editing manuscripts. A special thanks goes to professor Ville Peltola for supervision in study II with a precise and professional manner, while being supportive at the same time. Additionally, I thank Dan Laukka, M.D, Ph.D, for supervision and significant efforts considering study III.

I am lucky to have a great group of friends, “Raisiojengi”, which have been providing memorable moments outside work and research scheme for many years. Thank you, guys, for your support and interest in this rather long-lasting project. Thanks also to my great co-workers at Kirkkotie health station. I would also like to thank Sini Riivari for advice and tips during this project.

I would also like to impress my gratitude to my dear parents, Jari Niemelä and Pia Suvivuo, for your constant care and encouragements during this project. Dad, our regular meetings at the gym were an excellent opportunity to address all research-related problems while training. Thank you for those valuable moments. Mom, the inspiration to do research in the first place began in 2011 while I was watching your academic dissertation, and I therefore warmly thank you for giving me motivation and advice during this project. I would also thank my grandparents Matti and Eija Suvivuo and my brother Samppa for support.

Finally, my biggest and loving gratitude goes to my wonderful, dear wife Emmi Alimattila. Thank you for being there for me and always giving me the time and space to chase my academic goals. Emmi, you have supported me constantly during this challenging project, and your practical help with Excel, figures, tables, and proof-reading this thesis have been invaluable, and without your overwhelming assistance this thesis would not have been possible to complete. Thank you for your perseverance, support, and love during these challenging times.

References

ACOG committee members. Prevention of group B streptococcal early-onset disease in newborns: ACOG Committee Opinion, Number 797. Obstet Gynecol. 2020;135:e51–e72

Adil SM, Hodges SE, Charalambous LT, Kiyani M, Liu B, Lee HJ, Parente BA, Perfect JR, Lad SP. Paediatric bacterial meningitis in the USA: outcomes and healthcare resource utilization of nosocomial versus community-acquired infection. J Med Microbiol. 2021. Jan;70(1).

Aghi MK, Batchelor TT, Louis DN, Barker FG, Curry WT. Decreased rate of infection in glioblastoma patients with allelic loss of chromosome 10q. J Neurooncol. 2009;93:115–120.

Ali YM, Kenawy HI, Muhammad A, Sim RB, Andrew PW, Schwaeble WJ. Human L-ficolin, a recognition molecule of the lectin activation pathway of complement, activates complement by binding to pneumolysin, the major toxin of Streptococcus pneumoniae. PLoS One. 2013 Dec 12;8(12):e82583.

Arditi M, Mason EO Jr, Bradley JS, Tan TQ, Barson WJ, Schutze GE, Wald ER, Givner LB, Kim KS, Yogev R, Kaplan SL. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics, and outcome related to penicillin susceptibility and dexamethasone use. Pediatrics. 1998 Nov;102(5):1087–97.

Atkinson RA, Fikrey L, Vail A, Patel HC. Silver-impregnated external-ventricular-drain-related cerebrospinal fluid infections: A meta-analysis. J Hosp Infect 2016; 92:263–272.

Azimi T, Mirzadeh M, Sabour S, Nasser A, Fallah F, Pourmand MR. Coagulase-negative staphylococci (CoNS) meningitis: a narrative review of the literature from 2000 to 2020. New Microbes New Infect. 2020 Sep 7;37:100755.

Baker M, McNicholas A, Garrett N, Jones N, Stewart J, Koberstein V, Lennon D. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. Pediatr Infect Dis J. 2000;19(10):983–990.

Banerjee A, Kim BJ, Carmona EM, Cutting AS, Gurney MA, Carlos C, Feuer R, Prasadarao NV, Doran KS. Bacterial Pili exploit integrin machinery to promote immune activation and efficient blood-brain barrier penetration. Nat Commun. 2011 Sep 6;2:462.

Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J. 1993;12:389–94.

Başpınar EÖ, Dayan S, Bekçibaşı M, Tekin R, Ayaz C, Deveci Ö, Hoşoğlu S. Comparison of culture and PCR methods in the diagnosis of bacterial meningitis. Braz J Microbiol. 2017 Apr-Jun;48(2):232–236.

Battersby AJ, Knox-Macaulay HHM, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. Pediatr Blood Cancer. 2010;55(3):401–406.

Beers SR, Wisniewski SR, Garcia-Filion P, Tian Y, Hahner T, Berger RP, Bell MJ, Adelson PD. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. J Neurotrauma. 2012;29(6):1126–39.

Berardi A, Trevisani V, Di Caprio A, Bua J, China M, Perrone B, Pagano R, Lucaccioni L, Fanaro S, Iughetti L, Lugli L, Creti R. Understanding Factors in Group B Streptococcus Late-Onset Disease. Infect Drug Resist. 2021 Aug 17;14:3207–3218.

Bernard SC, Simpson N, Join-Lambert O, Federici C, Laran-Chich MP, Maïssa N, Bouzinba-Ségard H, Morand PC, Chretien F, Taouji S, Chevet E, Janel S, Lafont F, Coureuil M, Segura A, Niedergang F, Marullo S, Couraud PO, Nassif X, Bourdoulous S. Pathogenic Neisseria meningitidis utilizes CD147 for vascular colonization. Nat Med. 2014 Jul;20(7):725–31.

Bijlsma MW, Bekker V, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960–2012: an analysis of national surveillance data. Lancet Infect Dis. 2014 Sep;14(9):805–12. A.

Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, van der Ende A, van de Beek D. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. Lancet Infect Dis. 2016 Mar;16(3):339–47.

Bijlsma MW, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. A decade of herd protection after introduction of meningococcal serogroup C conjugate vaccination. Clin Infect Dis. 2014 Nov 1;59(9):1216–21. B.

Bineshfar N, Rezaei A, Mirahmadi A, Shokouhi S, Gharehbagh FJ, Haghighi M, Harandi AA, Shojaei M, Ramezani M, Zoghi A, Gharagozli K, Lotfollahi L, Darazam IA. Evaluation of the epidemiologic, clinical, radiologic, and treatment methods of patients with subacute and chronic meningitis. BMC Neurol. 2022 Sep 10;22(1):340.

Black S, Pizza M, Nissum M, Rappuoli R. Toward a meningitis-free world. Sci Transl Med. 2012 Feb 29;4(123):123ps5.

Block N, Naucler P, Wagner P, Morfeldt E, Henriques-Normark B. Bacterial meningitis: aetiology, risk factors, disease trends and severe sequelae during 50 years in Sweden. J Intern Med. 2022;292:350–64.

Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis. 2004 Mar;4(3):144–54.

Bogoslowski A, Butcher EC, Kubes P. Neutrophils recruited through high endothelial venules of the lymph nodes via PNAd intercept disseminating Staphylococcus aureus. Proc Natl Acad Sci USA. 2018;115:2449–2454.

Bogoslowski A, Kubes P. Lymph nodes: the unrecognized barrier against pathogens. ACS Infect Dis. 2018;4:1158–1161.

Bohman LE, Gallardo J, Hankinson TC, Waziri AE, Mandigo CE, McKhann GM 2nd, Sisti MB, Canoll P, Bruce JN. The survival impact of postoperative infection in patients with glioblastoma multiforme. Neurosurgery. 2009 May;64(5):828–34; discussion 834–5.

Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, van Werkhoven CH, van Deursen AM, Sanders EA, Verheij TJ, Patton M, McDonough A, Moradoghli-Haftvani A, Smith H, Mellelieu T, Pride MW, Crowther G, Schmoele-Thoma B, Scott DA, Jansen KU, Lobatto R, Oosterman B, Visser N, Caspers E, Smorenburg A, Emini EA, Gruber WC, Grobbee DE. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015 Mar 19;372(12):1114–25.

Braun JS, Novak R, Herzog KH, Bodner SM, Cleveland JL, Tuomanen EI. Neuroprotection by a caspase inhibitor in acute bacterial meningitis. Nat Med. 1999 Mar;5(3):298–302.

Brotis AG, Churis I, Karvouniaris M. Local complications of adjunct intrathecal antibiotics for nosocomial meningitis associated with gram-negative pathogens: a meta-analysis. Neurosurg Rev. 2021 Feb;44(1):139–152.

Brouwer MC, Keizerweerd GD, De Gans J, Spanjaard L, Van De Beek D. Community acquired Staphylococcus aureus meningitis in adults. Scand J Infect Dis. 2009;41(5):375–7.

Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev. 2010 Jul;23(3):467–92.

Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet. 2012 Nov 10;380(9854):1684–92.

Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. N Engl J Med. 2014 Jul 31;371(5):447–56.

Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2015 Sep 12;2015(9):CD004405.

Brouwer MC, Wijdicks EFM, van de Beek D. What's new in bacterial meningitis. Intensive Care Med. 2016 Mar;42(3):415–417.

Cabanes D, Sousa S, Cebriá A, Lecuit M, García-del Portillo F, Cossart P. Gp96 is a receptor for a novel Listeria monocytogenes virulence factor, Vip, a surface protein. EMBO J. 2005 Aug 3;24(15):2827–38.

Cao Y, Pu K, Li G, Yan X, Ma Y, Xue K, Sun Z, Li Q. The Role of Antibiotic Prophylaxis in Clean Neurosurgery. World Neurosurg. 2017 Apr;100:305–310.

Carlin AF, Uchiyama S, Chang YC, Lewis AL, Nizet V, Varki A. Molecular mimicry of host sialylated glycans allows a bacterial pathogen to engage neutrophil Siglec-9 and dampen the innate immune response. Blood. 2009 Apr 2;113(14):3333–6.

Carreras-Abad C, Ramkhelawon L, Heath PT, Le Doare K. A vaccine against group B streptococcus: recent advances. Infect Drug Resist. 2020;13:1263–1272.

Chen C, Zhang B, Yu S, Sun F, Ruan Q, Zhang W, Shao L, Chen S. The incidence and risk factors of meningitis after major craniotomy in China: a retrospective cohort study. PLoS One. 2014 Jul 8;9(7):e101961.

Chen CH, Chang CY, Lin LJ, Chen WL, Chang YJ, Wang SH, Cheng CY, Yen HC. Risk factors associated with postcraniotomy meningitis: A retrospective study. Medicine (Baltimore). 2016 Aug;95(31):e4329.

Chen Y-R, Ugiliweneza B, Burton E, Woo SY, Boakye M, Skirboll S. The effect of postoperative infection on survival in patients with glioblastoma. J Neurosurg. 2017;127:807–811.

Chewapreecha C, Harris SR, Croucher NJ, Turner C, Marttinen P, Cheng L, Pessia A, Aanensen DM, Mather AE, Page AJ, Salter SJ, Harris D, Nosten F, Goldblatt D, Corander J, Parkhill J, Turner P, Bentley SD. Dense genomic sampling identifies highways of pneumococcal recombination. Nat Genet. 2014 Mar;46(3):305–309.

Choi CH, Lee JS, Lee YC, Park TI, Lee JC. Acinetobacter baumannii invades epithelial cells and outer membrane protein A mediates interactions with epithelial cells. BMC Microbiol. 2008 Dec 10;8:216.

Corless CE, Guiver M, Borrow R, Edwards-Jones V, Fox AJ, Kaczmarski EB. Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. J Clin Microbiol. 2001 Apr;39(4):1553–8.

Corsini Campioli C, Challener D, Comba IY, Shah A, Wilson WR, Sohail MR, Van Gompel JJ, O'Horo JC. Overview and risk factors for postcraniotomy surgical site infection: A four-year experience. Antimicrob Steward Healthc Epidemiol. 2022;2(1):e14.

Costerus JM, Brouwer MC, van der Ende A, van de Beek D. Community-acquired bacterial meningitis in adults with cancer or a history of cancer. Neurology. 2016 Mar 1;86(9):860–6.

Coureuil M, Lécuyer H, Scott MG, Boularan C, Enslen H, Soyer M, Mikaty G, Bourdoulous S, Nassif X, Marullo S. Meningococcus Hijacks a β2-adrenoceptor/β-Arrestin pathway to cross brain microvasculature endothelium. Cell. 2010 Dec 23;143(7):1149–60.

Coureuil M, Bourdoulous S, Marullo S, Nassif X. Invasive meningococcal disease: a disease of the endothelial cells. Trends Mol Med. 2014 Oct;20(10):571–8.

Croucher NJ, Kagedan L, Thompson CM, Parkhill J, Bentley SD, Finkelstein JA, Lipsitch M, Hanage WP. Selective and genetic constraints on pneumococcal serotype switching. PLoS Genet. 2015 Mar 31;11(3):e1005095.

Cundell DR, Gerard NP, Gerard C, Idanpaan-Heikkila I, Tuomanen EI. Streptococcus pneumoniae anchor to activated human cells by the receptor for platelet-activating factor. Nature. 1995 Oct 5;377(6548):435–8.

Dashti SR, Baharvahdat H, Spetzler RF, Sauvageau E, Chang SW, Stiefel MF, Park MS, Bambakidis NC. Operative intracranial infection following craniotomy. Neurosurg Focus. 2008;24(6):E10.

Daugla DM, Gami JP, Gamougam K, Naibei N, Mbainadji L, Narbé M, Toralta J, Kodbesse B, Ngadoua C, Coldiron ME, Fermon F, Page AL, Djingarey MH, Hugonnet S, Harrison OB, Rebbetts LS, Tekletsion Y, Watkins ER, Hill D, Caugant DA, Chandramohan D, Hassan-King M, Manigart O, Nascimento M, Woukeu A, Trotter C, Stuart JM, Maiden M, Greenwood BM. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study [corrected]. Lancet. 2014 Jan 4;383(9911):40–47.

Davis LE. Acute Bacterial Meningitis. Contin Minneap Minn. 2018;24(5):1264–1283.

De Bonis P, Albanese A, Lofrese G, de Waure C, Mangiola A, Pettorini BL, Pompucci A, Balducci M, Fiorentino A, Lauriola L, Anile C, Maira G. Postoperative infection may influence survival in patients with glioblastoma: simply a myth? Neurosurgery. 2011 Oct;69(4):864–8; discussion 868–9.

de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2002 Nov 14;347(20):1549–56.

Delara M, Vadlamudi NK, Sadarangani M. Strategies to prevent early and late-onset group B streptococcal infection via interventions in pregnancy. Pathogens. 2023;12:229.

Deshmukh M, Patole S. Prophylactic Probiotic Supplementation for Preterm Neonates-A Systematic Review and Meta-Analysis of Nonrandomized Studies. Adv Nutr. 2021 Jul 30;12(4):1411–1423.

Doran KS, Engelson EJ, Khosravi A, Maisey HC, Fedtke I, Equils O, Michelsen KS, Arditi M, Peschel A, Nizet V. Blood-brain barrier invasion by group B Streptococcus depends upon proper cell-surface anchoring of lipoteichoic acid. J Clin Invest. 2005 Sep;115(9):2499–507.

Doran KS, Fulde M, Gratz N, Kim BJ, Nau R, Prasadarao N, Schubert-Unkmeir A, Tuomanen EI, Valentin-Weigand P. Host-pathogen interactions in bacterial meningitis. Acta Neuropathol. 2016 Feb;131(2):185–209.

Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr, Swartz MN. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med. 1993 Jan 7;328(1):21–8.

Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2010 May;10(5):317–28.

Edwards MS, Nizet V, Baker CJ: Group B Streptococcal Infections. In Remington and Klein's infectious diseases of the fetus and newborn infant, 8th ed. Elsevier/ Saunders, Philadelphia. 2016.

Erdem H, Inan A, Guven E, Hargreaves S, Larsen L, Shehata G, Pernicova E, Khan E, Bastakova L, Namani S, Harxhi A, Roganovic T, Lakatos B, Uysal S, Sipahi OR, Crisan A, Miftode E, Stebel R, Jegorovic B, Fehér Z, Jekkel C, Pandak N, Moravveji A, Yilmaz H, Khalifa A, Musabak U, Yilmaz S, Jouhar A, Oztoprak N, Argemi X, Baldeyrou M, Bellaud G, Moroti RV, Hasbun R, Salazar L, Tekin R, Canestri A, Čalkić L, Praticò L, Yilmaz-Karadag F, Santos L, Pinto A, Kaptan F, Bossi P, Aron J, Duissenova A, Shopayeva G, Utaganov B, Grgic S, Ersoz G, Wu AKL, Lung KC, Bruzsa A, Radic LB, Kahraman H, Momen-Heravi M, Kulzhanova S, Rigo F, Konkayeva M, Smagulova Z, Tang T, Chan P, Ahmetagic S, Porobic-Jahic H, Moradi F, Kaya S, Cag Y, Bohr A, Artuk C, Celik I, Amsilli M, Gul HC, Cascio A, Lanzafame M, Nassar M. The burden and epidemiology of community-acquired central nervous system infections: a multinational study. Eur J Clin Microbiol Infect Dis. 2017 Sep;36(9):1595–1611.

Eskola J, Takala A, Käyhty H, Peltola H, Mäkelä PH. Experience in Finland with Haemophilus influenzae type b vaccines. Vaccine. 1991 Jun;9 Suppl:S14–6; discussion S25.

Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. Lancet Infect Dis. 2007 Mar;7(3):191–200.

Fleischer E, Aronson PL. Rapid diagnostic tests for meningitis and encephalitis—BioFire. Pediatr Emerg Care. 2020;36:397–401.

Fortnum H, Davis A. Hearing impairment in children after bacterial meningitis: incidence and resource implications. Br J Audiol. 1993 Feb;27(1):43–52.

Garges HP, Moody MA, Cotten CM, Smith PB, Tiffany KF, Lenfestey R, Li JS, Fowler VG Jr, Benjamin DK Jr. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics. 2006 Apr;117(4):1094–100.

GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Lond Engl. 2017;390(10100):1151–210.

GBD 2016 Meningitis Collaborators Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1061–1082.

Gerber J, Nau R. Mechanisms of injury in bacterial meningitis. Curr Opin Neurol. 2010 Jun;23(3):312–8.

Gessner BD, Mueller JE, Yaro S. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. BMC Infect Dis. 2010;10:22.

Geteneh A, Kassa T, Alemu Y, Alemu D, Kiros M, Andualem H, Abebe W, Alemayehu T, Alemayehu DH, Mihret A, Mulu A, Mihret W. Enhanced identification of Group B streptococcus in infants with suspected meningitis in Ethiopia. PLoS One. 2020 Nov 19;15(11):e0242628.

Global Burden of Disease Study 2013 Collaborators Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Lond Engl. 2015;386(9995):743–800.

Grandgirard D, Leib SL. Meningitis in neonates: bench to bedside. Clin Perinatol. 2010;37:655–676.

Grandgirard D, Schurch C, Cottagnoud P, Leib SL. Prevention of brain injury by the nonbacteriolytic antibiotic daptomycin in experimental pneumococcal meningitis. Antimicrob Agents Chemother. 2007;51:2173–2178.

Greiffenberg L, Goebel W, Kim KS, Weiglein I, Bubert A, Engelbrecht F, Stins M, Kuhn M. Interaction of Listeria monocytogenes with human brain microvascular endothelial cells: InlB-dependent invasion, long-term intracellular growth, and spread from macrophages to endothelial cells. Infect Immun. 1998 Nov;66(11):5260–7.

Gudina EK, Tesfaye M, Wieser A, Pfister H-W, Klein M. Outcome of patients with acute bacterial meningitis in a teaching hospital in Ethiopia: a prospective study. PLoS ONE. 2018;13:e0200067.

Gunn AJ, Thoresen M. Neonatal encephalopathy and hypoxic-ischemic encephalopathy. Handb Clin Neurol. 2019;162:217–237.

Haffner DN, Machie M, Hone E, Said RR, Maitre NL. Predictors of neurodevelopmental impairment after neonatal bacterial meningitis. J Child Neurol. 2021;36:968–973.

Hannila-Handelberg T, Toropainen M, Nohynek H, Kuusi M, Mäkitie I. Varusmiesten invasiiviset meningokokkitaudit 2003–2012. SLL. 2015;70:121–126.

Harcourt BH, Anderson RD, Wu HM, Cohn AC, MacNeil JR, Taylor TH, Wang X, Clark TA, Messonnier NE, Mayer LW. Population-Based Surveillance of Neisseria meningitidis Antimicrobial Resistance in the United States. Open Forum Infect Dis. 2015 Aug 13;2(3):ofv117.

Hasanuzzaman M, Saha S, Malaker R, Rahman H, Sajib MSI, Das RC, Islam M, Hamer DH, Darmstadt GL, Saha SK. Comparison of Culture, Antigen Test, and Polymerase Chain Reaction for Pneumococcal Detection in Cerebrospinal Fluid of Children. J Infect Dis. 2021 Sep 1;224(12 Suppl 2):S209–S217.

Hasbun R, Rosenthal N, Balada-Llasat JM, Chung J, Duff S, Bozzette S, Zimmer L, Ginocchio CC. Epidemiology of Meningitis and Encephalitis in the United States, 2011–2014. Clin Infect Dis. 2017 Aug 1;65(3):359–363.

Hassan KA, Jackson SM, Penesyan A, Patching SG, Tetu SG, Eijkelkamp BA, Brown MH, Henderson PJ, Paulsen IT. Transcriptomic and biochemical analyses identify a family of chlorhexidine efflux proteins. Proc Natl Acad Sci USA. 2013 Dec 10;110(50):20254–9.

Heckenberg SG, Brouwer MC, van de Beek D. Bacterial meningitis. Handb Clin Neurol. 2014;121:1361–75.

Hodgson A, Smith T, Gagneux S, Adjuik M, Pluschke G, Mensah NK, Binka F, Genton B. Risk factors for meningococcal meningitis in northern Ghana. Trans R Soc Trop Med Hyg. 2001 Sep-Oct;95(5):477–80.

Hoogman M, van de Beek D, Weisfelt M, de Gans J, Schmand B. Cognitive outcome in adults after bacterial meningitis. J Neurol Neurosurg Psychiatry. 2007 Oct;78(10):1092–6.

Hsu HE, Shutt KA, Moore MR, Beall BW, Bennett NM, Craig AS, Farley MM, Jorgensen JH, Lexau CA, Petit S, Reingold A, Schaffner W, Thomas A, Whitney CG, Harrison LH. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med. 2009 Jan 15;360(3):244–56.

Hussein K, Bitterman R, Shofty B, Paul M, Neuberger A. Management of post-neurosurgical meningitis: narrative review. Clin Microbiol Infect. 2017 Sep;23(9):621–628.

Iovino F, Brouwer MC, van de Beek D, Molema G, Bijlsma JJ. Signalling or binding: the role of the platelet-activating factor receptor in invasive pneumococcal disease. Cell Microbiol. 2013 Jun;15(6):870–81. A.

Iovino F, Orihuela CJ, Moorlag HE, Molema G, Bijlsma JJ. Interactions between blood-borne Streptococcus pneumoniae and the blood-brain barrier preceding meningitis. PLoS One. 2013 Jul 16;8(7):e68408. B.

Ippolito M, Giarratano A, Cortegiani A. Healthcare-associated central nervous system infections. Curr Opin Anaesthesiol. 2022 Oct 1;35(5):549–554.

Jackson C, Westphal M, Quiñones-Hinojosa A. Complications of glioma surgery. Handb Clin Neurol. 2016;134:201–218.

Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015 Dec;40(12):2583–99.

Johansson Kostenniemi U, Norman D, Sellin M, Silfverdal SA. Sustained reductions of invasive infectious disease following general infant Haemophilus influenzae type b and pneumococcal vaccination in a Swedish Arctic region. Acta Paediatr. 2019;108:1871–1878.

Johansson L, Rytkonen A, Bergman P, Albiger B, Källström H, Hökfelt T, Agerberth B, Cattaneo R, Jonsson AB. CD46 in meningococcal disease. Science. 2003 Jul 18;301(5631):373–5.

Johnson HL, Deloria-Knoll M, Levine OS, Stoszek SK, Freimanis Hance L, Reithinger R, Muenz LR, O'Brien KL. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med. 2010 Oct 5;7(10):e1000348.

Join-Lambert OF, Ezine S, Le Monnier A, Jaubert F, Okabe M, Berche P, Kayal S. Listeria monocytogenes-infected bone marrow myeloid cells promote bacterial invasion of the central nervous system. Cell Microbiol. 2005 Feb;7(2):167–80.

Joubrel C, Tazi A, Six A, Dmytruk N, Touak G, Bidet P, Raymond J, Trieu Cuot P, Fouet A, Kerneis S, Poyart C. Group B streptococcus neonatal invasive infections, France 2007–2012. Clin Microbiol Infect. 2015;21:910–916.

Jung YJ. Short information: bacterial meningitis in very low birthweight infants in Korea from 2013–2016. Pediatr Int. 2022;64:e15057.

Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics. 2001 Nov;108(5):1169–74.

Karvouniaris M, Brotis AG, Tsiamalou P, Fountas KN. The Role of Intraventricular Antibiotics in the Treatment of Nosocomial Ventriculitis/Meningitis from Gram-Negative Pathogens: A Systematic Review and Meta-Analysis. World Neurosurg. 2018 Dec;120:e637–e650.

Kasanmoentalib ES, Brouwer MC, van der Ende A, van de Beek D. Hydrocephalus in adults with community-acquired bacterial meningitis. Neurology. 2010 Sep 7;75(10):918–23.

Kasanmoentalib ES, Valls Seron M, Morgan BP, Brouwer MC, van de Beek D. Adjuvant treatment with dexamethasone plus anti-C5 antibodies improves outcome of experimental pneumococcal meningitis: a randomized controlled trial. J Neuroinflammation. 2015 Aug 15;12:149.

Kim KJ, Chung JW, Kim KS. 67-kDa laminin receptor promotes internalization of cytotoxic necrotizing factor 1-expressing Escherichia coli K1 into human brain microvascular endothelial cells. J Biol Chem. 2005 Jan 14;280(2):1360–8.

Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis. 2010 Jan;10(1):32–42.

Kim KS. Mechanisms of microbial traversal of the blood-brain barrier. Nat Rev Microbiol. 2008 Aug;6(8):625–34.

Kim KS. Pathogenesis of bacterial meningitis: from bacteraemia to neuronal injury. Nat Rev Neurosci. 2003;4:376–385.

Kiyani M, Hodges SE, Adil SM, Charalambous LT, Liu B, Lee HJ, Parente B, Perfect JR, Lad SP. Outcomes and Health Care Resource Utilization of Adult Bacterial Meningitis in the United States. Neurol Clin Pract. 2021 Apr;11(2):117–126.

Kizilates F, Keskin AS, Onder KD. Clinical Features of Post-Operative Nosocomial Meningitis in Adults and Evaluation of Efficiency of Intrathecal Treatment. Surg Infect (Larchmt). 2021 Dec;22(10):1059–1063.

Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. Pediatrics. 2000;106(3):477–482.

Koedel U, Gorriz C, Lorenzl S, Pfister HW. Increased endothelin levels in cerebrospinal fluid samples from adults with bacterial meningitis. Clin Infect Dis. 1997 Aug;25(2):329–30.

Koedel U, Klein M, Pfister HW. New understandings on the pathophysiology of bacterial meningitis. Curr Opin Infect Dis. 2010 Jun;23(3):217–23.

Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van de Beek D, van der Ende A. Changing epidemiology of bacterial meningitis since introduction of conjugate vaccines: 3 decades of National Meningitis Surveillance in The Netherlands. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021;73(5):e1099–e1107.

Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, Bartlett L, Cutland C, Gravett MG, Heath PT, Ip M, Le Doare K, Madhi SA, Rubens CE, Saha SK, Schrag S, Sobanjo-Ter Meulen A, Vekemans J, O'Sullivan C, Nakwa F, Ben Hamouda H, Soua H, Giorgakoudi K, Ladhani S, Lamagni T, Rattue H, Trotter C, Lawn JE. Neurodevelopmental Impairment in Children After Group B Streptococcal Disease Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017 Nov 6;65(suppl_2):S190–S199.

Kong Y, Ye Y, Ma J, Shi G. Accuracy of heparin-binding protein for the diagnosis of nosocomial meningitis and ventriculitis. Crit Care. 2022 Mar 8;26(1):56.

Korinek AM, Baugnon T, Golmard JL, van Effenterre R, Coriat P, Puybasset L. Risk factors for adult nosocomial meningitis after craniotomy: role of antibiotic prophylaxis. Neurosurgery. 2008 Feb;62 Suppl 2:532–9.

Kourbeti IS, Vakis AF, Ziakas P, Karabetsos D, Potolidis E, Christou S, Samonis G. Infections in patients undergoing craniotomy: risk factors associated with post-craniotomy meningitis. J Neurosurg. 2015 May;122(5):1113–9.

Krenzlin H, Jankovic D, Alberter C, Kalasauskas D, Westphalen C, Ringel F, Keric N. Frailty in Glioblastoma Is Independent From Chronological Age. Front Neurol. 2021 Nov 30;12:777120.

Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. Clin Perinatol. 2015;42:29–45.

Kurtaran B, Kuscu F, Ulu A, Inal AS, Komur S, Kibar F, Cetinalp NE, Ozsoy KM, Arslan YK, Yilmaz DM, Aksu H, Tasova Y. The Causes of Postoperative Meningitis: The Comparison of Gram-Negative and Gram-Positive Pathogens. Turk Neurosurg. 2018;28(4):589–596.

Kuwano A, Saito T, Nitta M, Tsuzuki S, Koriyama S, Tamura M, Ikuta S, Masamune K, Muragaki Y, Kawamata T. Relationship between characteristics of glioma treatment and surgical site infections. Acta Neurochir (Wien). 2023 Mar;165(3):659–666.

Leber AL, Everhart K, Balada-Llasat JM, Cullison J, Daly J, Holt S, Lephart P, Salimnia H, Schreckenberger PC, DesJarlais S, Reed SL, Chapin KC, LeBlanc L, Johnson JK, Soliven NL, Carroll KC, Miller JA, Dien Bard J, Mestas J, Bankowski M, Enomoto T, Hemmert AC, Bourzac KM. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. J Clin Microbiol. 2016;54:2251–2261.

Lee B, Newland JG, Jhaveri R: Reductions in neonatal listeriosis: "Collateral benefit" of Group B streptococcal prophylaxis? J Infect. 2016; 72(3): 317–23.

Lewis LA, Vu DM, Vasudhev S, Shaughnessy J, Granoff DM, Ram S. Factor H-dependent alternative pathway inhibition mediated by porin B contributes to virulence of Neisseria meningitidis. mBio. 2013 Oct 15;4(5):e00339–13.

Liechti FD, Grandgirard D, Leppert D, Leib SL. Matrix metalloproteinase inhibition lowers mortality and brain injury in experimental pneumococcal meningitis. Infect Immun 2014; 82:1710–1718.

Lin CY, Hsu CH, Huang FY, Chang JH, Hung HY, Kao HA, Peng CC, Jim WT, Chi H, Chiu NC, Chang TY, Chen CY, Chen CP. The changing face of early-onset neonatal sepsis after the implementation of a maternal group B Streptococcus screening and intrapartum prophylaxis policy--a study in one medical center. Pediatr Neonatol. 2011 Apr;52(2):78–84.

Lindvall P, Ahlm C, Ericsson M, Gothefors L, Naredi S, Koskinen LO. Reducing intracranial pressure may increase survival among patients with bacterial meningitis. Clin Infect Dis. 2004 Feb 1;38(3):384–90.

Lingani C, Bergeron-Caron C, Stuart JM, Fernandez K, Djingarey MH, Ronveaux O, Schnitzler JC, Perea WA. Meningococcal Meningitis Surveillance in the African Meningitis Belt, 2004–2013. Clin Infect Dis. 2015 Nov 15;61(Suppl 5):S410–5.

Lovera D, Amarilla S, Araya S, Galeano F, González N, Martínez de Cuellar C, Apodaca S, Arbo A. Risk Factors for Death and Severe Neurological Sequelae in Childhood Bacterial Meningitis. Pediatr Emerg Care. 2022 Dec 1;38(12):637–643.

Lucas MJ, Brouwer MC, van de Beek D. Neurological sequelae of bacterial meningitis. J Infect. 2016; 73: 18–27.

Lucas MJ, Brouwer MC, van der Ende A, van de Beek D. Outcome in patients with bacterial meningitis presenting with a minimal Glasgow Coma Scale score. Neurol Neuroimmunol Neuroinflamm. 2014 May 15;1(1):e9.

Luciani L, Ninove L, Zandotti C, Nougairede A. COVID-19 pandemic and its consequences disrupt epidemiology of enterovirus meningitis, South-East France. J Med Virol 2021; 93:1929–1931.

Lynskey NN, Banerji S, Johnson LA, Holder KA, Reglinski M, Wing PA, Rigby D, Jackson DG, Sriskandan S. Rapid lymphatic dissemination of encapsulated group A streptococci via lymphatic vessel endothelial receptor-1 interaction. PLoS Pathog. 2015;11:e1005137.

MacFarquhar JK, Jones TF, Woron AM, Kainer MA, Whitney CG, Beall B, Schrag SJ, Schaffner W. Outbreak of late-onset group B Streptococcus in a neonatal intensive care unit. Am J Infect Control. 2010;38:283–288.

Maisey HC, Hensler M, Nizet V, Doran KS. Group B streptococcal pilus proteins contribute to adherence to and invasion of brain microvascular endothelial cells. J Bacteriol. 2007 Feb;189(4):1464–7.

Mastorakos P, McGavern D. The anatomy and immunology of vasculature in the central nervous system. Sci Immunol. 2019 Jul 12;4(37):eaav0492.

Matulyte E, Kiveryte S, Paulauskiene R, Liukpetryte E, Vaikutyte R, Matulionyte R. Retrospective analysis of the etiology, clinical characteristics and outcomes of community-acquired bacterial meningitis in the University Infectious Diseases Centre in Lithuania. BMC Infect Dis. 2020 Oct 7;20(1):733.

Mazamay S, Broutin H, Bompangue D, Muyembe JJ, Guégan JF. The environmental drivers of bacterial meningitis epidemics in the Democratic Republic of Congo, central Africa. PLoS Negl Trop Dis. 2020 Oct 7;14(10):e0008634.

McCracken GH Jr, Mustafa MM, Ramilo O, Olsen KD, Risser RC. Cerebrospinal fluid interleukin 1-beta and tumor necrosis factor concentrations and outcome from neonatal gram-negative enteric bacillary meningitis. Pediatr Infect Dis J. 1989 Mar;8(3):155–9.

McCracken GH Jr, Sarff LD, Glode MP, Mize SG, Schiffer MS, Robbins JB, Gotschlich EC, Orskov I, Orskov F. Relation between Escherichia coli K1 capsular polysaccharide antigen and clinical outcome in neonatal meningitis. Lancet. 1974 Aug 3;2(7875):246–50.

McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet Lond Engl. 2012;380(9854):1703–1711.

McMillan DA, Lin CY, Aronin SI, Quagliarello VJ. Community-acquired bacterial meningitis in adults: categorization of causes and timing of death. Clin Infect Dis. 2001 Oct 1;33(7):969–75.

Meehan M, Cafferkey M, Corcoran S, Foran A, Hapnes N, LeBlanc D, McGuinness C, Nusgen U, O'Sullivan N, Cunney R, Drew R. Real-time polymerase chain reaction and culture in the diagnosis of invasive group B streptococcal disease in infants: a retrospective study. Eur J Clin Microbiol Infect Dis. 2015;34:2413–2420.

Mertsola J, Kennedy WA, Waagner D, Sáez-Llorens X, Olsen K, Hansen EJ, McCracken GH Jr. Endotoxin concentrations in cerebrospinal fluid correlate with clinical severity and neurologic outcome of Haemophilus influenzae type B meningitis. Am J Dis Child. 1991 Oct;145(10):1099–103.

Mijovic H, Sadarangani M. To LP or not to LP? Identifying the etiology of pediatric meningitis. Pediatr Infect Dis J. 2019; 38: S39–S42.

Miller L, Arakaki L, Ramautar A, Bodach S, Braunstein SL, Kennedy J, Steiner-Sichel L, Ngai S, Shepard C, Weiss D. Elevated risk for invasive meningococcal disease among persons with HIV. Ann Intern Med. 2014 Jan 7;160(1):30–7.

Mitjà O, Pigrau C, Ruiz I, Vidal X, Almirante B, Planes AM, Molina I, Rodríguez D, Pahissa A. Predictors of mortality and impact of aminoglycosides on outcome in listeriosis in a retrospective cohort study. J Antimicrob Chemother. 2009 Aug;64(2):416–23.

Mittal R, Krishnan S, Gonzalez-Gomez I, Prasadarao NV. Deciphering the roles of outer membrane protein A extracellular loops in the pathogenesis of Escherichia coli K1 meningitis. J Biol Chem. 2011 Jan 21;286(3):2183–93.

Molyneux E, Nizami SQ, Saha S, Huu KT, Azam M, Bhutta ZA, Zaki R, Weber MW, Qazi SA; CSF 5 Study Group. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. Lancet. 2011 May 28;377(9780):1837–45.

Molyneux EM, Kawaza K, Phiri A, Chimalizeni Y, Mankhambo L, Schwalbe E, Kataja M, Pensulo P, Chilton L, Peltola H. Glycerol and acetaminophen as adjuvant therapy did not affect the outcome of bacterial meningitis in Malawian children. Pediatr Infect Dis J. 2014 Feb;33(2):214–6.

Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. Clin Microbiol Rev. 2011 Jul;24(3):557–91.

Morgan BP, Harris CL. Complement, a target for therapy in inflammatory and degenerative diseases. Nat Rev Drug Discov. 2015 Dec;14(12):857–77.

Morshed RA, Young JS, Gogos AJ, Haddad AF, McMahon JT, Molinaro AM, Sudhakar V, Al-Adli N, Hervey-Jumper SL, Berger MS. Reducing complication rates for repeat craniotomies in glioma patients: a single-surgeon experience and comparison with the literature. Acta Neurochir (Wien). 2022 Feb;164(2):405–417.

Morton B, Mitsi E, Pennington SH, Reiné J, Wright AD, Parker R, Welters ID, Blakey JD, Rajam G, Ades EW, Ferreira DM, Wang D, Kadioglu A, Gordon SB. Augmented Passive Immunotherapy with P4 Peptide Improves Phagocyte Activity in Severe Sepsis. Shock. 2016 Dec;46(6):635–641.

Mourvillier B, Tubach F, van de Beek D, Garot D, Pichon N, Georges H, Lefevre LM, Bollaert PE, Boulain T, Luis D, Cariou A, Girardie P, Chelha R, Megarbane B, Delahaye A, Chalumeau-Lemoine L, Legriel S, Beuret P, Brivet F, Bruel C, Camou F, Chatellier D, Chillet P, Clair B, Constantin JM, Duguet A, Galliot R, Bayle F, Hyvernat H, Ouchenir K, Plantefeve G, Quenot JP, Richecoeur J, Schwebel C, Sirodot M, Esposito-Farèse M, Le Tulzo Y, Wolff M. Induced

hypothermia in severe bacterial meningitis: a randomized clinical trial. JAMA. 2013 Nov 27;310(20):2174–83.
Mukai AO, Krebs VL, Bertoli CJ, Okay TS. TNF-alpha and IL-6 in the diagnosis of bacterial and aseptic meningitis in children. Pediatr Neurol. 2006 Jan;34(1):25–9.
Muralidharan R, Mateen FJ, Rabinstein AA. Outcome of fulminant bacterial meningitis in adult patients. Eur J Neurol. 2014 Mar;21(3):447–53.
Muri L, Le ND, Zemp J, Grandgirard D, Leib SL. Metformin mediates neuroprotection and attenuates hearing loss in experimental pneumococcal meningitis. J Neuroinflammation. 2019 Jul 27;16(1):156.
Mustafa MM, Lebel MH, Ramilo O, Olsen KD, Reisch JS, Beutler B, McCracken GH Jr. Correlation of interleukin-1 beta and cachectin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. J Pediatr. 1989 Aug;115(2):208–13.
Müller O, Krawinkel M. Malnutrition and health in developing countries. CMAJ. 2005 Aug 2;173(3):279–86.
Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with Listeria monocytogenes. 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine (Baltimore). 1998 Sep;77(5):313–36.
Natukka T, Raitanen J, Haapasalo H, Auvinen A. Incidence trends of adult malignant brain tumors in Finland, 1990–2016. Acta Oncol. 2019;58:990–996.
Nau R, Blei C, Eiffert H. Intrathecal antibacterial and antifungal therapies. Clin Microbiol Rev 2020; 33:e00190–19.
Nau R, Soto A, Brück W. Apoptosis of neurons in the dentate gyrus in humans suffering from bacterial meningitis. J Neuropathol Exp Neurol. 1999 Mar;58(3):265–74.
Nelson JD (ed). 2019. Nelson's pediatric antimicrobial therapy 2020, 26th ed. American Academy of Pediatrics, Washington, DC.
Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, Dang QT, Nguyen DP, Nguyen HP, To SD, Nguyen vV, Nguyen MD, Campbell J, Schultsz C, Parry C, Torok ME, White N, Nguyen TC, Tran TH, Stepniewska K, Farrar JJ. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med. 2007 Dec 13;357(24):2431–40.
Nigrovic LE, Kuppermann N, Malley R; Bacterial Meningitis Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Children with bacterial meningitis presenting to the emergency department during the pneumococcal conjugate vaccine era. Acad Emerg Med. 2008 Jun;15(6):522–8.
Nigrovic LE, Kuppermann N, Macias CG, Cannavino CR, Moro-Sutherland DM, Schremmer RD, Schwab SH, Agrawal D, Mansour KM, Bennett JE, Katsogridakis YL, Mohseni MM, Bulloch B, Steele DW, Kaplan RL, Herman MI, Bandyopadhyay S, Dayan P, Truong UT, Wang VJ, Bonsu BK, Chapman JL, Kanegaye JT, Malley R; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. JAMA. 2007 Jan 3;297(1):52–60.
Noguchi T, Nagao M, Yamamoto M, Matsumura Y, Kitano T, Takaori-Kondo A, Ichiyama S. Staphylococcus epidermidis meningitis in the absence of a neurosurgical device secondary to catheter-related bloodstream infection: a case report and review of the literature. J Med Case Rep. 2018 Apr 25;12(1):106.
Nusman CM, Snoek L, van Leeuwen LM, Dierikx TH, van der Weijden BM, Achten NB, Bijlsma MW, Visser DH, van Houten MA, Bekker V, de Meij TGJ, van Rossem E, Felderhof M, Plötz FB. Group B *Streptococcus* Early-Onset Disease: New Preventive and Diagnostic Tools to Decrease the Burden of Antibiotic Use. Antibiotics (Basel). 2023 Mar 1;12(3):489.
Oggioni MR, Koedel U. The Glymphatic System: a Potential Key Player in Bacterial Meningitis. mBio. 2022 Dec 20;13(6):e0235022.

Oliveira CR, Morriss MC, Mistrot JG, Cantey JB, Doern CD, Sánchez PJ. Brain magnetic resonance imaging of infants with bacterial meningitis. J Pediatr. 2014 Jul;165(1):134–9.

Oordt-Speets AM, Bolijn R, van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: a systematic review and meta-analysis. PLoS ONE. 2018;13(6):e0198772.

Orihuela CJ, Mahdavi J, Thornton J, Mann B, Wooldridge KG, Abouseada N, Oldfield NJ, Self T, Ala'Aldeen DA, Tuomanen EI. Laminin receptor initiates bacterial contact with the blood brain barrier in experimental meningitis models. J Clin Invest. 2009 Jun;119(6):1638–46.

Ouchenir L, Renaud C, Khan S, Bitnun A, Boisvert AA, McDonald J, Bowes J, Brophy J, Barton M, Ting J, Roberts A, Hawkes M, Robinson JL. The Epidemiology, Management, and Outcomes of Bacterial Meningitis in Infants. Pediatrics. 2017 Jul;140(1):e20170476.

Pachter JS, de Vries HE, Fabry Z. The blood-brain barrier and its role in immune privilege in the central nervous system. J Neuropathol Exp Neurol. 2003 Jun;62(6):593–604.

Paireau J, Chen A, Broutin H, Grenfell B, Basta NE. Seasonal dynamics of bacterial meningitis: a time-series analysis. Lancet Glob Health. 2016;4(6):e370–377.

Panic H, Gjurasin B, Santini M, Kutlesa M, Papic N. Etiology and Outcomes of Healthcare-Associated Meningitis and Ventriculitis-A Single Center Cohort Study. Infect Dis Rep. 2022 Jun 3;14(3):420–427.

Pascucci MG, Di Gregori V, Frasca G, Rucci P, Finarelli AC, Moschella L, Borrini BM, Cavrini F, Liguori G, Sambri V, Bonanni P, Fantini MP. Impact of meningococcal C conjugate vaccination campaign in Emilia-Romagna, Italy. Hum Vaccin Immunother. 2014;10(3):671–6.

Paul R, Lorenzl S, Koedel U, Sporer B, Vogel U, Frosch M, Pfister HW. Matrix metalloproteinases contribute to the blood-brain barrier disruption during bacterial meningitis. Ann Neurol. 1998 Oct;44(4):592–600.

Pelkonen T, Roine I, Cruzeiro ML, 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 Aug;11(8):613–21.

Peltola H, Kilpi T, Anttila M. Rapid disappearance of Haemophilus influenzae type b meningitis after routine childhood immunisation with conjugate vaccines. Lancet. 1992;340:592–4.

Perez-Alba E, Bocanegra-Ibarias P, Garza-González E, Martínez-Ponce de León ÁR, Delgado-Brito M, Camacho-Ortiz A. Comment on: Multidrug-resistant Acinetobacter meningitis in neurosurgical patients with intraventricular catheters: assessment of different treatments. J Antimicrob Chemother. 2020 Mar 1;75(3):781–782.

Perry VL, Young RS, Aquila WJ, During MJ. Effect of experimental Escherichia coli meningitis on concentrations of excitatory and inhibitory amino acids in the rabbit brain: in vivo microdialysis study. Pediatr Res. 1993 Aug;34(2):187–91.

Polkowska A, Rinta-Kokko H, Toropainen M, Palmu AA, Nuorti JP. Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland. Vaccine. 2021 May 27;39(23):3216–3224.

Polkowska A, Toropainen M, Ollgren J, Lyytikäinen O, Nuorti JP. Bacterial meningitis in Finland, 1995–2014: a population-based observational study. BMJ Open. 2017;7(5):e015080.

Portnoy A, Jit M, Lauer J, Blommaert A, Ozawa S, Stack M, Murray J, Hutubessy R. Estimating costs of care for meningitis infections in low- and middle-income countries. Vaccine. 2015 May 7;33 Suppl 1:A240–7.

Prasad R, Kapoor R, Srivastava R, Mishra OP, Singh TB. Cerebrospinal fluid TNF-α, IL-6, and IL-8 in children with bacterial meningitis. Pediatr Neurol. 2014 Jan;50(1):60–5.

Prasadarao NV, Wass CA, Stins MF, Shimada H, Kim KS. Outer membrane protein A-promoted actin condensation of brain microvascular endothelial cells is required for Escherichia coli invasion. Infect Immun. 1999 Nov;67(11):5775–83.

Proulx N, Fréchette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM. 2005 Apr;98(4):291–8.

Puopolo KM, Lynfield R, Cummings JJ; COMMITTEE ON FETUS AND NEWBORN; COMMITTEE ON INFECTIOUS DISEASES. Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics. 2019 Aug;144(2):e20191881.

Ramchandar N, Coufal NG, Warden AS, Briggs B, Schwarz T, Stinnett R, Xie H, Schlaberg R, Foley J, Clarke C, Waldeman B, Enriquez C, Osborne S, Arrieta A, Salyakina D, Janvier M, Sendi P, Totapally BR, Dimmock D, Farnaes L. Metagenomic Next-Generation Sequencing for Pathogen Detection and Transcriptomic Analysis in Pediatric Central Nervous System Infections. Open Forum Infect Dis. 2021 Mar 6;8(6):ofab104.

Ravikumar V, Ho AL, Pendhakar AV, Sussman ES, Chow KK, Li G. The Use of Vancomycin Powder for Surgical Prophylaxis Following Craniotomy. Neurosurgery. 2017;80:754–758.

Raymond J, Lopez E, Bonacorsi S, Poyart C, Moriette G, Jarreau PH, Bingen E. Evidence for transmission of Escherichia coli from mother to child in late-onset neonatal infection. Pediatr Infect Dis J. 2008 Feb;27(2):186–8.

Reichert MC, Medeiros EA, Ferraz FA. Hospital-acquired meningitis in patients undergoing craniotomy: incidence, evolution, and risk factors. Am J Infect Control. 2002 May;30(3):158–64.

Ribes S, Taberner F, Domenech A, Cabellos C, Tubau F, Liñares J, Fernández Viladrich P, Gudiol F. Evaluation of ceftriaxone, vancomycin and rifampicin alone and combined in an experimental model of meningitis caused by highly cephalosporin-resistant Streptococcus pneumoniae ATCC 51916. J Antimicrob Chemother. 2005 Nov;56(5):979–82.

Ridpath AD, Halse TA, Musser KA, Wroblewski D, Paddock CD, Shieh WJ, Pasquale-Styles M, Scordi-Bello I, Del Rosso PE, Weiss D. Postmortem diagnosis of invasive meningococcal disease. Emerg Infect Dis. 2014 Mar;20(3):453–5.

Robbins JB, McCracken GH Jr, Gotschlich EC, Orskov F, Orskov I, Hanson LA. Escherichia coli K1 capsular polysaccharide associated with neonatal meningitis. N Engl J Med. 1974 May 30;290(22):1216–20.

Robinson CP, Busl KM. Meningitis and encephalitis management in the ICU. Curr Opin Crit Care. 2019;25:423–429.

Roed C, Omland LH, Skinhoj P, Rothman KJ, Sorensen HT, Obel N. Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis. JAMA. 2013 Apr 24;309(16):1714–21.

Rouphael NG, Stephens DS. Neisseria meningitidis: biology, microbiology, and epidemiology. Methods Mol Biol. 2012;799:1–20.

Saha SK, Khan NZ, Ahmed AS, Amin MR, Hanif M, Mahbub M, Anwar KS, Qazi SA, Kilgore P, Baqui AH; Meningitis Study Group Bangladesh. Neurodevelopmental sequelae in pneumococcal meningitis cases in Bangladesh: a comprehensive follow-up study. Clin Infect Dis. 2009 Mar 1;48 Suppl 2:S90–6.

Saha SK, Darmstadt GL, Yamanaka N, Billal DS, Nasreen T, Islam M, Hamer DH. Rapid diagnosis of pneumococcal meningitis: implications for treatment and measuring disease burden. Pediatr Infect Dis J. 2005 Dec;24(12):1093–8.

Salamat S, Fischer D, van der Linden M, Buxmann H, Schlösser R. Neonatal group B streptococcal septicemia transmitted by contaminated breast milk, proven by pulsed field gel electrophoresis in 2 cases. Pediatr Infect Dis J. 2014 Apr;33(4):428.

Salle H, Deluche E, Couvé-Deacon E, Beaujeux AC, Pallud J, Roux A, Dagain A, de Barros A, Voirin J, Seizeur R, Belmabrouk H, Lemnos L, Emery E, Fotso MJ, Engelhardt J, Jecko V, Zemmoura I, Le Van T, Berhouma M, Cebula H, Peyre M, Preux PM, Caire F. Surgical Site Infections after glioblastoma surgery: results of a multicentric retrospective study. Infection. 2021 Apr;49(2):267–275.

Sari ND, Baltali S, Serin I, Antar V. Evaluation of Intraventricular/Intrathecal Antimicrobial Therapy in the Treatment of Nosocomial Meningitis Caused by Multidrug-Resistant Gram-Negative Bacteria after Central Nervous System Surgery. Can J Infect Dis Med Microbiol. 2021 Aug 27;2021:9923015.

Schaper M, Gergely S, Lykkesfeldt J, Zbären J, Leib SL, Täuber MG, Christen S. Cerebral vasculature is the major target of oxidative protein alterations in bacterial meningitis. J Neuropathol Exp Neurol. 2002 Jul;61(7):605–13.

Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis. 2002 Dec 1;186 Suppl 2:S225–33.

Schlech WF 3rd, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study. JAMA. 1985 Mar 22-29;253(12):1749–54.

Schneider O, Michel U, Zysk G, Dubuis O, Nau R. Clinical outcome in pneumococcal meningitis correlates with CSF lipoteichoic acid concentrations. Neurology. 1999 Oct 22;53(7):1584–7.

Schweppe DK, Harding C, Chavez JD, Wu X, Ramage E, Singh PK, Manoil C, Bruce JE. Host-Microbe Protein Interactions during Bacterial Infection. Chem Biol. 2015 Nov 19;22(11):1521–1530.

Sgro M, Shah PS, Campbell D, Tenuta A, Shivananda S, Lee SK; Canadian Neonatal Network. Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008. J Perinatol. 2011 Dec;31(12):794–8.

Sheldon JR, Laakso HA, Heinrichs DE. Iron Acquisition Strategies of Bacterial Pathogens. Microbiol Spectr. 2016 Apr;4(2).

Sherwin R, Winters ME, Vilke GM, Wardi G. Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? J Emerg Med. 2017 Oct;53(4):588–595.

Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014 Jan;27(1):21–47.

Smani Y, Fàbrega A, Roca I, Sánchez-Encinales V, Vila J, Pachón J. Role of OmpA in the multidrug resistance phenotype of Acinetobacter baumannii. Antimicrob Agents Chemother. 2014;58(3):1806–8.

Snaebjarnardóttir K, Erlendsdóttir H, Reynisson IK, Kristinsson K, Halldórsdóttir S, Hardardóttir H, Gudnason T, Gottfredsson M, Haraldsson Á. Bacterial meningitis in children in Iceland, 1975–2010: a nationwide epidemiological study. Scand J Infect Dis. 2013 Nov;45(11):819–24.

Sonabend AM, Korenfeld Y, Crisman C, Badjatia N, Mayer SA, Connolly ES Jr. Prevention of ventriculostomy-related infections with prophylactic antibiotics and antibiotic-coated external ventricular drains: a systematic review. Neurosurgery. 2011 Apr;68(4):996–1005.

Spranger M, Schwab S, Krempien S, Winterholler M, Steiner T, Hacke W. Excess glutamate levels in the cerebrospinal fluid predict clinical outcome of bacterial meningitis. Arch Neurol. 1996 Oct;53(10):992–6.

Sridhar S, Greenwood B, Head C, Plotkin SA, Sáfadi MA, Saha S, Taha MK, Tomori O, Gessner BD. Global incidence of serogroup B invasive meningococcal disease: a systematic review. Lancet Infect Dis. 2015 Nov;15(11):1334–46.

Stephani C, Choi AHK, Moerer O. Point-of-care detection of lactate in cerebrospinal fluid. Intensive Care Med Exp. 2021 Apr 6;9(1):18.

Stevens JP, Lively A, Jerris R, Yildirim I, Lantis P. Recognition and outcomes of pneumococcal meningitis in 2 tertiary pediatric hospitals since the introduction of the 13- valent pneumococcal conjugate vaccine. Pediatr Emerg Care. 2022;38:e354–9.

Sunwoo JS, Shin HR, Lee HS, Moon J, Lee ST, Jung KH, Park KI, Jung KY, Kim M, Lee SK, Chu K. A hospital-based study on etiology and prognosis of bacterial meningitis in adults. Sci Rep. 2021 Mar 16;11(1):6028.

Svendsen MB, Ring Kofoed I, Nielsen H, Schønheyder HC, Bodilsen J. Neurological sequelae remain frequent after bacterial meningitis in children. Acta Paediatr. 2020;109:361–7.

Swanson D. Meningitis. Pediatr Rev. 2015 Dec;36(12):514–24.

Tann CJ, Martinello KA, Sadoo S, Lawn JE, Seale AC, Vega-Poblete M, Russell NJ, Baker CJ, Bartlett L, Cutland C, Gravett MG, Ip M, Le Doare K, Madhi SA, Rubens CE, Saha SK, Schrag S, Sobanjo-Ter Meulen A, Vekemans J, Heath PT; GBS Neonatal Encephalopathy Investigator Group.

Neonatal Encephalopathy With Group B Streptococcal Disease Worldwide: Systematic Review, Investigator Group Datasets, and Meta-analysis. Clin Infect Dis. 2017 Nov 6;65(suppl_2):S173–S189.

Tavares T, Pinho L, Bonifácio Andrade E. Group B Streptococcal Neonatal Meningitis. Clin Microbiol Rev. 2022 Apr 20;35(2):e0007921.

Tazi A, Disson O, Bellais S, Bouaboud A, Dmytruk N, Dramsi S, Mistou MY, Khun H, Mechler C, Tardieux I, Trieu-Cuot P, Lecuit M, Poyart C. The surface protein HvgA mediates group B streptococcus hypervirulence and meningeal tropism in neonates. J Exp Med. 2010 Oct 25;207(11):2313–22.

Tenenbaum T, Bloier C, Adam R, Reinscheid DJ, Schroten H. Adherence to and invasion of human brain microvascular endothelial cells are promoted by fibrinogen-binding protein FbsA of Streptococcus agalactiae. Infect Immun. 2005 Jul;73(7):4404–9.

Tenenbaum T, Spellerberg B, Adam R, Vogel M, Kim KS, Schroten H. Streptococcus agalactiae invasion of human brain microvascular endothelial cells is promoted by the laminin-binding protein Lmb. Microbes Infect. 2007 May;9(6):714–20.

Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, Harrison LH, Farley MM, Reingold A, Bennett NM, Craig AS, Schaffner W, Thomas A, Lewis MM, Scallan E, Schuchat A; Emerging Infections Programs Network. Bacterial meningitis in the United States, 1998–2007. N Engl J Med. 2011 May 26;364(21):2016–25.

Thomas KE, Hasbun R, Jekel J, Quagliarello VJ. The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. Clin Infect Dis. 2002 Jul 1;35(1):46–52.

Tian R, Hao S, Hou Z, Gao Z, Liu B. The characteristics of post-neurosurgical bacterial meningitis in elective neurosurgery in 2012: A single institute study. Clin Neurol Neurosurg. 2015;139:41–45.

Tibussek D, Sinclair A, Yau I, Teatero S, Fittipaldi N, Richardson SE, Mayatepek E, Jahn P, Askalan R. Late-onset group B streptococcal meningitis has cerebrovascular complications. J Pediatr. 2015 May;166(5):1187–1192.

Tiku V. Acinetobacter baumannii: Virulence Strategies and Host Defense Mechanisms. DNA Cell Biol. 2022 Jan;41(1):43–48.

Tsimogianni A, Alexandropoulos P, Chantziara V, Vassi A, Micha G, Lagiou F, Chinou E, Michaloudis G, Georgiou S. Intrathecal or intraventricular administration of colistin, vancomycin and amikacin for central nervous system infections in neurosurgical patients in an intensive care unit. Int J Antimicrob Agents. 2017 Mar;49(3):389–390.

Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld WM, van de Beek D, Bleck TP, Garton HJL, Zunt JR. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis. 2017 Mar 15;64(6):e34–e65.

Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004 Nov 1;39(9):1267–84.

Ueda NK, Nakamura K, Go H, Takehara H, Kashiwabara N, Arai K, Takemura H, Namai Y, Kanemitsu K. Neonatal meningitis and recurrent bacteremia with group B Streptococcus transmitted by own mother's milk: A case report and review of previous cases. Int J Infect Dis. 2018 Sep;74:13–15.

Unkmeir A, Latsch K, Dietrich G, Wintermeyer E, Schinke B, Schwender S, Kim KS, Eigenthaler M, Frosch M. Fibronectin mediates Opc-dependent internalization of Neisseria meningitidis in human brain microvascular endothelial cells. Mol Microbiol. 2002 Nov;46(4):933–46.

Valdoleiros SR, Torrão C, Freitas LS, Mano D, Gonçalves C, Teixeira C. Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review. Acute Crit Care. 2022 Feb;37(1):61–70.

van de Beek D, Brouwer M, Hasbun R, Koedel U, Whitney CG, Wijdicks E. Community-acquired bacterial meningitis. Nat Rev Dis Primers. 2016 Nov 3;2:16074. A.

van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351(18):1849–1859. A.

van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. N Engl J Med. 2010 Jan 14;362(2):146–54. A.

van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC; ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016 May;22 Suppl 3:S37–62. B.

van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006 Jan 5;354(1):44–53. A.

van de Beek D, de Gans J. Dexamethasone and pneumococcal meningitis. Ann Intern Med. 2004 Aug 17;141(4):327.

van de Beek D, Farrar JJ, de Gans J, Mai NT, Molyneux EM, Peltola H, Peto TE, Roine I, Scarborough M, Schultsz C, Thwaites GE, Tuan PQ, Zwinderman AH. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol. 2010 Mar;9(3):254–63. B.

van de Beek D, Schmand B, de Gans J, Weisfelt M, Vaessen H, Dankert J, Vermeulen M. Cognitive impairment in adults with good recovery after bacterial meningitis. J Infect Dis. 2002 Oct 1;186(7):1047–52.

van de Beek D, de Gans J, McIntyre P, Prasad K. Steroids in adults with acute bacterial meningitis: a systematic review. Lancet Infect Dis. 2004 Mar;4(3):139–43. B.

van de Beek D, Weisfelt M, de Gans J, Tunkel AR, Wijdicks EF. Drug Insight: adjunctive therapies in adults with bacterial meningitis. Nat Clin Pract Neurol. 2006 Sep;2(9):504–16. B.

van Furth AM, Roord JJ, van Furth R. Roles of proinflammatory and anti-inflammatory cytokines in pathophysiology of bacterial meningitis and effect of adjunctive therapy. Infect Immun. 1996 Dec;64(12):4883–90.

van Soest TM, Chekrouni N, van Sorge NM, Brouwer MC, van de Beek D. Bacterial meningitis presenting with a normal cerebrospinal fluid leukocyte count. J Infect. 2022;84:615–620.

van Loon MC, Hensen EF, de Foer B, Smit CF, Witte B, Merkus P. Magnetic resonance imaging in the evaluation of patients with sensorineural hearing loss caused by meningitis: implications for cochlear implantation. Otol Neurotol. 2013 Jul;34(5):845–54.

Vasilopoulou VA, Karanika M, Theodoridou K, Katsioulis AT, Theodoridou MN, Hadjichristodoulou CS. Prognostic factors related to sequelae in childhood bacterial meningitis: data from a Greek meningitis registry. BMC Infect Dis. 2011 Aug 10;11:214.

Vekemans J, Moorthy V, Friede M, Alderson MR, Sobanjo-Ter Meulen A, Baker CJ, Heath PT, Madhi SA, Mehring-Le Doare K, Saha SK, Schrag S, Kaslow DC. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. Vaccine. 2019 Nov 28;37(50):7391–7393.

Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1–36.

Vergouwen MD, Schut ES, Troost D, van de Beek D. Diffuse cerebral intravascular coagulation and cerebral infarction in pneumococcal meningitis. Neurocrit Care. 2010 Oct;13(2):217–27.

Vila J, Sáez-López E, Johnson JR, Römling U, Dobrindt U, Cantón R, Giske CG, Naas T, Carattoli A, Martínez-Medina M, Bosch J, Retamar P, Rodríguez-Baño J, Baquero F, Soto SM. Escherichia coli: an old friend with new tidings. FEMS Microbiol Rev. 2016 Jul 1;40(4):437–463.

von Gottberg A, de Gouveia L, Tempia S, Quan V, Meiring S, von Mollendorf C, Madhi SA, Zell ER, Verani JR, O'Brien KL, Whitney CG, Klugman KP, Cohen C; GERMS-SA Investigators. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med. 2014 Nov 13;371(20):1889–99.

Wall EC, Chan JM, Gil E, Heyderman RS. Acute bacterial meningitis. Curr Opin Neurol. 2021 Jun 1;34(3):386–395.

Wall EC, Everett DB, Mukaka M, Bar-Zeev N, Feasey N, Jahn A, Moore M, van Oosterhout JJ, Pensalo P, Baguimira K, Gordon SB, Molyneux EM, Carrol ED, French N, Molyneux ME, Heyderman RS. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and Haemophilus influenzae type b vaccination, 2000–2012. Clin Infect Dis. 2014 May;58(10):e137–45.

Watt JP, Wolfson LJ, O'Brien KL, Henkle E, Deloria-Knoll M, McCall N, Lee E, Levine OS, Hajjeh R, Mulholland K, Cherian T; Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. Lancet. 2009 Sep 12;374(9693):903–11.

Weber JR, Tuomanen EI. Cellular damage in bacterial meningitis: an interplay of bacterial and host driven toxicity. J Neuroimmunol. 2007 Mar;184(1–2):45–52.

Welinder-Olsson C, Dotevall L, Hogevik H, Jungnelius R, Trollfors B, Wahl M, Larsson P. Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis. Clin Microbiol Infect. 2007 Sep;13(9):879–86.

Whiteside SA, Razvi H, Dave S, Reid G, Burton JP. The microbiome of the urinary tract--a role beyond infection. Nat Rev Urol. 2015 Feb;12(2):81–90.

Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, Facklam RR, Jorgensen JH, Schuchat A; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003 May 1;348(18):1737–46.

Wilson MR, Sample HA, Zorn KC, Arevalo S, Yu G, Neuhaus J, Federman S, Stryke D, Briggs B, Langelier C, Berger A, Douglas V, Josephson SA, Chow FC, Fulton BD, DeRisi JL, Gelfand JM, Naccache SN, Bender J, Dien Bard J, Murkey J, Carlson M, Vespa PM, Vijayan T, Allyn PR, Campeau S, Humphries RM, Klausner JD, Ganzon CD, Memar F, Ocampo NA, Zimmermann LL, Cohen SH, Polage CR, DeBiasi RL, Haller B, Dallas R, Maron G, Hayden R, Messacar K, Dominguez SR, Miller S, Chiu CY. Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. N Engl J Med. 2019 Jun 13;380(24):2327–2340.

Wolburg H, Paulus W. Choroid plexus: biology and pathology. Acta Neuropathol. 2010 Jan;119(1):75–88.

Worsøe L, Cayé-Thomasen P, Brandt CT, Thomsen J, Østergaard C. Factors associated with the occurrence of hearing loss after pneumococcal meningitis. Clin Infect Dis. 2010 Oct 15;51(8):917–24.

Yikilmaz A, Taylor GA. Sonographic findings in bacterial meningitis in neonates and young infants. Pediatr Radiol. 2008 Feb;38(2):129–37.

Yu JC, Khodadadi H, Malik A, Davidson B, Salles ÉDSL, Bhatia J, Hale VL, Baban B. Innate Immunity of Neonates and Infants. Front Immunol. 2018 Jul 30;9:1759.

Zaleznik DF, Rench MA, Hillier S, Krohn MA, Platt R, Lee ML, Flores AE, Ferrieri P, Baker CJ. Invasive disease due to group B Streptococcus in pregnant women and neonates from diverse population groups. Clin Infect Dis. 2000 Feb;30(2):276–81.

Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. Cochrane Database Syst Rev. 2013 Oct 25;2013(10):CD004785.

Zheng G, Li S, Zhao M, Yang X, Zhang Y, Deng J, Luo Y, Lv H, Zhang G. Time to positive culture can differentiate post-neurosurgical coagulase-negative Staphylococci other than S epidermidis meningitis from contamination: A case-control observational study. J Clin Lab Anal. 2020 Oct;34(10):e23447.

Zhu J, Qiu X, Ji C, Wang F, Tao A, Chen L. Frailty as a predictor of neurosurgical outcomes in brain tumor patients: A systematic review and meta-analysis. Front Psychiatry. 2023;14:1126123.

Original Publications

Niemelä S, Lempinen L, Löyttyniemi E, Oksi J & Jero J (2023)
Bacterial meningitis in adults: a retrospective study among 148 patients in an 8-year period in a university hospital, Finland.
BMC Infect Dis

I

BMC Infectious Diseases

RESEARCH Open Access

Bacterial meningitis in adults: a retrospective study among 148 patients in an 8-year period in a university hospital, Finland

Sakke Niemelä[1*], Laura Lempinen[2], Eliisa Löyttyniemi[3], Jarmo Oksi[4] and Jussi Jero[5]

Abstract

Background Bacterial meningitis (BM) causes significant morbidity and mortality. We investigated predisposing factors, clinical characteristics, spectrum of etiological bacteria, and clinical outcome of community-acquired and nosocomial BM.

Methods In this retrospective study we analyzed data of 148 adults (age > 16 years) with BM treated in Turku University Hospital, Southwestern Finland, from 2011 to 2018. Besides culture- or polymerase chain reaction (PCR)-positive cases we also included culture-negative cases with laboratory parameters strongly suggestive of BM and those with meningitis-related findings in imaging. We used Glasgow Outcome Scale (GOS) score 1–4 to determine unfavorable outcome.

Results The median age of patients was 57 years and 48.6% were male. Cerebrospinal fluid (CSF) culture for bacteria showed positivity in 50 (33.8%) cases, although pre-diagnostic antibiotic use was frequent (85, 57.4%). The most common pathogens in CSF culture were *Streptococcus pneumoniae* (11, 7.4%), *Staphylococcus epidermidis* (7, 4.7%), *Staphylococcus aureus* (6, 4.1%) and *Neisseria meningitidis* (6, 4.1%). Thirty-nine patients (26.4%) presented with the triad of fever, headache, and neck stiffness. A neurosurgical procedure or an acute cerebral incident prior BM was recorded in 74 patients (50%). Most of the patients had nosocomial BM (82, 55.4%) and the rest (66, 44.6%) community-acquired BM. Ceftriaxone and vancomycin were the most used antibiotics. Causative pathogens had resistances against the following antibiotics: cefuroxime with a frequency of 6.8%, ampicillin (6.1%), and tetracycline (6.1%). The case fatality rate was 8.8% and the additional likelihood of unfavorable outcome 40.5%. Headache, decreased general condition, head computed tomography (CT) and magnetic resonance imaging (MRI), hypertension, altered mental status, confusion, operative treatment, neurological symptoms, pre-diagnostic antibiotic use and oral antibiotics on discharge were associated with unfavorable outcome.

Conclusions The number of cases with nosocomial BM was surprisingly high and should be further investigated. The usage of pre-diagnostic antibiotics was also quite high. Headache was associated with unfavorable outcome. The frequency of unfavorable outcome of BM was 40.5%, although mortality in our patients was lower than in most previous studies.

Keywords Bacterial meningitis, Adults, Nosocomial, Glasgow Outcome Scale

*Correspondence:
Sakke Niemelä
sasani@utu.fi
Full list of author information is available at the end of the article

Background

Bacterial meningitis (BM) is a severe, life-threatening infection, which causes notable morbidity and mortality [1]. Meningitis has many etiologies: bacteria, fungi, viruses, and parasites or additionally it may be associated with cancerous conditions, medications or autoimmune diseases [2]. Worldwide number of BM cases may exceed 16 million cases, [3] with mortality up to 30% as estimated a few years ago [2, 4, 5].

BM can be classified into two groups; nosocomial (including postoperative BM) or community acquired [6]. The usage of conjugate vaccines during childhood against *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae B*, has significantly diminished the overall incidence of BM worldwide [7, 8]. *S. epidermidis* and *S. aureus* have been the main Gram stain positive cocci causing nosocomial meningitis [9]. Recently, however, the proportion of Gram stain negative bacteria such as *Acinetobacter baumannii, Klebsiella pneumoniae* and *Escherichia coli* has increased [10, 11]. BM cases rose between 2006 and 2016 with poverty being a strong predisposing factor [2]. The geographical location affects the incidence significantly though; in well-developed countries the incidence has been lately 0.5–1.5/100,000/year [12–14], but in developing countries the incidence may peak at even 1000/100,000 cases [2] due to epidemics [15–18].

The incidence is highest among young children and the elderly [6]. In the past 20 years the incidence, management and epidemiology of BM has changed [7]. The risk factors of BM consist of immunosuppression, human immunodeficiency virus (HIV)-infection [19], indoor air pollution [20], overcrowded houses [21], malnutrition [22] and sickle cell anemia [23]. The typical symptom triad of meningitis consists of headache, fever and meningismus [6]. Meningitis requires instant treatment and intense medical attention. In recent years the use of adjunctive dexamethasone with antibiotics has been associated to lower incidence of neurologic sequelae in survivors [6]. The diagnosis of meningitis is confirmed by cerebrospinal fluid (CSF) culture or polymerase chain reaction (PCR) on the CSF specimen [6]. Survivors of BM often present a variety of neurological difficulties afterwards, such as hearing loss and deafness, cognitive impairment, motor deficiencies, seizures, and paralysis [24].

Our aim was to study the epidemiology of BM in Southwestern Finland and the significance of possible predisposing factors and indicators of unfavorable outcome.

Methods

The medical records of all patients over 16 years (n = 148) treated between 2011 and 2018 due to BM at Turku University Hospital, a tertiary referral center in the hospital district of Southwest Finland (480,000 inhabitants), were retrospectively reviewed.

We performed a database search with International Classification of Diseases 10th Revision (ICD-10)—codes for meningitis (Table 1 legend). From 747 hits we excluded all viral and aseptic meningitis by going through clinical findings of all patients, test results on blood and CSF specimens, and analysis of imaging data one by one. Finally, 148 adults were included with all types of BM: nosocomial and community-acquired. BM was defined nosocomial, if the patient was already admitted to hospital when developing BM or, if there was a history of surgery in the preceding 54 days. BM was defined community-acquired if the patient had no history of surgery or hospitalization during the preceding 54 days. Most of the published studies on BM has collected data on only CSF culture-positive meningitis, although it is known that a considerable proportion of BM cases may be culture-negative especially with antibiotics given prediagnosis [25]. In this study, besides culture- or PCR-positive cases we included cases with symptomatology of BM with neutrophilic pleocytosis and at least one of the following: decreased CSF glucose levels (< 2.2 mmol/L), high protein levels (> 1000 mg/L) or high CSF lactate levels (> 3.0 mmol/L), and those with meningitis-related findings in imaging. Neuroborreliosis cases were excluded. All methods of data collection remained consistent through 2011–2018.

A minimum of 2 ml CSF was gathered from adult patients with suspected BM. First, the appropriate chemical and cytological analyses were performed and a Gram staining was performed to screen the potentials bacterial pathogens. Then, the samples were centrifuged (2500*g*) for 15 min, and a drop of sediment was spread over culture media—chocolate agar plates and sheep blood agar plates. Moreover, a drop of sediment was added into fastidious anaerobe broth (FAB). Also, if postoperative BM was suspected, a fastidious anaerobe agar (FAA) plate was cultured. The aerobic media were incubated at 35 °C in 5% CO2 atmosphere. The aerobic plates and FAB were read on the first and second day after the inoculation. If no growth was detected, negative result was given. The FAA plates were read on the second and fourth day after the inoculation, after which the negative result was given if no growth was detected. The media were further incubated until total 7 days, and if growth was detected at that point, the clinician was informed.

When growth was detected on any media, the pathogens were identified with matrix-assisted laser-desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry (MALDI Biotyper® System, Bruker Daltonics, Bremen, Germany).

Table 1 Baseline characteristics, underlying conditions, associated background infections, and signs and symptoms of patients with BM

Variable	BM patients n = 148
Demographics	
Age (years)	57.3 (median)
Men	72 (48.6%)
Finnish nationality	145 (98%)
Predisposing conditions	
Sinusitis	7 (4.7%)
Otitis	9 (6.1%)
Dental infection	9 (6.1%)
Neurosurgery-related infection	74 (50%)
Brain abscess	6 (4.1%)
Urinary tract infection	3 (2%)
Recurrent meningitis	7 (4.7%)
Smoking	21 (14.2%)
Alcohol overuse	18 (12.2%)
Sepsis	42 (28.4%)
Cancer	22 (14.9%)
Diabetes (type I and II)	17 (11.5%)
Hypertension	44 (29.7%)
Asthma	7 (4.7%)
Previous operative treatment	67 (45.3%)
Mental disability	1 (0.7%)
Respiratory infections	
Pneumonia	15 (10.1%)
Bronchitis	1 (0.7%)
Aspergillosis	1 (0.7%)
Upper respiratory	15 (10.1%)
Tonsillitis	1 (0.7%)
Skin infections	
Head area	11 (7.4%)
Other	11 (7.4%)
History of acute illness	
Seizures prior admission to hospital	8 (5.4%)
Pre-diagnostic antibiotic	85 (57.4%)
Pre-diagnostic corticosteroids	33 (22.3%)
Clinical findings at admission to hospital	
Decreased general condition	90 (60.8%)
Decreased consciousness	62 (41.9%)
Fever	123 (83.1%)
Headache	83 (56.1%)
Neck stiffness	73 (49.3%)
Triad of fever, headache, and neck stiffness	39 (26.4%)
Triad of fever, neck stiffness and altered mental status	20 (13.5%)
Vomiting	36 (24.3%)
Skin color change	12 (8.1%)
Confusion	58 (39.2%)
Aphasia or dysphasia	13 (8.8%)
Visual deviation	3 (2%)
Psychic retardation	3 (2%)
Pupil-asymmetry	3 (2%)
Babinski sign	2 (1.4%)
Nystagmus	2 (1.4%)
Eyes-fixed-gaze	2 (1.4%)
Hearing loss	1 (0.7%)
Dysarthria	1 (0.7%)
Vertigo	1 (0.7%)
Double vision	1 (0.7%)
Strabismus	1 (0.7%)
ICD-10 codes* for data search for BM	

*A87.9, B94.80, G00.9, G01*A32.1, G01*A39.0, G01*A69.2, G05.2*B83.2, A17.0, A32.1, A87, B01.0+, B02.1, B05.1+, B37.5, B38.4+, B45.1, B94.80, G00, G01, G02, G03, G05

Species-specific PCR-methods were not available for bacteria in our hospital. When requested by the clinician, general PCR for bacteria (16S rRNA—ribosomal ribonucleic acid-sequencing) was used to identify bacterial pathogens from CSF. Bacterial deoxyribonucleic acid (DNA) was isolated in our laboratory and sent for sequencing to Eurofins Genomics laboratory (Ebersberg, Germany) and the resulting DNA sequence was compared with BLAST-software (https://blast.ncbi.nlm.nih.gov) to GeneBank database.

Blood culture samples were collected into Bactec™ Plus Aerobic/F and Bactec™ Plus anaerobic/F bottles (BD Diagnostic Systems, Sparks, Maryland, USA). The bottles were incubated in Bactec™ 9240 or Bactec™ FX culture system (BD Diagnostic Systems), for 120 h or until signaled positive. The bacteria were identified by MALDI Biotyper® System (Bruker Daltonics, Bremen, Germany).

Disk diffusion, minimum inhibitory concentration (MIC) gradient -method and the VITEK® 2 Compact automated ID/AST system (bioMerieux E-test) were used to analyze susceptibility to variety of antibiotics. The results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

Imaging data was interpreted by radiologists. Patients with meningitis-related findings in imaging according to radiologists were included.

We defined a scale on outcome with Glasgow Outcome Scale (GOS-1 = death, 2 = vegetative state—unable to interact with the environment, 3 = severe disability—unable to live independently, 4 = moderate disability—can live independently but unable to return to previous work, 5 = mild or no disability) at discharge. Unfavorable outcome was chosen to be scores 1–4.

Statistical analysis

The categorical variables are summarized with counts and percentages (%), continuous variables with range, mean for normally distributed variable or median otherwise.

To find out factors affecting to unfavorable outcome (GOS scores 1–4), log binomial model was performed separately for each factor (univariate approach) and reported with relative risk (and it's 95% confidence intervals, CI) together with p-value. All tested factors are presented in Additional file 1.

Association with two categorical variables was tested with Fisher's exact test.

The data analysis was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Background

The medical records of 148 adults with BM were included in this study. There were 72 (48.6%) males and 76 (51.4%) females. Median age was 57.3 years (range 16–95). Almost all (145, 98%) of patients were of Finnish nationality. Baseline characteristics, underlying conditions, associated background infections, and signs and symptoms of patients on admission are presented in Table 1. The age distribution is presented in Fig. 1.

Most patients were first contacted with hospital emergency department (120, 81.1%) and some to local health center (24, 16.2%) and a few with private medical clinics (4, 2.7%). Most individuals had nosocomial BM (82, 55.4%) and the rest (66, 44.6%) community-acquired BM. Neurosurgical procedure or acute cerebral incident prior BM were seen in 74 patients (50%). Forty-nine patients (33.1%) had no previous infection or operation. Nine patients (6.1%) had otogenic, another 9 patients (6.1%) odontogenic, and seven patients (4.7%) sinonasal etiology of BM. Seven patients (4.7%) had recurrent BM. Almost all cases were diagnosed in the hospital district of Southwest Finland (139, 93.9%), but 9 patients (6.1%) were transferred to our hospital from regional hospitals elsewhere. Vaccination coverage was poorly mentioned in the patient records, only one (0.7%) was reported to having received all vaccinations in the Finnish national vaccination program.

Active cancer, diabetes, lower and upper respiratory infections, excessive alcohol use, smoking, and skin infections were frequent (Table 1.) Sixty-seven patients (45.3%) had previous surgery and two (1.4%) of them were ear related.

Clinical picture

The median length of symptoms before admission to hospital was one day (mean 2.34; range 0–30 days). Eight patients (5.4%) had previous seizures (3 generalized, 1 focal, 4 undefined) prior admission to hospital. In the emergency department 8 (5.4%) patients had seizures. Decreased level of consciousness was observed in 62 (41.9%) patients, 4 of them being in coma—one in a ventilator and three sedated due to difficult general condition. Eighteen patients (12.2%) had two or three neurological symptoms simultaneously. One (0.7%) monoparesis and two (1.4%) hemiparesis were observed, but those were related to acute ischemic brain attack prior to BM. Skin color changes were observed in 12 (8.1%) patients: petechiae in 9, marble skin in 2 patients (1.4%), and in one patient yellowish skin. All signs and symptoms are presented in Table 1.

Laboratory results

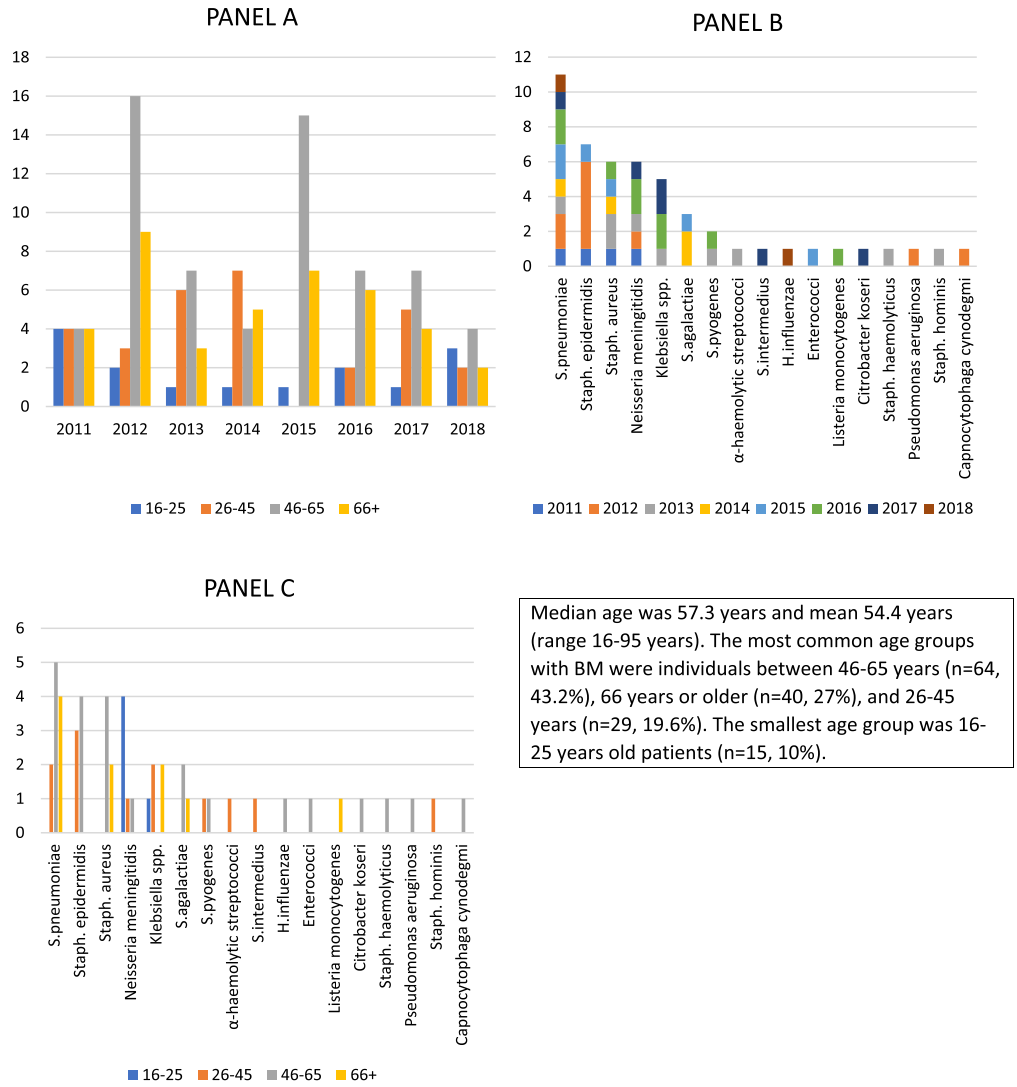
Blood, plasma, and CSF laboratory results are presented in Table 2.

Causative pathogens

Blood culture for bacteria was positive with 42 (28.4%) patients. CSF culture for bacteria was performed in 146 (98.7%) cases showing positivity in 50 (33.8%) cases. PCR of CSF samples was performed with 46 individuals (31.1%) showing positivity in 10 (20.4%) cases. Same pathogen in CSF and in blood was detected in 17 (11.5%) individuals. The most common pathogens were *S. pneumoniae* (11, 7.4%), *S. epidermidis* (7, 4.7%), *S. aureus* (6, 4.1%), *N. meningitidis* (6, 4.1%) and *Klebsiella* spp. (5, 3.4%). *S. epidermidis* was defined as a causative pathogen of BM if the patient had BM symptoms, CSF culture or PCR was positive for *S. epidermidis* and there was simultaneous CSF pleocytosis. Culture method was used to identify seven *S. epidermidis* cases and PCR was used once.

There were nine (6.1%) Gram stain negative rods cultured from CSF in our study: Five *Klebsiella* spp, one each *H. influenzae, Citrobacter koseri, Pseudomonas aeruginosa* and *Capnocytophaga cynodegmi. Pasteurella multocida* was detected once with PCR.

All causative pathogens cultured from CSF are presented in Fig. 1. Besides from CSF, bacteria were cultured from other sources. Most common pathogens retrieved from blood were *S. pneumoniae* (12, 28.6%), *S. aureus* (7, 16.7%), *S. pyogenes* (5, 11.9%), *N. meningitidis* (4, 9.5%), *S. epidermidis* and *S. agalactiae* (both 3, 7.1%). *Klebsiella* spp, *H. influenzae*, *S. salivarius, Anaerobic streptococci, E. cloacae, P. multocida,*



Median age was 57.3 years and mean 54.4 years (range 16-95 years). The most common age groups with BM were individuals between 46-65 years (n=64, 43.2%), 66 years or older (n=40, 27%), and 26-45 years (n=29, 19.6%). The smallest age group was 16-25 years old patients (n=15, 10%).

Fig. 1 **A** Incidence of bacterial meningitis. **B** Bacteria cultured from CSF by year of meningitis. Panel **C**. Bacteria from CSF culture by age groups

Staphylococcus pettenkoferi, and *A. baumannii* were all detected once.

Pathogens most cultured from pus (from ear, sinuses, neurosurgical wound, or abscess) were *S. aureus* (3, 17.6%) and *S. pyogenes* (2, 11.8%). *S. pneumoniae, S. epidermidis, Klebsiella* spp, *S. agalactiae, α-haemolytic streptococci, S. intermedius, H. influenzae, P. aeruginosa, E. cloacae, Raoultella* spp, *Eikenella corrodens* and *Serratia marcescens* were all detected once.

Staphylococcus epidermidis (4, 66.7%) was responsible for most cultured pathogens from intracranial material. *Propionibacterium* and *S. aureus* were detected once.

Intracranial material was defined as cannula, shunt, or suture. In 7 (4.7%) cases the bacterium was detected by PCR from a CSF specimen when culture was negative; *N. meningitidis* (3), *S. epidermidis* (1), *P. multocida* (1), *Cellulosimicrobium* (1) and *Bacillus cereus* (1). In three (2%) cases two different pathogens were simultaneously detected in the CSF.

Antibiotic resistance

CSF pathogens causing BM were most likely resistant to cefuroxime (10, 6.8%), ampicillin (9, 6.1%) and tetracycline (9, 6.1%). All CSF culture resistance profiles are

Table 2 Values of fundamental laboratory results at admission to hospital

Laboratory results	Median	Normal values
C-reactive protein (mg/L)	61	< 10
Leukocyte count in blood ($\times 10^9$/L)	12.2	3.4–8.2
Plasma glucose (mmol/L)	6.0	< 6.0
Leukocyte count in CSF ($\times 10^6$/L)	566	0–5
Granulocyte percentage in CSF (%)	75	0
Glucose levels in CSF (mmol/L)	1.5	2.2–4.2
Lactate levels in CSF (mmol/L)	5.7	1.1–2.2
Protein levels in CSF (mg/L)	1563	150–650

shown in Fig. 2 Panel A. Seven (4.7%) bacteria from CSF were resistant to one antibiotic, three (2%) to two different antibiotics, one (0.7%) to three different antibiotics, five (3.4%) to four different antibiotics, two (1.4%) to six different antibiotics, three (2%) to eight different antibiotics, three (2%) to 11 different antibiotics and one (0.7%) to 12 different antibiotics. It is worth noticing that there were no species of bacteria resistant to vancomycin or ceftriaxone. Multi-drug resistance (resistance to three or more antibiotics) was seen in 13 (8.8%) patients, mostly patients with nosocomial BM (8, 5.4%).

In other samples (blood, pus or intracranial material), 30 (20.3%) cases presented resistance to at least one antibiotic was detected. More specifically, 13 (8.8%) bacterial species were resistant to one antibiotic, and 4 (2.7%) to two, 2 (1.4%) to three, 5 (3.4%) to four, 2 (1.4%) to six, and 2 (1.4%) to seven different antibiotics. On one occasion each, resistance was detected to eight, nine and 11 different antibiotics. There were six (4%) coexistent fungal infections.

Imaging

On admission, head CT was performed to most patients (119, 80.4%) and MRI to 26 (17.6%) patients. In 14 (9.5%) cases imaging findings were consistent with meningitis, e.g., leptomeningeal or pachymeningeal intensification, most frequently seen with MRI (8, 57.1%), but also with CT (6, 42.9%), presenting specificity of 30.8% with MRI and 5.0% with CT. In 15 (10.1%) patients imaging showed findings consistent with elevated intracranial pressure. Imaging controls were performed most frequently by MRI (62, 41.9%). CT controls were performed to 43 (29.1%) patients. Fifty (33.8%) patients had at least once imaging control performed 1 month to two years after discharge from hospital.

Treatment

Pre-diagnostic antibiotics, including perioperative ones, were given to 85 (57.4%) patients. Of them, 49 (57.6%) suffered from postoperative meningitis.

Pre-diagnostic corticosteroids were used with 33 (22.3%) patients: tablets, intravenous products, inhalators, nasal sprays, and intravenous products, in 19, 10, 3, and 1 patient, respectively. The most frequent corticosteroid used was dexamethasone (12, 8.1%) followed by hydrocortisone, betamethasone, prednisolone, fluticasone propionate, methyl prednisolone, mometasone furoate and fludrocortisone, with 5, 5, 4, 3, 2, 1, and 1 patient, respectively. In 23 (15.5%) patients' treatment with acyclovir was initiated on admission.

After the diagnosis of BM, ceftriaxone was the most frequently used empiric antibiotic regimen (117 cases, 79.1%), followed by meropenem and vancomycin with 11 (7.4%) cases each. Altogether 11 different antibiotics were used as a first choice. The most used second antibiotic in conjunction with the first one was vancomycin

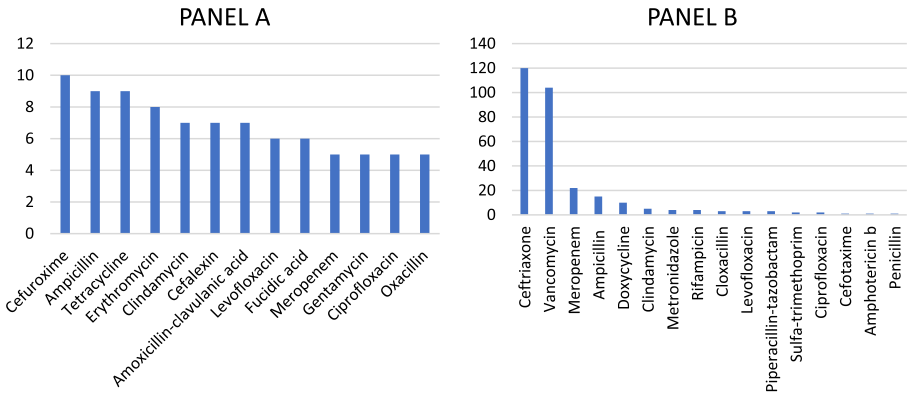


Fig. 2 **A** Antibiotic resistant bacterium species cultured from CSF. **B** Quantity of patients with antibiotics used intravenously after the diagnosis of bacterial meningitis

(93, 62.8%), meropenem (11, 7.4%), doxycycline (8, 5.4%), ampicillin and clindamycin (both 5, 3.4%). Antibiotic monotherapy was given to 13 (8.8%) patients. Eighteen patients received three-modal antibiotic therapy with the most common third antibiotic being ampicillin (8, 5.4%). The total number of intravenous antibiotics used are shown in Fig. 2. Ceftriaxone and vancomycin were the most used empiric antibiotics among all occasions and so were them also after confirmed etiology.

The most common number of different concomitant antibiotics used were three (50, 33.8%), two (34, 23%), four (22, 14.9%), five (19, 12.8%), seven (8, 5.4%), six (6, 4.1%), eight and nine (both 3, 2%), one (2, 1.4%) and ten (1, 0.7%). The numbers include perioperative, intravenous, and in some cases oral antibiotics at discharge.

After the diagnosis of BM, corticosteroids were used in 79 patients (53.4%). Operative treatment was required for 56 (37.8%) patients with most cases being neurosurgical. Mastoidectomy was performed to six (4.1%) patients of whom all had otogenic meningitis.

The median duration of intravenous antibiotic treatment was 18 days (range 2–125). At discharge, 29 (19.6%) patients were prescribed oral antibiotics with the duration ranging commonly from 5 to 30 days, and in a few patients for 100–270 days as a suppressive antibiotic treatment for various reasons. Five most common oral antibiotics used were amoxicillin clavulanic acid (5, 3.4%) followed by clindamycin, moxifloxacin, penicillin and cefalexin (all 4, 2.7%). Median value of the days on antibiotics (combined all intravenous and oral) was 21 days.

Outcome

The median length of hospital stay was 20 days. Neurological sequelae after BM a total of 49 patients (33.1%) had developed at least one neurological deficit at the time of discharge. Most common deficits were memory difficulties (15, 10.1%), mental regression (13, 8.8%), dysphasia or aphasia (9, 6.1%), visual disorders (9, 6.1%), vertigo and hydrocephalus (7, 4.7% each), decreased level of consciousness (5, 3.4%), hemiparesis and change in personality (4, 2.7%). Twelve (8.1%) patients had their hearing checked with audiogram during their hospital stay. In the period from the moment of discharge to one-year control visit, eight (5.4%) patients had permanent hearing impairment. There was no deafness diagnosed in any patient. Naturally, most of the neurological sequelae were related to neurosurgical procedures.

Fourteen patients (9.5%) died (GOS score 1), all but one directly to BM. From the survivors 5 (3.4% of all patients), 18 (12.2%), 23 (15.6%) and 89 (60.1%) patients had the GOS score 2, 3, 4, and 5, respectively. In total, 40.5% (60/148) had unfavorable outcome (GOS scores 1–4). 30-day all-cause mortality was 10.8% with one-year and two-year overall mortality being 14.2% and 19.6%, respectively.

Patients who suffered from otogenic meningitis had unfavorable outcome likelihood of 22.2%, those from sinonasal meningitis 28.6%, from odontogenic meningitis 33.3%, from neurosurgery-related meningitis 44.6% and patients with no specific source of infection 38.8%. CSF-culture appeared to be most frequently negative with neurosurgery-related meningitis with 16/58 (21.6%) individuals.

Headache ($p = 0.0001$, 95% CI 0.16–0.35), decreased general condition ($p = 0.0001$, 95% CI 0.23–0.67), head CT ($p = 0.0001$, 95% CI 0.073–0.64) and MRI ($p = 0.040$, 95% CI 0.92–4.0), hypertension ($p = 0.0002$, 95% CI 0.34–0.70), altered mental status ($p = 0.0002$, 95% CI 0.47–0.73), confusion ($p = 0.0011$, 95% CI 0.36–0.78), operative treatment ($p = 0.012$, 95% CI 0.42–0.89), neurological symptoms ($p = 0.023$, 95% CI 0.44–0.93), pre-diagnostic antibiotic use ($p = 0.026$, 95% Cl 0.40–0.97) and oral antibiotics on discharge ($p = 0.039$, 95% CI 0.94–3.6) were correlated with unfavorable outcome.

All statistical analyses are shown in Additional file 1.

Discussion

This study shows extensively the variety of clinical picture, pathogens, and outcome of infection with different etiologies of BM in Southwestern Finland. Our study included all types of meningitis, culture-positive and -negative cases of BM, covering larger entities than if only culture-positive meningitis were included [25]. Due to severity of the disease it's essential to regularly evaluate possible predictors of unfavorable outcome.

S. pneumoniae was the most frequently (11, 7.4%) detected pathogen confirming the results of earlier studies [26, 27]. In addition to *S. pneumoniae*, *N. meningitidis* is a common causative pathogen of BM in all age groups presented earlier [28], but in our study the *N. meningitidis* cases were most commonly seen with young adults aged 16–25 years. Surprisingly there were only one *Listeria monocytogenes* and *H. influenzae* meningitis although it is shown that these pathogens cause around 9% and 7% of BM worldwide, respectively [6]. Still, it is possible that patients with septicemia and concomitant meningitis had an ICD-10 diagnosis number of only sepsis in their patient records.

We presented median CSF leucocyte count of 566×10^6/L and median protein levels of 1563 mg/L. However, even normal CSF leucocyte levels can indicate BM, especially combined with high protein levels. In those cases, the outcome may be even worse than normally, with incidence of unfavorable outcome even 59% and mortality 31% [29].

In 2011 to 2018 we found seven patients with culture-negative CSF specimens positive for bacteria with PCR, a technique shown to be a lot more sensitive than culture [25]. CSF culture has shown varying sensitivities of 43–85%, and a specificity up to 97%, at least in patients without the use of pre-diagnostic antibiotics [30–32]. The use of antibiotics reduces the identification of pathogens at least by 30% [33]. Compared to culture, multiplex or quantitative PCR has shown up to two-fold better sensitivities and specificities up to 100% [31, 33]. Our results of CSF culture positivity (33.8%) are compatible with previous studies, especially with frequently used pre-diagnostic antibiotics (57.4%). Our 16sRNA based PCR method presented clearly inferior to newer methods described below. CT was used with most patients (80.4%) and MRI with only 17.6% of patients, which may be due to lack of resources for use of MRI-equipment and the need for quicker results. Our results presented 30.8% and 5.0% specificity with MRI and CT, respectively, on identifying meningitis-related findings in imaging. Previous study indicated MRI being more specific but with a lower specificity of 16% [34].

Previous studies have shown that CSF sterilization may occur in hours after using parenteral antibiotics. Meningococci may be sterilized within 2 h and pneumococci within 4 h after administering parenteral antibiotic therapy [35]. Our results showed pre-diagnostic antibiotic use correlated with both negative blood- and CSF culture. Positive blood culture was correlated with positive CSF culture. Therefore, in some cases pre-diagnostic administration of antibiotics before lumbar puncture may cause lack of detectable bacteria despite BM. However, in emergency situations such as sepsis and suspicion of BM the fast administration of antibiotics is essential [36].

Triad of fever, neck stiffness and altered mental status has been previously reported with 41–59% BM cases [37, 38]. In our study, the prevalence of the presentation with this triad was much lower (13.5%). However, another triad—fever, neck stiffness and headache—was more frequent (39, 26.4%). Therefore, it is clear that the absence of the classical triad cannot be used to rule out the possibility of BM. In an older study headache was not reported to be correlated with unfavorable outcome [26], but with a more recent study [37] headache was correlated with unfavorable outcome, as was the case also in our study. Therefore, clinicians should pay even more attention to BM patients suffering from headache and not only altered mental status, which may be a sign of a more advanced disease.

The treatment administered after the diagnosis of BM remained highly efficacious due to the lack of resistance of bacteria to the most used antibiotics ceftriaxone and vancomycin, as proved earlier with ceftriaxone [37].

Community-acquired BM has been shown to cover most of BM cases with even proportion of 86%, with pneumococci being responsible for most of the episodes in adults. Nosocomial BM, on the other hand, has been shown to cover varying proportions of all BM with 14%-73%, most cases being staphylococci dominant. Nosocomial BM cases has seen an increase during the conjugate-vaccine era [39–42]. Insufficiency of antibiotic prophylaxis in neurosurgical operations may explain present considerable proportion of individuals with nosocomial BM [41].

The number of cases with nosocomial BM was relatively high. This is planned to be a topic of our further research. Pre-diagnostic antibiotic use seems to be linked with unfavorable outcome. This may be due to preoperative antibiotics given to patients with neurosurgery and the operative risks. Neurological symptoms and confusion were associated with unfavorable outcome, as presented earlier [39]. Severe symptoms on admission require more often imaging to exclude other disorders, therefore relating both logically to unfavorable outcome. Oral antibiotics prescribed at discharge were also correlated with unfavorable outcome, probably due to more severe clinical picture and the need for longer antibiotic therapy.

The frequency of unfavorable outcome of BM being 40.5% in our study was compatible with previous research showing the frequency of 38% [26], but this previous European study excluded all cases with nosocomial meningitis. Previous studies have reported overall mortality of 10–17% [26, 27], but in our study the mortality was only 8.8%. A recent study [37] from Lithuania presented likelihood of unfavorable outcome (GOS 1–3 in their study) to be 15.7% and a mortality (GOS 1) of 5.7%. For comparison, the respective proportions in our study were 24.3% for GOS 1–3 and mortality (GOS 1) of 8.8%. However, straight comparison cannot be done, since we also included patients with nosocomial BM.

Nosocomial meningitis requires often surgical intervention with significant risks. Therefore, it could be interpreted that our results of unfavorable outcome are compatible with previous studies [37, 39, 43].

The worldwide disease burden of BM is high especially in developing countries. Prevention of the disease with vaccines falls behind many other vaccine-preventable notorious diseases. Despite good progress of vaccine development against pathogens of BM, corresponding figures of measles (93.0%) and tetanus (90.7%) vaccination coverage imply that against BM also this could be better [44].

Our study has limitations. The fact that it was a single center study, is a limitation due to somewhat small number of patients, but the design allows uniform data

collection and reliable transfer to analyses. Retrospective nature of this study may have caused inaccurate data collection in some cases. Our patients may not represent the whole population of patients in Finland. Also, we are unable to exclude the possibility of neurosurgery itself causing unfavorable outcome on patients. In the future, comprehensive prospective studies are needed to better determine prognostic factors of BM.

Conclusions

Streptococcus pneumoniae was the most frequent causative pathogen of BM in our study. The proportion of nosocomial BM was surprisingly high, and so was the use of pre-diagnostic antibiotics. Ceftriaxone and vancomycin were the most used antibiotics, and no pathogen presented resistance to them. Headache was associated with unfavorable outcome. Pre-diagnostic antibiotic use predicted unfavorable outcomes, but the reasons may be multifactorial.

The likelihood of unfavorable outcome was compatible with previous studies. However, mortality in our patients was lower than in most previous studies.

The need for developing vaccines against wider spectrum of pathogens causing BM remains of utmost importance. Further research is needed on risk factors, pre- and perioperative antibiotic prophylaxis, and knowledge on different causative pathogens of meningitis to specify appropriate treatments, to recognize special populations, and to improve recovery of patients with BM [2].

Abbreviations

BM	Bacterial meningitis
HIV	Human immunodeficiency virus
CSF	Cerebrospinal fluid
PCR	Polymerase chain reaction
ICD-10	International Classification of Diseases 10th Revision
CRP	C-reactive protein
GOS	Glasgow Outcome Scale
MALDI-TOF	Matrix-assisted laser-desorption-ionization time-of-flight
FAA	Fastidious anaerobe agar
FAB	Fastidious anaerobe broth
MIC	Minimum inhibitory concentration
EUCAST	European Committee on Antimicrobial Susceptibility Testing
rRNA	Ribosomal ribonucleic acid
DNA	Deoxyribonucleic acid
CT	Computed tomography
MRI	Magnetic resonance imaging

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-023-07999-2.

Additional file 1: Table S1. All statistical analyses performed.

Acknowledgements
We thank Juha O. Grönroos for support with microbiological methodology and Emmi Alimattila for technical support.

Author contributions
Conceptualization and design of the study: SN, LL, JO and JJ. Methodology: SN, JO and JJ Acquisition of the data: SN and JJ. Analysis and interpretation of data: all authors. Software and validation: SN, EL, JO and JJ. Drafting of the original version: SN, LL, JO and JJ. Drafting, critical revising, and editing: all authors. Visualization: SN, LL, JO and JJ. Supervision: JO and JJ. All authors read and approved the final manuscript.

Funding
No funding was received for conducting this study.

Availability of data and materials
The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All methods were carried out in accordance with relevant guidelines and regulations. The informed consent is waived by Ethics Committee of the Hospital District of Southwestern Finland in view of the retrospective nature. All experimental protocols were approved by Turku Clinical Research Center.

Consent for publication
Not applicable.

Competing interests
J.O reports receiving compensations for lectures or advisory boards outside the submitted work from AstraZeneca, Biocodex, Gilead, GlaxoSmithKline, MSD-Finland, Orion, Pfizer, Roche, Rokotustutkimuskeskus, and for congress travel from UnimedicPharma. All other authors declare no conflicts of interest.

Author details
[1]Department of Otorhinolaryngology, Turku University Hospital and University of Turku, Savitehtaankatu 5, 20540 Turku, Finland. [2]Department of Radiology, HUS Medical Imaging Center, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland. [3]Unit of Biostatistics, Department of Clinical Medicine, University of Turku, Turku, Finland. [4]Department of Infectious Diseases, Turku University Hospital and University of Turku, Turku, Finland. [5]Department of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland.

Received: 20 September 2022 Accepted: 10 January 2023
Published online: 23 January 2023

References

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351(18):1849–59.
2. GBD 2016 Meningitis Collaborators. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1061–82.
3. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Lond Engl. 2015;386(9995):743–800.
4. Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. Pediatrics. 2000;106(3):477–82.
5. McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. Lancet Lond Engl. 2016;388(10063):3036–47.
6. Davis LE. Acute Bacterial Meningitis. Contin Minneap Minn. 2018;24(5):1264–83.
7. McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet Lond Engl. 2012;380(9854):1703–11.
8. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the

introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348(18):1737–46.
9. Robinson CP, Busl KM. Meningitis and encephalitis management in the ICU. Curr Opin Crit Care. 2019;25:423–9.
10. Valdoleiros SR, et al. Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review. Acute Crit Care. 2022;37:61–70.
11. Kurtaran B, et al. The causes of postoperative meningitis: the comparison of gram-negative and gram-positive pathogens. Turk Neurosurg. 2018;28:589–96.
12. Hasbun R, Rosenthal N, Balada-Llasat JM, Chung J, Duff S, Bozzette S, et al. Epidemiology of Meningitis and Encephalitis in the United States, 2011–2014. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017;65(3):359–63.
13. Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van de Beek D, van der Ende A. Changing epidemiology of bacterial meningitis since introduction of conjugate vaccines: 3 decades of National Meningitis Surveillance in The Netherlands. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021;73(5):e1099–107.
14. Erdem H, Inan A, Guven E, Hargreaves S, Larsen L, Shehata G, et al. The burden and epidemiology of community-acquired central nervous system infections: a multinational study. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2017;36(9):1595–611.
15. Gessner BD, Mueller JE, Yaro S. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. BMC Infect Dis. 2010;10:22.
16. Paireau J, Chen A, Broutin H, Grenfell B, Basta NE. Seasonal dynamics of bacterial meningitis: a time-series analysis. Lancet Glob Health. 2016;4(6):e370-377.
17. Wall EC, Everett DB, Mukaka M, Bar-Zeev N, Feasey N, Jahn A, et al. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and *Haemophilus influenzae* type b vaccination, 2000–2012. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014;58(10):e137-145.
18. Mazamay S, Broutin H, Bompangue D, Muyembe JJ, Guégan JF. The environmental drivers of bacterial meningitis epidemics in the Democratic Republic of Congo, central Africa. PLoS Negl Trop Dis. 2020;14(10): e0008634.
19. Miller L, Arakaki L, Ramautar A, Bodach S, Braunstein SL, Kennedy J, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Ann Intern Med. 2014;160(1):30–7.
20. Hodgson A, Smith T, Gagneux S, Adjuik M, Pluschke G, Mensah NK, et al. Risk factors for meningococcal meningitis in northern Ghana. Trans R Soc Trop Med Hyg. 2001;95(5):477–80.
21. Baker M, McNicholas A, Garrett N, Jones N, Stewart J, Koberstein V, et al. Household crowding a major risk factor for epidemic meningococcal disease in Auckland children. Pediatr Infect Dis J. 2000;19(10):983–90.
22. Müller O, Krawinkel M. Malnutrition and health in developing countries. CMAJ Can Med Assoc J J Assoc Medicale Can. 2005;173(3):279–86.
23. Battersby AJ, Knox-Macaulay HHM, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. Pediatr Blood Cancer. 2010;55(3):401–6.
24. Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, et al. Neurodevelopmental impairment in children after group B Streptococcal disease worldwide: systematic review and meta-analyses. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017;65(suppl2):S190–9.
25. Başpınar EÖ, Dayan S, Bekçibaşı M, Tekin R, Ayaz C, Deveci Ö, et al. Comparison of culture and PCR methods in the diagnosis of bacterial meningitis. Braz J Microbiol Publ Braz Soc Microbiol. 2017;48(2):232–6.
26. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. Lancet Infect Dis. 2016;16(3):339–47.
27. Polkowska A, Toropainen M, Ollgren J, Lyytikäinen O, Nuorti JP. Bacterial meningitis in Finland, 1995–2014: a population-based observational study. BMJ Open. 2017;7(5): e015080.
28. Oordt-Speets AM, Bolijn R, van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: a systematic review and meta-analysis. PLoS ONE. 2018;13(6): e0198772.
29. van Soest TM, Chekrouni N, van Sorge NM, Brouwer MC, van de Beek D. Bacterial meningitis presenting with a normal cerebrospinal fluid leukocyte count. J Infect. 2022;84:615–20.
30. Welinder-Olsson C, et al. Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis. Clin Microbiol Infect. 2007;13:879–86.
31. Hasanuzzaman M, et al. Comparison of culture, antigen test, and polymerase chain reaction for pneumococcal detection in cerebrospinal fluid of children. J Infect Dis. 2021;224:S209–17.
32. Heckenberg SGB, Brouwer MC, van de Beek D. Bacterial meningitis. Handb Clin Neurol. 2014;121:1361–75.
33. Corless CE, et al. Simultaneous detection of *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* in suspected cases of meningitis and septicemia using real-time PCR. J Clin Microbiol. 2001;39:1553–8.
34. Bineshfar N, et al. Evaluation of the epidemiologic, clinical, radiologic, and treatment methods of patients with subacute and chronic meningitis. BMC Neurol. 2022;22:340.
35. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics. 2001;108(5):1169–74.
36. Sherwin R, Winters ME, Vilke GM, Wardi G. Does early and appropriate antibiotic administration improve mortality in emergency department patients with severe sepsis or septic shock? J Emerg Med. 2017;53(4):588–95.
37. Matulyte E, et al. Retrospective analysis of the etiology, clinical characteristics and outcomes of community-acquired bacterial meningitis in the University Infectious Diseases Centre in Lithuania. BMC Infect Dis. 2020;20:733.
38. van de Beek D, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22(Suppl 3):S37-62.
39. Sunwoo J-S, et al. A hospital-based study on etiology and prognosis of bacterial meningitis in adults. Sci Rep. 2021;11:6028.
40. Block N, Naucler P, Wagner P, Morfeldt E, Henriques-Normark B. Bacterial meningitis: aetiology, risk factors, disease trends and severe sequelae during 50 years in Sweden. J Intern Med. 2022;292:350–64.
41. Kiyani M, et al. Outcomes and health care resource utilization of adult bacterial meningitis in the United States. Neurol Clin Pract. 2021;11:117–26.
42. Durand ML, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med. 1993;328:21–8.
43. Gudina EK, Tesfaye M, Wieser A, Pfister H-W, Klein M. Outcome of patients with acute bacterial meningitis in a teaching hospital in Ethiopia: a prospective study. PLoS ONE. 2018;13: e0200067.
44. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Lond Engl. 2017;390(10100):1151–210.

Publisher's Note

Niemelä S, Lempinen L, Löyttyniemi E, Grönroos JO, Luoto R, Peltola V & Jero J (2024)
Finnish paediatric study found a low incidence of bacterial meningitis from 2011 to 2018 but a substantial proportion of nosocomial meningitis.
Acta Paediatr

II

Received: 1 June 2023 | Revised: 25 September 2023 | Accepted: 27 September 2023

DOI: 10.1111/apa.16991

ACTA PÆDIATRICA
NURTURING THE CHILD
WILEY

ORIGINAL ARTICLE

Finnish paediatric study found a low incidence of bacterial meningitis from 2011 to 2018 but a substantial proportion of nosocomial meningitis

Sakke Niemelä[1] | Laura Lempinen[2] | Eliisa Löyttyniemi[3] | Juha O. Grönroos[4] | Raakel Luoto[5] | Ville Peltola[5] | Jussi Jero[6]

[1]Department of Otorhinolaryngology, Turku University Hospital, University of Turku, Turku, Finland

[2]Department of Radiology, HUS Medical Imaging Center, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

[3]Department of Biostatistics, Turku University Hospital, University of Turku, Turku, Finland

[4]Department of Clinical Microbiology, Turku University Hospital, University of Turku, Turku, Finland

[5]Department of Paediatrics and Adolescent Medicine, Turku University Hospital, University of Turku, Turku, Finland

[6]Department of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

Correspondence
Sakke Niemelä, Department of Otorhinolaryngology, Turku University Hospital, University of Turku, Savitehtaankatu 5, 20540 Turku, Finland.
Email: sasani@utu.fi

Abstract

Aim: This study examined the predisposing factors, clinical picture, bacterial aetiology and clinical outcomes of infants and children with bacterial meningitis (BM).

Methods: The medical records of patients under 16 years of age, treated by Turku University Hospital, Finland, from 2011 to 2018, were screened for meningitis using the International Classification of Diseases, Tenth Revision codes. Patients were included if bacteria were detected in cerebrospinal fluid (CSF) or other predefined laboratory variables indicated BM, despite CSF testing negative for bacteria. The Glasgow Outcome Scale (GOS) was used to determine outcomes.

Results: We identified 37 children with BM: 22 infants aged 0–89 days and 15 children aged 90 days to 15 years. The overall incidence was approximately 5.7/100 000/year. Nosocomial meningitis was documented in 51%. Bacterial growth was detected in the CSF or blood cultures of the majority of patients (57%). *Escherichia coli* (14%), group B streptococcus (11%) and *Streptococcus pneumoniae* (8%) were the most common pathogens. There were 14% of patients with unfavourable outcomes, namely GOS scores of 1–4, but no deaths.

Conclusion: The incidence of paediatric BM was low during the study period, but the proportion of nosocomial meningitis was substantial. The frequency of unfavourable long-term outcomes was relatively low.

KEYWORDS
bacterial meningitis, Glasgow Outcome Scale, group B streptococcus, nosocomial infection, *Streptococcus pneumoniae*

Abbreviations: BM, bacterial meningitis; CSF, cerebrospinal fluid; GBS, group B streptococcus; GOS, Glasgow Outcome Scale; Hib, *Haemophilus influenzae* type b; ICD-10, International Classification of Diseases, Tenth Revision; PCR, polymerase chain reaction.

1 | INTRODUCTION

Bacterial meningitis (BM) is the tenth most common cause of death in children under 5 years of age in the world and causes significant morbidity and mortality worldwide.[1,2] Group B streptococcus (GBS) and *Escherichia coli* have dominated the bacterial aetiology in infants from 0 to 89 days of age. Since universal vaccinations, *Streptococcus pneumoniae* and *Neisseria meningitidis* have been the most important causative agents in children and adolescents over that age. *Haemophilus influenzae* type b (Hib) was also on that list before BM immunisation.[1,2]

The incidence of BM has decreased substantially in areas with high vaccination coverage against *S. pneumoniae*, *N. meningitidis* and Hib. In the Netherlands, the implementation of Hib vaccination has reduced the incidence of BM caused by *H. influenzae* from 1.44 to 0.04 episodes per 100 000 population per year.[2] In the USA, the Hib conjugate vaccine was associated with a 55% reduction in bacterial meningitis in the early 1990s and the 7-valent pneumococcal conjugate vaccine was associated with a 59% reduction in pneumococcal meningitis in children.[3,4] The implementation of the meningococcal group C vaccination has also been effective in the Netherlands. It decreased the incidence of *N. meningitidis* meningitis from 2.87 to 0.20 per 100 000 individuals between 1989–1993 and 2014–2019.[2] Neonatal BM is more difficult to prevent, because maternal intrapartum antibiotic prophylaxis does not protect children from late-onset GBS disease.[5]

Meningitis survivors risk neurological sequelae, such as hearing loss, cerebral palsy and mental retardation.[6] Although hearing loss can spontaneously improve, studies have reported that it was permanent in around 30% of pneumococcal meningitis survivors.[7,8] Prematurity, male gender and seizures are predictors of unfavourable outcomes in neonates.[9] Data about the prognosis of BM in high-income countries has been scarce and continuously affected by changing epidemiology and improvements in diagnostics and treatment.

Our aim was to describe the epidemiology of paediatric BM patients treated at Turku University Hospital, Finland, from 2011 to 2018. We also evaluated the predisposing factors, aetiology, clinical manifestations and treatment of BM, together with indicators of unfavourable outcomes.

Key notes

- We examined bacterial meningitis (BM) in 22 infants aged 0–89 days and 15 children aged 90 days to 15 years.
- Bacterial growth was detected in the cerebrospinal fluid or blood cultures of 57% and *Escherichia coli* (14%), group B streptococcus (11%) and *Streptococcus pneumoniae* (8%) were the most common pathogens.
- There were 14% with unfavourable outcomes, defined as Glasgow Outcome Scale scores of 1–4, but no deaths.

2 | METHODS

2.1 | Study design

Turku University Hospital is a tertiary referral centre in the Hospital District of Southwest Finland, which also receives patients from Western Finland. At the time of the study, its catchment area was approximately 480 000 people, including 75 000 children below 16 years of age, and some 4000 live births per year. We performed a database search of patients under 16 years of age who were hospitalised between 1 January 2011 and 31 December 2018 using the International Classification of Diseases, Tenth Revision (ICD-10) codes for meningitis: A87.9, B94.80, G00.9, G01*A32.1, G01*A39.0, G01*A69.2, G05.2*B83.2, A17.0, A32.1, A87, B01.0+, B02.1, B05.1+, B37.5, B38.4+, B45.1, B94.80, G00, G01, G02, G03, G05. The children's medical records were reviewed. Meningitis caused by non-bacterial pathogens, such as viruses, fungi or parasites were excluded and so were neuroborreliosis cases. We included cases with positive cerebrospinal fluid (CSF) cultures or polymerase chain reaction (PCR) results with an ICD-10 code for meningitis. Previous research has found that a substantial proportion of BM cases were culture-negative, because of pre-diagnostic antibiotic therapy or other causes.[10] Therefore, we also included CSF culture-negative patients with clinical symptoms of BM and CSF pleocytosis ($>30\times10^6$/L). They also had to have at least one of the following laboratory findings: a positive blood bacterial culture, a high CSF protein level (>1000 mg/L) or elevated plasma C-reactive protein (>50 mg/L). The inclusion criteria for neonatal early-onset BM cases, defined as 0–6 days of age, were clinical symptoms of BM and a CSF leucocyte count of $>30\times10^6$/L. In CSF *Staphylococcus epidermidis* was considered to be a causative agent of BM if the patient was having BM symptoms and there was simultaneous CSF pleocytosis.

Of the 149 children with an ICD-10 code for meningitis, 37 had a confirmed case of BM and were included in the study. The ICD-10 codes for meningitis included viral, aseptic and bacterial meningitis. The patients who were excluded had a confirmed or probable case of viral or aseptic meningitis or they did not fill the inclusion criteria for BM. The patients were then classified into two age groups: infants from 0 to 89 days of age and children and adolescents from 90 days to 15 years of age. Nosocomial BM was defined as early-onset meningitis, meningitis acquired during the patient's hospital stay or meningitis after a neurosurgical operation, which occurred <30 days after discharge. All other patients were defined as having community-acquired BM.

Since 2010, the Finnish national vaccination programme has offered children the 10-valent pneumococcal conjugate vaccine at 3, 5 and 12 months. This covers *S. pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Hib vaccines have been given at the same ages since 1993. Meningococcal vaccines are not included in the Finnish national vaccination programme for children.

The microbiological laboratory methods are described in Appendix S1.

2.2 | Outcomes

We evaluated the outcomes with the five-point Glasgow Outcome Scale (GOS), based on the information in the patient's medical records.[11] The scale comprises death (one point), vegetative state (two points), severe disability (three points), moderate disability (four points) and mild or no disability (five points). The outcomes were evaluated at discharge and 8 months after discharge. An unfavourable outcome was defined as a score from 1 to 4. When we determined the GOS scores, we considered the age of the patient and the disability was assessed in relation to their age-appropriate behaviour.

Hearing was tested with an appropriate method, either a brainstem auditory evoked response, an audiogram, otoacoustic emissions or mechanical source of voice. Hearing deficiency was defined by a better ear hearing level of 20 dB or above.

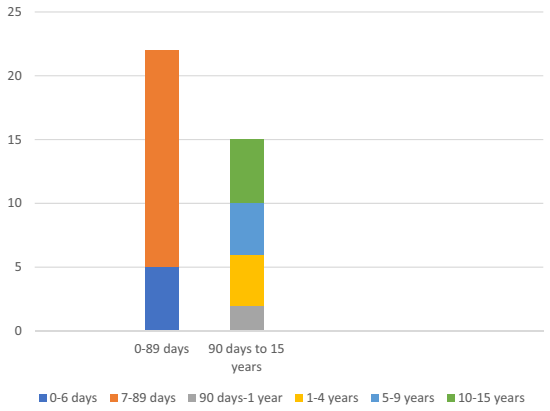


FIGURE 1 Age distribution of the 37 patients.

2.3 | Statistical analysis

The incidence of BM was calculated by dividing the number of patients in the Hospital District by the number of study years and the population below 16 years of age. The incidence in infants was obtained by dividing the annual number of infant cases by the number of live births.

The age groups were compared with the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Associations between two categorical variables were tested with Fisher's exact test. Furthermore, a separate log-binomial model was performed with unfavourable outcomes, defined as GOS scores 1–4, for each factor as a univariate approach. We were not able to perform a multivariate analysis because of the low number of children with an unfavourable outcome. Two-tailed p values of <0.05 were regarded as statistically significant. The data analysis was generated using SAS for Windows, Version 9.4 (SAS Institute Inc).

2.4 | Ethics

The study received institutional approval and was not subject to the Ethics Committee approval.

3 | RESULTS

3.1 | Incidence, demographics and causative agents

We identified 37 children (54% male) with BM treated at Turku University Hospital between 2011 and 2018. There were 22 infants aged 0–89 days and 15 children or adolescents aged 90 days to 15 years (Figure 1).

Three of the patients had been transferred from other hospitals in Finland. The incidence was approximately 5.7/100 000/year based on the 34 children living in the Hospital District. The estimated incidence among infants was 0.7/1000 live births. The median age of the 37 children was 1 month, with an interquartile range of 9 days to 3 years and 9 months. The majority (51%) of the BM cases were nosocomial (Table 1).

Pathogens were detected in either the CSF or blood of 57% of the patients (Table 2). The CSF culture was positive for bacteria in 41% of cases and the PCR of the CSF was positive in one culture-negative case (Figure 2). A blood culture detected a pathogen in five cases when the CSF culture was negative. GBS (11%), *S. pneumoniae* (8%) and *E. coli* (5%) were the most frequent pathogens in the CSF cultures. All the causative pathogens are shown in Figure 2. The CSF culture was positive in 15% of the 20 patients who received antibiotics before their lumbar puncture and in 71% of the 17 patients who only received antibiotics after the lumbar puncture ($p = 0.001$).

3.1.1 | Background characteristics

Most (55%) of the 22 infants (59% male) aged 0–89 days of age (Table 1) were born preterm before 37 + 0 weeks of gestation: 14% before 28 + 0 and 18% between 28 + 0 and 31 + 6 weeks. Four mothers were carrying GBS. The data on BM by age group are presented in Table 3.

Two of the 15 children (47% male) aged 90 days to 15 years (Table 1) had both otitis media and mastoiditis. Pneumonia, pyelonephritis, a brain abscess and a dental infection were each detected in one patient prior to or simultaneously with, BM. The subgroups of BM by age group are presented in Table 3.

3.1.2 | Clinical characteristics, causative agents and treatment

The clinical characteristics of the infants aged 0–89 days are presented in Table 1. The most common pathogens cultured from either

TABLE 1 Comparison of the clinical findings, laboratory values and outcomes of 37 children with bacterial meningitis (BM), by age.

Variable	Children aged 0–89 days $n=22$ n/N (%) or median	Children aged 90 days to 15 years $n=15$ n/N (%) or median	All children $n=37$ n/N (%) or median	p-Value	Proportion difference (%) and 95% confidence interval
Type of bacterial meningitis					
Community-acquired	9 (41)	9 (60)	18 (49)	0.32	19 (−13 to 51)
Previous surgery	3 (14)	7 (47)	10 (27)	0.056	33 (4 to 62)
Neurosurgical BM	3 (14)	4 (27)	7 (19)	0.41	13 (−14 to 40)
Nosocomial	13 (59)	6 (40)	19 (51)	0.32	−19 (−51 to 13)
Clinical findings at presentation					
Pre-diagnostic antibiotics	15 (68)	5 (33)	20 (54)	0.050	−35 (−66 to −4)
Neurological symptoms[a]	3 (14)	5 (33)	8 (22)	0.41	13 (−14 to 40)
Decreased general condition	19 (86)	12 (80)	31 (84)	0.67	−6 (−31 to 18)
Irritability	18 (82)	6 (40)	24 (65)	0.015	−42 (−71 to −12)
Fever	9 (41)	14 (93)	23 (62)	0.002	52 (28 to 77)
Decreased consciousness	11 (50)	5 (33)	16 (43)	0.50	−17 (−48 to 15)
Vomiting	Not available	12 (80)	12 (32)	0.0001	Not available
Neck stiffness	0	9 (60)	9 (24)	0.0001	60 (35 to 85)
Headache	Not available	8 (53)	8 (22)	0.0001	Not available
Petechiae	0	3 (20)	3 (8)	0.059	20 (0 to 40)
Seizures	1 (5)	2 (13)	3 (8)	0.55	9 (−10 to 28)
Confusion	0	2 (13)	2 (5)	0.16	13 (−4 to 31)
Facial paresis	0	1 (7)	1 (3)	0.41	7 (−6 to 19)
Pupil-asymmetry	1 (5)	0	1 (3)	1.0	−5 (−13 to 4)
Bulging fontanel	1 (5)	0	1 (3)	1.0	−5 (−13 to 4)
Laboratory and imaging results (interquartile range)					
C-reactive protein (mg/L)	19.5 (4.8–75)	85 (28–133)	45 (5–86)	0.033	−61 (−124 to-31)
Leucocyte count in blood ($\times 10^9$/L)	9.2 (4.5–12.5)	14.9 (8.3–22)	9.6 (6.8–16.6)	0.016	−6 (−13 to 1)
Leukocyte count in CSF ($\times 10^6$/L)	360 (45–1848)	1600 (414–2430)	738 (92–2220)	0.052	1230 (−2102 to-10)
Granulocyte percentage in CSF (%)	44 (0–78)	79 (66–96)	75 (10–85)	0.016	−29 (−75 to −4)
Glucose levels in CSF (mmol/L)	2.1 (1.2–3)	3.2 (1–3.4)	2.3 (1.1–3.4)	0.22	−1 (−2 to 1)
Lactate levels in CSF (mmol/L)	3.4 (2.6–3.9)	6.3 (3.1–8.7)	3.5 (2.9–7.0)	0.040	−3 (−5 to 0)
Protein levels in CSF (mg/L)	1784 (1063–2645)	1105 (566–1791)	1277 (702–2569)	0.092	555 (119 to 1524)
Head magnetic resonance imaging performed	5 (23)	7 (47)	12 (32)	0.16	24 (−7 to 55)
Imaging findings consistent with BM	2 (9)	5 (33)	7 (19)	0.095	24 (−7 to 55)

TABLE 1 (Continued)

Variable	Children aged 0–89 days $n = 22$ n/N (%) or median	Children aged 90 days to 15 years $n = 15$ n/N (%) or median	All children $n = 37$ n/N (%) or median	*p*-Value	Proportion difference (%) and 95% confidence interval
CSF culture positive	7 (32)	8 (53)	15 (41)	0.31	22 (−10 to 53)
Blood culture positive	10 (45)	4 (27)	14 (38)	0.31	−19 (−49 to 12)
Treatment and outcome					
Hospital stay in days (median): 1st to 3rd quartile	21 (14–51)	7 (5–14)	15 (7–33)	0.0015	14 (7 to 17)
Intravenous antibiotic therapy in days (median): 1st to 3rd quartile	14 (12–21)	11 (7–25)	14 (10–21)	0.50	3 (−3 to 8)
Unfavourable outcome at discharge	6 (27)	3 (20)	9 (24)	0.71	−7 (−35 to 20)
Unfavourable outcome at 8 months control	3 (14)	2 (13)	5 (14)	1.0	0 (−23 to 22)
Hearing tests performed	18 (82)	10 (67)	28 (76)	0.71	−11 (−40 to 19)
Permanent hearing deficiency	1 (5)	1 (7)	2 (5)	1.0	−2 (−17 to 13)

[a]Neurological symptoms were defined as seizures, confusion, facial paresis, pupil-asymmetry and bulging fontanel.

Abbreviations: BM, bacterial meningitis; CSF, cerebrospinal fluid.

CSF or blood were *E. coli* (18%), GBS (18%) and *Staphylococcus aureus* (9%). Two infants of 0–6 days of age had GBS and so did two infants of 7–89 days of age. All the detected pathogens are presented in Figure 2. Multi-drug resistance, which was defined as resistance to three or more relevant antibiotics, was seen in two bacterial isolates: *S. epidermidis* and *Staphylococcus hominis*. One CSF sample was positive with PCR for *Sphingomonas species* when the CSF culture was negative.

The most frequently used antibiotics were ampicillin (55%), cefotaxime (41%) and gentamycin (27%). Multimodal antibiotic therapy was used to treat 77% of the patients with BM and this ranged from three to seven different antibiotics. There were no cases where the cultured bacteria that caused BM were resistant to the empirically initiated antibacterial treatment. Two patients underwent neurosurgery: one had a brain haemorrhage and one had hydrocephalus. Two patients needed invasive respiratory support.

The clinical characteristics of the children aged 90 days to 15 years are presented in Table 1. The most common pathogen, cultured from either their CSF or blood, was *S. pneumoniae* (20%). *Escherichia coli*, *Staphylococcus capitis* and *N. meningitidis* were all detected once. There was one CSF sample with two cultured bacteria. All the pathogens detected are presented in Figure 2.

Pre-diagnostic antibiotics were administered to 33% of the patients. The most frequently used antibiotics after BM diagnoses were ceftriaxone (87%) and vancomycin (33%). Multimodal antibiotic therapy was used to treat 53% of the patients with BM and this ranged from three to seven different antibiotics. Corticosteroid treatment was given to 60% of the patients as well as antibiotics. Three patients needed neurosurgery and ear-related operations. Six patients received oral antibiotics after discharge and the duration ranged from 7 to 14 days.

3.1.3 | Outcome

The majority (82%) of the infants who were 0–89 days of age underwent hearing tests, using a brainstem auditory evoked response (89%) or otoacoustic emissions and a mechanical source voice (11%). Permanent hearing deficiency was documented in one patient and two received a ventriculoperitoneal shunt. One patient was diagnosed with epilepsy. Six patients had an unfavourable outcome at discharge: four had a GOS score of three and two had a GOS score of four. Three of the patients with a GOS score of three had an unfavourable outcome 8 months after discharge. There were no deaths.

More than two-thirds (67%) of the children aged 90 days to 15 years had hearing tests, using an audiogram (70%), a brainstem auditory evoked response (20%) or otoacoustic emissions (10%). One had a permanent hearing deficiency and another had a ventriculoperitoneal shunt. Other negative outcomes were visual difficulties in one patient and a change in personality in another. Three patients had an unfavourable outcome at discharge: one had a GOS score of three and two had a score of four. The two patients with a

TABLE 2 Bacteria detected in cerebrospinal fluid (CSF) or blood culture by age groups.

Pathogens in CSF or blood culture	Infants aged 0–89 days *n* = 22 *n*/*N* (%)	Children aged 90 days to 15 years *n* = 15 *n*/*N* (%)	All children *n* = 37 *n*/*N* (%)
Escherichia coli	4 (18)	1 (7)	5 (14)
Group B streptococcus	4 (18)	0	4 (11)
Streptococcus pneumoniae	0	3 (20)	3 (8)
Staphylococcus aureus	2 (9)	0	2 (5)
Neisseria meningitidis	0	1 (7)	1 (3)
Staphylococcus epidermidis	1 (5)	0	1 (3)
Staphylococcus capitis	0	1 (7)	1 (3)
Actinomyces sp.	0	1 (7)	1 (3)
Staphylococcus hominis	1 (5)	0	1 (3)
Anaerobic gram-positive cocci	0	1 (7)	1 (3)

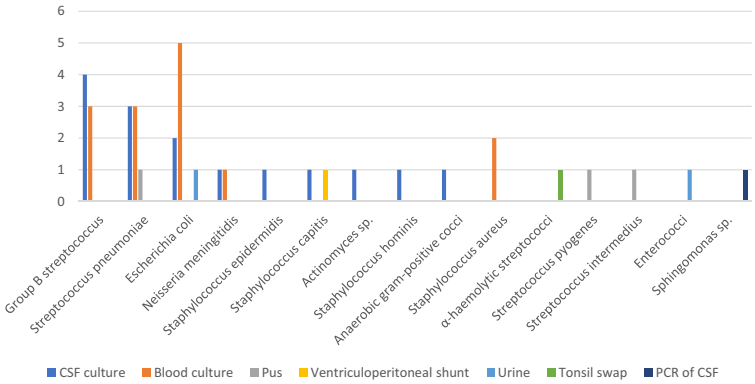


FIGURE 2 Numbers of bacterial detections by culture of cerebrospinal fluid (CSF), blood, pus, ventriculoperitoneal shunt, urine or tonsil swap specimen or by polymerase chain reaction of CSF.

TABLE 3 Subgroups of bacterial meningitis by age groups.

	n (%)
Children aged 0–89 days (*n* = 22)	
Early-onset (0–6 days)	5 (23)
Late-onset (7–89 days)	17 (77)
Late-onset community-acquired	6 (27)
Late-onset nosocomial (not neurosurgical)	8 (36)
Neurosurgical postoperative	3 (14)
Children aged 90 days to 15 years (*n* = 15)	
Community-acquired	9 (60)
Nosocomial (not neurosurgical)	2 (13)
Neurosurgical postoperative	4 (27)

GOS score of four had unfavourable outcomes 8 months after discharge. There were no deaths.

The univariate analysis showed that a positive CSF culture was associated with an unfavourable outcome at discharge ($p = 0.02$), but not 8 months after discharge ($p = 0.1$; Appendix S1). Nosocomial meningitis ($p = 0.007$) and preterm birth ($p = 0.04$) were associated with an unfavourable outcome 8 months after discharge.

4 | DISCUSSION

The incidence of paediatric BM was low in Southwestern Finland during 2011–2018. In particular, community-acquired BM was rare in children aged 90 days to 15 years, but the proportion of infants aged 0–89 days with nosocomial BM was prominent. A large number of cases continued to have negative CSF and blood bacterial cultures. The outcomes in both age groups were generally good.

Between 2010 and 2015 the incidence rates of BM in Northern Sweden were 1.9–3.4/100 000 in infants and children.[12] The incidence was highest among infants and lowest among adolescents and was approximately the same level as in our study (5.7/100 000/year). The global incidence of BM in children has decreased and a major reason for this progress has been the increased use of vaccines against the predominant pathogens. Differences in the diagnostics, recording and definitions of BM have hampered the assessment of the true incidence of BM and comparisons between studies. The pre-diagnostic administration of antibiotics was frequent in our study population and bacterial PCR tests on CSF specimens were infrequently carried out. To avoid missing cases due to this, we also included culture-negative cases based on the relevant ICD-10 codes, clinical presentation and laboratory findings.

Streptococcus pneumoniae is a dominant pathogen that causes BM in childhood. For example, this was reported by a study from the United States that covered the period 1998–2007, which found that *S. pneumoniae* causes over a third of all BM in infants and children.[13] However, we only detected three cases of pneumococcal meningitis in children from 90 days to 15 years of age. The 10-valent pneumococcal conjugate vaccine was added to the Finnish national vaccination programme in 2010, just before the current study began. This was followed by a rapid decrease in the incidence of pneumococcal meningitis in children in Finland: 54% in children aged 5–17 years and 64% in children aged 0–4 years of age.[14] Replacement by non-vaccine serotypes has been seen mainly in older adults.[14] Although meningococcal vaccines are not included in the Finnish national vaccination programme for children, only one case of *N. meningitidis* BM was found in this study. Other studies have indicated that meningococcal diseases are more common in some other European countries than in Finland. For example, one Icelandic study reported that *N. meningitidis* was the most common causative pathogen of BM.[15] No cases of BM due to Hib were documented in our study, as it has disappeared due to the high coverage of vaccinations.[16]

Our study showed the incidence of BM in infants 0–89 days of age was high compared to children aged 0–60 days in another study.[13] Our incidence rate of 0.7 per 1000 live births was in line with the estimated incidences of neonatal BM of 0.3 per 1000 live births in high-income countries and up to 3–6 per 1000 live births in low-income and middle-income countries.[17] As expected, GBS and *E. coli* were the dominant pathogens in infants. It is worth noting that no BM cases caused by *Listeria monocytogenes* were detected. Maternal GBS prophylaxis with antibiotics has been reported to be efficient against early-onset disease, but not against late-onset disease.[18] Maternal GBS vaccines are urgently needed to prevent late-onset GBS disease.[5] Neonatal nosocomial infections can, to some extent, be prevented by breastfeeding, probiotics and strict infection prevention programmes in neonatal units.[19] The rapid initiation of antibiotic treatment for any suspicion of sepsis may prevent the infection developing into BM.[20] Despite these measures, newborn infants, particularly those born prematurely, are susceptible to invasive bacterial infections, due to their immature and inexperienced innate and adaptive immune systems. Preterm infants also have inadequate protection against infectious agents through maternal immunity. Our findings demonstrated this, as 55% of the infants were born prematurely and 14% of them before 28 + 0 and 18% between 28 + 0 and 31 + 6 weeks of gestation. Moreover, the innate cytokine response against pathogens in a neonate can be inadequate or, conversely, overwhelming and has been associated with increased disease severity.[21]

We found that 41% of the CSF cultures were positive and that negative cultures were associated with administering antibiotics before a lumbar puncture. Pre-diagnostic antibiotics were used for 54% of the patients in our study, compared to 35%–46% in other studies.[22] Certain bacteria can be completely sterilised in CSF within 2 h of parenteral antibiotics[6] and an interval of over 6 h between administering antibiotics and a lumbar puncture can reduce culture positivity from 100% to 40%.[23] Using PCR testing as well as culturing bacteria in CSF resulted in a more sensitive and rapid yield, compared to just the using cultures.[24] PCR was not routinely used during our study period, but these data do support its use.

We found a lower rate of permanent hearing deficiency (5%) than previously reported (22%–30%).[7] This may have been due to the success of pneumococcal vaccines, by decreasing the proportion pneumococcal BM, as *S. pneumoniae* is a key pathogen that causes hearing loss after BM.[7] The overall functional outcome was unfavourable in 14% of the children, in accordance with previous studies (10%–18%).[25,26] In our study, nosocomial meningitis and preterm birth were correlated with unfavourable outcomes 8 months after discharge. However, these findings should be interpreted with caution, because unfavourable outcomes only occurred in a small number of subjects and the results were based on univariate analyses. Despite this, our study highlighted the increased role of nosocomial BM and its potential to cause long-term morbidity. It also supported earlier evidence that prematurity can predict unfavourable outcomes.[27] There were no deaths in our study, but a larger study population would have provided a more reliable estimate of the mortality rate. Global mortality due to childhood BM has been reported to range from 2% to 33%.[28,29]

Our study had some limitations. It was a single-centre study with a small number of patients, but the design enabled uniform and detailed data collection. Nevertheless, there was a risk of inaccuracies in the retrospectively documented clinical data. The study population was heterogenic, which meant we had very small subgroups of patients, but our findings do provide an overview of paediatric BM in our area. Using the GOS with small infants and children may present challenges and it may also be difficult to differentiate moderate disability from mild disability using medical records. However, we believe that our main finding of generally good outcomes after BM was reliably determined by using the GOS scale. The patients included in this study may not represent the whole population of children in Finland. We were unable to exclude the possibility of neurosurgery itself being the cause of complications or an unfavourable outcome in some patients. Furthermore, we had no long-term follow-up data, or information on quality of life after BM, which has been reported to be impaired.[30]

5 | CONCLUSION

This study found a low incidence of BM in infants and children in Southwest Finland between 2011 and 2018. GBS and *E. coli* were the dominant bacteria in children of 0–89 days of age. The proportion of nosocomial BM was high. The likelihood of an unfavourable outcome was relatively low and there were no deaths. The changing epidemiology of BM should be considered when developing further strategies to improve prevention and treatment.

AUTHOR CONTRIBUTIONS

Sakke Niemelä: Conceptualization; data curation; formal analysis; investigation; methodology; resources; validation; visualization; writing – original draft; writing – review and editing. **Laura Lempinen:** Conceptualization; formal analysis; methodology; resources; validation; visualization; writing – review and editing. **Eliisa Löyttyniemi:** Data curation; formal analysis; software; writing – review and editing. **Juha O. Grönroos:** Methodology; validation; writing – review and editing. **Raakel Luoto:** Conceptualization; data curation; investigation; methodology; validation; writing – original draft; writing – review and editing. **Ville Peltola:** Conceptualization; data curation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing. **Jussi Jero:** Conceptualization; data curation; methodology; project administration; supervision; validation; visualization; writing – original draft.

ACKNOWLEDGEMENTS

We thank Elizabeth Nyman for language consultations and Emmi Alimattila for technical support.

FUNDING INFORMATION

This study did not receive any specific funding.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ORCID

Sakke Niemelä https://orcid.org/0000-0002-8479-9096

REFERENCES

1. Mijovic H, Sadarangani M. To LP or not to LP? Identifying the etiology of pediatric meningitis. Pediatr Infect Dis J. 2019;38:S39-42.
2. Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van de Beek D, van der Ende A. Changing epidemiology of bacterial meningitis since introduction of conjugate vaccines: 3 decades of national meningitis surveillance in the Netherlands. Clin Infect Dis. 2021;73:e1099-107.
3. Schlech WF, Ward JI, Band JD, et al. Bacterial meningitis in the United States, 1978 through 1981: the national bacterial meningitis surveillance study. JAMA. 1985;253:1749-54.
4. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348:1737-46.
5. Delara M, Vadlamudi NK, Sadarangani M. Strategies to prevent early and late-onset group B streptococcal infection via interventions in pregnancy. Pathogens. 2023;12:229.
6. Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis. 2010;10:32-42.
7. Arditi M, Mason EO Jr, Bradley JS, et al. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics, and outcome related to penicillin susceptibility and dexamethasone use. Pediatrics. 1998;102:1087-97.
8. Lucas MJ, Brouwer MC, van de Beek D. Neurological sequelae of bacterial meningitis. J Infect. 2016;73:18-27.
9. Haffner DN, Machie M, Hone E, Said RR, Maitre NL. Predictors of neurodevelopmental impairment after neonatal bacterial meningitis. J Child Neurol. 2021;36:968-73.
10. Corless CE, Guiver M, Borrow R, Edwards-Jones V, Fox AJ, Kaczmarski EB. Simultaneous detection of *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* in suspected cases of meningitis and septicemia using real-time PCR. J Clin Microbiol. 2001;39:1553-8.
11. Beers SR, Wisniewski SR, Garcia-Filion P, et al. Validity of a pediatric version of the Glasgow Outcome Scale-extended. J Neurotrauma. 2012;29:1126-39.
12. Johansson Kostenniemi U, Norman D, Sellin M, Silfverdal SA. Sustained reductions of invasive infectious disease following general infant *Haemophilus influenzae* type b and pneumococcal vaccination in a Swedish Arctic region. Acta Paediatr. 2019;108:1871-8.
13. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. N Engl J Med. 2011;364:2016-25.
14. Polkowska A, Rinta-Kokko H, Toropainen M, Palmu AA, Nuorti JP. Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland. Vaccine. 2021;39:3216-24.
15. Snaebjarnardóttir K, Erlendsdóttir H, Reynisson IK, et al. Bacterial meningitis in children in Iceland, 1975–2010: a nationwide epidemiological study. Scand J Infect Dis. 2013;45:819-24.
16. Peltola H, Kilpi T, Anttila M. Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunisation with conjugate vaccines. Lancet. 1992;340:592-4.
17. Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. Clin Perinatol. 2015;42:29-45.
18. Nusman CM, Snoek L, van Leeuwen LM, et al. Group B streptococcus early-onset disease: new preventive and diagnostic tools to decrease the burden of antibiotic use. Antibiotics (Basel). 2023;12:489.
19. Deshmukh M, Patole S. Prophylactic probiotic supplementation for preterm neonates – a systematic review and meta-analysis of non-randomized studies. Adv Nutr. 2021;12:1411-23.
20. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770-80.
21. Yu JC, Khodadadi H, Malik A, et al. Innate immunity of neonates and infants. Front Immunol. 2018;9:1759.
22. Peltola H, Roine I, Kallio M, Pelkonen T. Unusual gram-negative bacteria cause more severe bacterial meningitis than the three classical agents in children. Acta Paediatr. 2022;111:1404-11.
23. Stevens JP, Lively A, Jerris R, Yildirim I, Lantis P. Recognition and outcomes of pneumococcal meningitis in 2 tertiary pediatric hospitals since the introduction of the 13-valent pneumococcal conjugate vaccine. Pediatr Emerg Care. 2022;38:e354-9.
24. Leber AL, Everhart K, Balada-Llasat J-M, et al. Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. J Clin Microbiol. 2016;54:2251-61.
25. Svendsen MB, Ring Kofoed I, Nielsen H, Schønheyder HC, Bodilsen J. Neurological sequelae remain frequent after bacterial meningitis in children. Acta Paediatr. 2020;109:361-7.
26. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J. 1993;12:389-94.
27. Ouchenir L, Renaud C, Khan S, et al. The epidemiology, management, and outcomes of bacterial meningitis in infants. Pediatrics. 2017;140:e20170476.
28. Jung YJ. Short information: bacterial meningitis in very low birthweight infants in Korea from 2013–2016. Pediatr Int. 2022;64:e15057.

29. Lovera D, Amarilla S, Araya S, et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis. Pediatr Emerg Care. 2022;38:637-43.
30. Rugemalira E, Karppinen M, Savonius O, et al. Health-related quality of life after childhood bacterial meningitis. Pediatr Infect Dis J. 2021;40:987-92.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Niemelä S, Lempinen L, Löyttyniemi E, Grönroos JO, Luoto R, Peltola V, et al. Finnish paediatric study found a low incidence of bacterial meningitis from 2011 to 2018 but a substantial proportion of nosocomial meningitis. Acta Paediatr. 2024;113:327–335. https://doi.org/10.1111/apa.16991

Niemelä S, Oksi J, Jero J, Löyttyniemi E, Rahi M, Rinne J, Posti JP & Laukka D (2024)
Glioma grade and post-neurosurgical meningitis risk.
Acta Neurochir

III

Acta Neurochirurgica (2024) 166:300
https://doi.org/10.1007/s00701-024-06193-w

ORIGINAL ARTICLE

Glioma grade and post-neurosurgical meningitis risk

Sakke Niemelä[1] · Jarmo Oksi[2] · Jussi Jero[3] · Eliisa Löyttyniemi[4] · Melissa Rahi[5,6] · Jaakko Rinne[5,6] · Jussi P. Posti[5,6] · Dan Laukka[5,6]

Received: 29 April 2024 / Accepted: 7 July 2024

Abstract

Background Post-neurosurgical meningitis (PNM) constitutes a grave complication associated with substantial morbidity and mortality. This study aimed to determine the risk factors predisposing patients to PNM following surgery for low- and high-grade gliomas.

Methods We conducted a retrospective analysis encompassing all patients who underwent glioma surgery involving craniotomy at Turku University Hospital, Turku, Finland, between 2011 and 2018. Inclusion criteria for PNM were defined as follows: (1) Positive cerebrospinal fluid (CSF) culture, (2) CSF leukocyte count $\geq 250 \times 10^6$/L with granulocyte percentage $\geq 50\%$, or (3) CSF lactate concentration ≥ 4 mmol/L, detected after glioma surgery. Glioma grades 3–4 were classified as high-grade (n = 261), while grades 1–2 were designated as low-grade (n = 84).

Results Among the 345 patients included in this study, PNM developed in 7% (n = 25) of cases. The median time interval between glioma surgery and diagnosis of PNM was 12 days. Positive CSF cultures were observed in 7 (28%) PNM cases, with identified pathogens encompassing *Staphylococcus epidermidis* (3), *Staphylococcus aureus* (2), *Enterobacter cloacae* (1), and *Pseudomonas aeruginosa* (1). The PNM group exhibited a higher incidence of reoperations (52% vs. 18%, $p < 0.001$) and revision surgery (40% vs. 6%, $p < 0.001$) in comparison to patients without PNM. Multivariable analysis revealed that reoperation (OR 2.63, 95% CI 1.04–6.67) and revision surgery (OR 7.08, 95% CI 2.55–19.70) were significantly associated with PNM, while glioma grade (high-grade vs. low-grade glioma, OR 0.81, 95% CI 0.30–2.22) showed no significant association.

Conclusions The PNM rate following glioma surgery was 7%. Patients requiring reoperation and revision surgery were at elevated risk for PNM. Glioma grade did not exhibit a direct link with PNM; however, the presence of low-grade gliomas may indirectly heighten the PNM risk through an increased likelihood of future reoperations. These findings underscore the importance of meticulous post-operative care and infection prevention measures in glioma surgeries.

Keywords Bacterial meningitis · Complication · Post-neurosurgical meningitis · Glioma surgery

✉ Sakke Niemelä
sasani@utu.fi

Jarmo Oksi
jarmo.oksi@tyks.fi

Jussi Jero
jussijero@gmail.com

Eliisa Löyttyniemi
eliisa.loyttyniemi@utu.fi

Melissa Rahi
melissa.rahi@tyks.fi

Jaakko Rinne
jaakko.rinne@tyks.fi

Jussi P. Posti
jussi.posti@tyks.fi

Dan Laukka
dan.laukka@tyks.fi

[1] Department of Otorhinolaryngology, Turku University Hospital and University of Turku, Turku, Finland

[2] Department of Infectious Diseases, Turku University Hospital and University of Turku, Turku, Finland

[3] Department of Otorhinolaryngology, Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[4] Unit of Biostatistics, University of Turku and Turku University Hospital, Turku, Finland

[5] Clinical Neurosciences, University of Turku, Turku, Finland

[6] Department of Neurosurgery, Neurocenter, Turku University Hospital, Turku, Finland

Published online: 18 July 2024

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
CSF	Cerebrospinal fluid
OR	Odds ratio
PNM	Post-neurosurgical meningitis
Q1	Lower quartile
Q3	Upper quartile

Introduction

Gliomas are serious medical conditions consisting of approximately 80% of all malignant brain tumors [32]. The incidence rate of gliomas is around 7/100 000 in Finland [25]. High-grade gliomas (grade 3–4) constitute 85% of all gliomas while the rest are low grade gliomas (grade 1–2) [27]. Five-year survival rate for high-grade gliomas ranges from 3 to 22% and for low grade gliomas from 54 to 82% [27].

The incidence of surgical site infections following craniotomy ranges from 1 to 10%, while the occurrence of post-neurosurgical meningitis (PNM) varies between 2%-9% [16, 20, 29]. Approximately 3% of patients undergoing glioma surgery necessitate reoperations due to post-operative infections [22]. PNM causes clinically significant morbidity and mortality and prolongs treatment periods and causes potentially adverse effects regarding patient survival [13, 16, 29, 31].

Risk factors for PNM include reoperations, placement of postoperative ventricular shunts and lumbar catheters, male sex, diabetes mellitus, corticosteroid use, cerebrospinal fluid (CSF) leak, prolonged surgery, and genetic predisposition [1, 16, 17, 19, 20, 29]. Gliomas are associated with immunosuppression while immune profiles may vary between different glioma grades [3, 14]. Therefore, glioma grade might affect perioperative risk of infection.

Prophylactic antibiotics have been shown to reduce superficial and deep infections during neurosurgery [17], however, some studies prefer the correct sewing technique over antibiotic prophylaxis to prevent postoperative infections as the prevention of CSF leak is of utmost importance to prevent [4]. The recommended regimen is targeted mainly against gram-positive agents, such as *Staphylococcus epidermidis* and *Staphylococcus aureus*, which have been the main pathogens causing PNM [30]. Perhaps due to this selection of prophylactic antibiotics, gram-negative bacteria such as *Acinetobacter baumannii, Klebsiella pneumoniae* and *Escherichia coli* have become increasingly common agents causing PNM according to recent studies [18, 34].

Careful practices during suture sewing are essential to prevent infections. Deep infections often require surgical debridement or reoperation along with systemic antibiotics to overcome the infection [17]. Along with gold-standard CSF culture for detection of pathogens, imaging with magnetic resonance imaging of suspected PNM patients is often required to rule out abscess or empyema, and to possibly detect hydrocephalus [16].

While many previous studies have focused on surgical site infections following glioma surgery, the incidence of PNM and its associated risk factors remain uncertain. It is also unclear whether the grade of glioma impacts the risk of PNM, as most studies have included only high-grade gliomas. Implementing effective infection prevention strategies and vigilant surveillance for post-operative infections are essential to optimize outcomes in this patient population.

Our aim was to investigate the incidence of PNM after surgery for gliomas of different grades, and risk factors associating with PNM in Turku University Hospital, Finland, between 2011–2018.

Methods

Patient selection

This was a retrospective, descriptive cohort study. Data collection was retrolective. A database search for glioma patients treated with craniotomies between 2011–2018 in Turku University Hospital, Finland, was performed. Our institution serves as a tertiary referral center within the Hospital District of Southwest Finland, overseeing the management of all central nervous tumors among a population of approximately 490 000.

The investigation assessed patients who underwent craniotomy for World Health Organization grade 1–4 glioma. We systematically examined the pathological reports of a consecutive cohort comprising 1 161 individuals undergoing craniotomy for intracranial tumors between 2011 and 2018. International Classification of Diseases 10th edition codes C71.*, The Nordic Medico-Statistical Committee codes AAB00, AAB10 and AW*** were used to identify appropriate patients. Out of this cohort, 345 patients received a glioma diagnosis and were subsequently enrolled in the study. The patients operated for gliomas were defined as the intervention group.

Included patients for PNM had at least one of the possible symptoms of PNM defined as either fever, headache, decreased mental status, seizures, or neck stiffness. Additionally, they had to have at least one of the following inclusion criteria: 1. CSF culture positivity, 2. CSF leukocyte count $\geq 250 \times 10^6$/L with granulocyte percentage $\geq 50\%$ [15] or 3. CSF lactate ≥ 4 mmol/L [16]. Finally, 25 patients with PNM were identified. CSF samples were usually obtained by lumbar puncture after imaging of the head showed that

there was no evidence of increased intracranial pressure and laboratory results showed that there were no abnormalities in blood coagulation. Occasionally, a CSF sample was obtained from a craniotomy wound site on admission following the safety measures described above. Outcome was classified into either patients who developed PNM (cases) and patients without PNM (controls).

Definitions

Revision surgery was defined as a reoperation occurring earlier than 100 days after primary surgery, and reoperation was defined as a repetitive glioma surgery in the patient history without time limits. The revision and reoperation surgeries were performed from the same site as the index surgery.

The reason for reoperations were confirmed or suspected cases of recurring or residue gliomas after imaging assessment. The reasons for revision surgeries were any complication requiring revision surgery such as hydrocephalus, CSF leak from the wound or surgical site infection or intracranial infections.

The suspect of a local wound infection rose if the wound had swelling, redness, pain, or secretion of pus.

Preoperative management

The skin of operative area is cleaned with chlorhexidine. Patients received routinely cefuroxime 3 g intravenous infusion in the operation room before the start of surgery. Patients not tolerating cefuroxime, intravenous clindamycin 600 mg was used as prophylaxis instead. Patients did not routinely receive any follow-up antibiotics. All patients undergoing revision surgery or reoperations received the above stated antibiotic prophylaxis. The skin is closed subcutaneously and intradermally with antibacterial sutures [23] and the skin is closed with clips. The techniques for sterilization of the scalp, the type and duration of prophylactic antibiotics were similar in all aspects for low-grade glioma surgery and high-grade glioma surgery. The only exception is reoperations, which are more common in low-grade glioma patients and for which some neurosurgeons advocate the use of postoperative antibiotics for 24–48 h.

Statistical analysis

Distributions were evaluated using visual evaluation, normal quantile plot, skewness and kurtosis measures. Due to the skewness of the distributions, we used medians in reporting results. Continuous data were summarized with median and lower (Q1) and upper (Q3) quartile and compared between patients with PNM and those without PNM with Wilcoxon rank sum test. Association between two categorical variables was first evaluated with Fisher's exact test. Furthermore, logistic regression was performed to reoperation and revision surgery, separately for each explanatory variable (univariate approach) and reported with odds ratio (OR) and its 95% confidence intervals (CI). After univariate modelling, multivariable model was built up based on univariate results. P values of < 0.05 (two-tailed) were regarded as statistically significant. The data analysis was generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Data availability statement

The data generated during this study is available from the corresponding author on a reasonable request.

Results

Background information and univariate analysis

Out of the 345 patients who underwent glioma surgery, the median age was 60 years (Q1-Q3: 44–68 years), with 46% (n = 159) being female. High-grade glioma was diagnosed in 76% of cases, while low-grade glioma was diagnosed in 24% of cases, and 20% of the surgeries were reoperations due to recurrent glioma.

PNM rate was 7% (n = 25), with a median time interval between glioma surgery and the diagnosis of PNM being 12 days (Q1-Q3: 7–20 days). Patients who sustained PNM were significantly younger, with a median age of 49 years (Q1-Q3: 32–62 years) compared to 60 years (Q1-Q3: 46–68 years) in those without PNM ($p = 0.013$). Additionally, patients with PNM had low-grade gliomas 44% (11/25) compared to high-grade gliomas 56% (14/25), $p = 0.027$. However, with low-grade gliomas, PNM was occurring more often (13%, 11/84) versus high-grade (5.4%, 14/261). Patients with PNM had a greater frequency of reoperations (52% vs. 18%, $p < 0.001$) and revision surgeries (40% vs. 6%, $p < 0.001$) compared to those without PNM. Statistically significant associations between gender and reoperation ($p = 0.35$), revision surgery ($p = 0.43$) or low-grade/high-grade gliomas ($p = 0.45$) were not found. Other statistical analyses shown in Table 1.

Nearly all patients who had received previous radiotherapy also underwent re-operation. Due to this significant overlap, we determined that including both factors in the same analysis would not be logical, as it could confound the results. Additionally, we noted that re-operations were more frequent than previous radiotherapy in the PNM group.

Table 1 Univariate Analysis of Risk Factors for post-neurosurgical meningitis (PNM)

VARIABLE	PNM (n = 25)	No PNM (n = 320)	p-value
Age, median (Q1-Q3)	49 (32–62)	60 (46–68)	0.01
Sex (female)	14 (56%)	145 (45%)	0.31
Sex (male)	11 (44%)	175 (55%)	0.31
BMI, median (Q1-Q3)	28 (23–31)	26 (24–30)	0.54
ASA classification			0.97
ASA 1	0 (0%)	4 (1%)	
ASA 2	2 (8%)	27 (8%)	
ASA 3	15 (60%)	197 (62%)	
ASA 4	8 (32%)	87 (27%)	
ASA 5	0 (0%)	1 (0%)	
Glioma grade			0.03
Grade 1	4 (16%)	13 (4%)	
Grade 2	7 (28%)	60 (19%)	
Grade 3	3 (12%)	41 (13%)	
Grade 4	11 (44%)	206 (64%)	
High-grade vs. Low-grade glioma			0.027
Low-grade (grade 1–2)	11 (44%)	73 (23%)	
High-grade (grade 3–4)	14 (56%)	247 (77%)	
Reoperation	13 (52%)	57 (18%)	0.001
Revision surgery	10 (40%)	18 (6%)	0.001
Emergency surgery	3 (12%)	11 (3%)	0.07
Operation time (min), median (Q1-Q3)	202 (165–301)	207 (156–251)	0.22
CSF sample available	25 (100%)	24 (8%)	0.001
CSF leukocyte count (cells/mm^3), median (Q1-Q3)	425 (86–1140)	7 (1–35)	0.001
CSF neutrophil count (%), median (Q1-Q3)	79 (55–92)	2 (0–9)	0.001

ASA American Society of Anesthesiologists, ***BMI*** body mass index,, ***CSF*** cerebrospinal fluid, ***PNM*** post-neurosurgical meningitis, ***Q1*** lower quartile, ***Q3*** upper quartile

Table 2 Results of multivariable analysis

Covariate	OR (95% CI)	P-value
Age	0.98 (0.95–1.0)	0.11
Glioma grade (grade 3–4 vs. grade 1–2)	0.81 (0.30–2.2)	0.69
Revision surgery	7.1 (2.6–19.7)	< 0.001
Reoperation	2.6 (1.0–6.7)	0.042

CI Confidence interval, ***OR*** Odds ratio

Multivariable analysis

Multivariable analysis revealed that reoperation (OR 2.63, 95% CI 1.04–6.67) and revision surgery (OR 7.08, 95% CI 2.55–19.70) were significantly associated with PNM, while age (OR 0.98, 95% CI 0.95–1.01) and glioma grade (high-grade vs. low-grade, OR 0.81, 95% CI 0.30–2.22) showed no significant associations (Table 2).

Causative pathogens

Positive CSF cultures were observed in 7 (28%) PNM cases, The pathogens acquired from CSF culture were *S. epidermidis* (3), *S. aureus* (2), *Enterobacter cloacae* (1) and *Pseudomonas aeruginosa* (1). There were 40 (12%) patients with suspected wound infection, of which 19 (6%) presented pathogen in bacterial culture causing the local infection. Five patients with culture confirmed local wound infection also had CSF culture confirmed PNM. The difference was not statistically significant (p = 0.1). Blood cultures were taken from 58 (17%) of total patients with only one (0.3%) blood culture positive patient. All pathogens detected are presented in Fig. 1.

Discussion

This study retrospectively analyzed the characteristics of PNM occurring after glioma surgery at Turku University Hospital, Finland, between 2011–2018. The incidence of

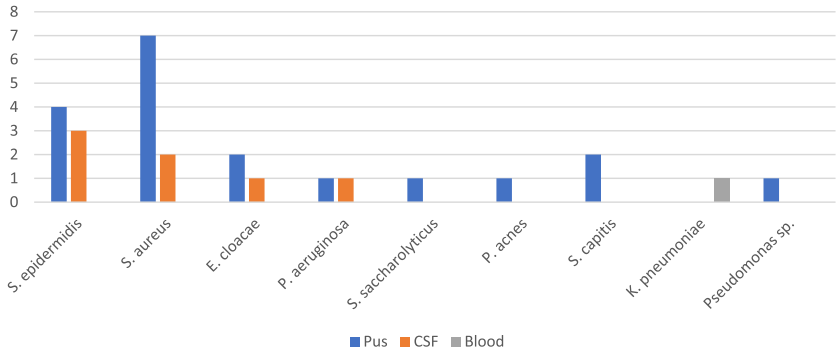


Fig. 1 All bacteria detected from 345 patients after glioma surgery. Y-axis shows the number of bacteria

PNM after glioma surgery was 7%. The grade of glioma was not an independent risk factor for PNM, but low-grade gliomas had a higher rate of PNM because of the higher proportion of reoperations. Reoperation and revision surgery for post-operative wound complications were independent risk factors for PNM.

Patients with high-grade gliomas are older and thus have more comorbidities than their younger counterparts [25]. Therefore, it would be plausible that patients with high-grade gliomas would be more prone for PNM than patients with low-grade gliomas. Surprisingly, our study found that the PNM rate was higher in low-grade gliomas when compared to high-grade gliomas, as it would be reasonable to think the other way around, because for example operation time is usually longer considering high-grade gliomas, and thus the risk of postoperative infections could be higher.

However, in the multivariable analysis, glioma grade did not reach independent risk factor for PNM. Incidence of PNM was in the upper proportion when compared to previously reported incidences of 0.5%-8.9% [11, 19, 29]. The perioperative measures to prevent infections during craniotomy are in need of constant evaluation and improvements. A study by Cao et al. in 2017 found that prophylactic antibiotics did not prevent postoperative infections in clean craniotomies but caused more CSF negative cultures and more multidrug-resistant bacteria [4]. They concluded that precise sewing techniques may be even more important than antibiotic prophylaxis in the prevention of postoperative infections, for example to prevent CSF leakage, which is a major risk factor for developing PNM [4]. The role of diathermy compared to scalpel in regards on SSI were investigated in a Cochrane review, and no statistical differences were found, although the trials were underpowered [5, 23]. The overall careful tissue handling, and the use of antibacterial sutures is proven to reduce SSIs [23]. This is worth consideration, but antibiotic prophylaxis is nevertheless recommended [17, 31]. Using vancomycin intravenously combined with cephalosporins as prophylactic antibiotics during craniotomies seems to decrease the risk of surgical site infections [10]. Also, the use of vancomycin powder has been proven to reduce postoperative infections [28]. Routine CSF sampling among asymptomatic patients should be avoided [16].

A study performed in 2009 found that there was no statistically significant difference on survival between patients with or without postoperative infections after glioma surgery [2]. A few years after, a study with contradictory findings by De Bonis et al. presented that postoperative infections may in fact prolong the survival of patients (medians 16 months vs. 30 months) after glioblastoma surgery, perhaps by activating immune system [12]. However, another study found that glioma patients with postoperative infections tend to have 30% decreased median overall survival [31]. Even more recently, a study with a large population of 3784 patients found that there was no statistically significant difference on survival between patients with or without postoperative infections (median 5 months vs. 6 months, $p = 0.17$) [8]. PNM after glioma surgery often leads to delays in postoperative treatments such as radiotherapy or chemotherapy [31]. PNM also causes prolongation of hospital stay and thus more costs [16, 22].

Reoperations are a significant risk factor for developing PNM after glioma surgery [7, 19, 22, 29]. Risks of reoperations should be noted and carefully considered with each patient's medical history in mind. Frailty has been recognized as an indicator of unfavorable outcome, post-operative complications, and mortality among patients with glioblastoma [21, 35], but unfortunately, we were not able to implement frailty-index in our study. There were no statistical differences on developing PNM with ASA class or duration of the surgery, as previously reported in some studies [17], but another study presented that ASA class or glioma grade were not statistically associated with elevated risk for developing PNM [22]. Glioma grade does not seem to be associated with postoperative complications in general by a recent paper by Morshed et al. [24].

The demographic data of patients with and without PNM were quite similar, which is important to note in clinical work. We proved that PNM is a compartmentalized central

nervous system infection, because a large part of blood cultures remained negative (98%).

The rate of detected CSF culture positivity of 28% was lower compared with previous studies [26, 29]. However, recently the incidence of CSF culture positive postoperative meningitis has been decreasing according to a study performed in China in 2014, where only 10% of patients had a CSF culture positive PNM after craniotomy [6]. The use of prophylactic antibiotics at the beginning of the surgery has been proven to be effective in prevention of postoperative superficial and deep infections [17] – however, pre-diagnostic antibiotics reduces the positivity rate of the standard CSF culture [9], but the strategy would nevertheless be supported. The use of multiplex or quantitative polymerase chain reaction has been proven to be more sensitive and specific methods detecting pathogens compared to CSF culture, which should be used more often in the future [9].

Emergency surgeries were relatively rare (4%) in patients undergoing craniotomy. The frequency of PNM was higher in patients undergoing emergency surgery, but there was no statistically significant difference compared to patients undergoing elective surgery ($p = 0.07$). Old age and emergency surgeries have been identified as risk factors for PNM in previous studies [7, 33]. However, in our study, younger age of patients seemed to controversially be a risk factor for PNM. That may be because younger patients undergo revision surgeries or reoperations more often, and therefore they are at higher risk of PNM. The reasons for the 7% incidence of PNM after glioma surgery could be due to careful case ascertainment, and furthermore, the background is complex and cannot be further investigated in the current study setting.

This study has some limitations. Being a single center study is a limitation, and secondly, the risk of inaccuracy in the retrospectively documented data of patients is always possible. We were not able to include imaging results of patients, which is also a limitation. All patients received perioperative antibiotic prophylaxis, but we were not able to gather information on the rate of antibiotic administration to treat PNM before lumbar puncture. It is possible that some culture-negative PNM cases may have been aseptic meningitis. However, the solid definition of inclusion of PNM patients was a strength in this study, and it probably ruled out aseptic meningitis cases. It is also possible, that the included patients may not represent the whole population of glioma surgery patients in Finland.

Conclusions

This study found a 7% incidence of PNM after glioma surgery. CSF culture positivity rate was 28%. Reoperations and revision surgeries were independent risk factors for PNM. We found a higher rate of PNM in patients with low-grade than high-grade gliomas, possibly due to higher proportion of reoperations. Glioma grade was not an independent risk factor for PNM. Further research is needed in future to develop efficient strategies to prevent PNM complications by identifying risk factors.

Acknowledgements We thank Emmi Alimattila for technical support.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sakke Niemelä and Dan Laukka. Statistical analysis were performed by statistician Eliisa Löyttyniemi. The first draft of the manuscript was written by Sakke Niemelä and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding Open Access funding provided by University of Turku (including Turku University Central Hospital). SN is funded by Rauno and Anne Puolimatka Foundation and Centre of Excellence in Infections and Microbiomes of Turku University Hospital -organization.

JPP is funded by the Academy of Finland (grant 17379) and the Maire Taponen foundation.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Hospital District of Southwest Finland and Turku Clinical Research Center and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Aghi MK, Batchelor TT, Louis DN, Barker FG, Curry WT (2009) Decreased rate of infection in glioblastoma patients with allelic loss of chromosome 10q. J Neurooncol 93:115–120
2. Bohman LE, Gallardo J, Hankinson TC, Waziri AE, Mandigo CE, McKhann GM 2nd, Sisti MB, Canoll P, Bruce JN (2009)

The survival impact of postoperative infection in patients with glioblastoma multiforme. Neurosurgery 64:828–834
3. Bracci PM, Rice T, Hansen HM, Francis SS, Lee S, McCoy LS, Shrestha PP, Warrier G, Clarke JL, Molinaro AM, Taylor JW, Wiencke JK, Wrensch MR (2022) Pre-surgery immune profiles of adult glioma patients. J Neurooncol 159(1):103–115
4. Cao Y, Pu K, Li G, Yan X, Ma Y, Xue K, Sun Z, Li Q (2017) The role of antibiotic prophylaxis in clean neurosurgery. World Neurosurg 100:305–310
5. Charoenkwan K, Chotirosniramit N, Rerkasem K (2012) Scalpel versus electrosurgery for abdominal incisions. Cochrane Database Syst Rev (6):CD005987. Update in: Cochrane Database Syst Rev 6:CD005987
6. Chen C, Zhang B, Yu S, Sun F, Ruan Q, Zhang W, Shao L, Chen S (2014) The incidence and risk factors of meningitis after major craniotomy in China: a retrospective cohort study. PLoS One 9:e101961
7. Chen CH, Chang CY, Lin LJ, Chen WL, Chang YJ, Wang SH, Cheng CY, Yen HC (2016) Risk factors associated with postcraniotomy meningitis: A retrospective study. Medicine (Baltimore) 95:e4329
8. Chen Y-R, Ugiliweneza B, Burton E, Woo SY, Boakye M, Skirboll S (2017) The effect of postoperative infection on survival in patients with glioblastoma. J Neurosurg 127:807–811
9. Corless CE, Guiver M, Borrow R, Edwards-Jones V, Fox AJ, Kaczmarski EB (2001) Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. J Clin Microbiol 39:1553–1558
10. CorsiniCampioli C, Challener D, Comba IY, Shah A, Wilson WR, Sohail MR, Van Gompel JJ, O'Horo JC (2022) Overview and risk factors for postcraniotomy surgical site infection: A four-year experience. Antimicrob Steward Healthc Epidemiol 2(1):e14
11. Dashti SR, Baharvahdat H, Spetzler RF, Sauvageau E, Chang SW, Stiefel MF, Park MS, Bambakidis NC (2008) Operative intracranial infection following craniotomy. Neurosurg Focus 24:E10
12. De Bonis P, Albanese A, Lofrese G, de Waure C, Mangiola A, Pettorini BL, Pompucci A, Balducci M, Fiorentino A, Lauriola L, Anile C, Maira G (2011) Postoperative infection may influence survival in patients with glioblastoma: simply a myth? Neurosurgery 69:864–868
13. Dickinson H, Carico C, Nuño M, Mukherjee D, Ortega A, Black KL, Patil CG (2015) Unplanned readmissions and survival following brain tumor surgery. J Neurosurg 122:61–68
14. Grabowski MM, Sankey EW, Ryan KJ, Chongsathidkiet P, Lorrey SJ, Wilkinson DS, Fecci PE (2021) Immune suppression in gliomas. J Neurooncol 151(1):3–12
15. Hernández Ortiz OH, GarcíaGarcía HI, Muñoz Ramírez F, Cardona Flórez JS, Gil Valencia BA, Medina Mantilla SE, Moreno Ochoa MJ, Sará Ochoa JE, Jaimes F (2018) Development of a prediction rule for diagnosing postoperative meningitis: a cross-sectional study. J Neurosurg 128:262–271
16. Hussein K, Bitterman R, Shofty B, Paul M, Neuberger A (2017) Management of post-neurosurgical meningitis: narrative review. Clin Microbiol Infect 23:621–628
17. Jackson C, Westphal M, Quiñones-Hinojosa A (2016) Complications of glioma surgery. Handb Clin Neurol 134:201–218
18. Kim BN, Peleg AY, Lodise TP, Lipman J, Li J, Nation R, Paterson DL (2009) Management of meningitis due to antibiotic-resistant Acinetobacter species. Lancet Infect Dis 9:245–255
19. Korinek AM, Baugnon T, Golmard JL, van Effenterre R, Coriat P, Puybasset L (2008) Risk factors for adult nosocomial meningitis after craniotomy: role of antibiotic prophylaxis. Neurosurgery 62(2):532–539
20. Kourbeti IS, Vakis AF, Ziakas P, Karabetsos D, Potolidis E, Christou S, Samonis G (2015) Infections in patients undergoing craniotomy: risk factors associated with post-craniotomy meningitis. J Neurosurg 122:1113–1119
21. Krenzlin H, Jankovic D, Alberter C, Kalasauskas D, Westphalen C, Ringel F, Keric N (2021) Frailty in glioblastoma is independent from chronological age. Front Neurol 12:777120
22. Kuwano A, Saito T, Nitta M, Tsuzuki S, Koriyama S, Tamura M, Ikuta S, Masamune K, Muragaki Y, Kawamata T (2023) Relationship between characteristics of glioma treatment and surgical site infections. Acta Neurochir (Wien) 165:659–666
23. Leaper D, Ousey K (2015) Evidence update on prevention of surgical site infection. Curr Opin Infect Dis 28(2):158–163
24. Morshed RA, Young JS, Gogos AJ, Haddad AF, McMahon JT, Molinaro AM, Sudhakar V, Al-Adli N, Hervey-Jumper SL, Berger MS (2022) Reducing complication rates for repeat craniotomies in glioma patients: a single-surgeon experience and comparison with the literature. Acta Neurochir (Wien) 164:405–417
25. Natukka T, Raitanen J, Haapasalo H, Auvinen A (2019) Incidence trends of adult malignant brain tumors in Finland, 1990–2016. Acta Oncol 58:990–996
26. Niemelä S, Lempinen L, Löyttyniemi E, Oksi J, Jero J (2023) Bacterial meningitis in adults: a retrospective study among 148 patients in an 8-year period in a university hospital, Finland. BMC Infect Dis 23:45
27. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, Guldberg R, Gradel KO (2017) Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the the Danish Neuro-Oncology Registry. J Neurooncol 135:571–579
28. Ravikumar V, Ho AL, Pendhakar AV, Sussman ES, Chow KK, Li G (2017) The use of vancomycin powder for surgical prophylaxis following craniotomy. Neurosurgery 80:754–758
29. Reichert MCF, Medeiros EAS, Ferraz FAP (2002) Hospital-acquired meningitis in patients undergoing craniotomy: incidence, evolution, and risk factors. Am J Infect Control 30:158–164
30. Robinson CP, Busl KM (2019) Meningitis and encephalitis management in the ICU. Curr Opin Crit Care 25:423–429
31. Salle H, Deluche E, Couvé-Deacon E, Beaujeux AC, Pallud J, Roux A, Dagain A, de Barros A, Voirin J, Seizeur R, Belmabrouk H, Lemnos L, Emery E, Fotso MJ, Engelhardt J, Jecko V, Zemmoura I, Le Van T, Berhouma M, Cebula H, Peyre M, Preux PM, Caire F (2021) Surgical Site Infections after glioblastoma surgery: results of a multicentric retrospective study. Infection 49:267–275
32. Schaff LR, Mellinghoff IK (2023) Glioblastoma and other primary brain malignancies in adults: a review. JAMA 329:574–587
33. Tian R, Hao S, Hou Z, Gao Z, Liu B (2015) The characteristics of post-neurosurgical bacterial meningitis in elective neurosurgery in 2012: A single institute study. Clin Neurol Neurosurg 139:41–45
34. Valdoleiros SR, Torrão C, Freitas LS, Mano D, Gonçalves C, Teixeira C (2022) Nosocomial meningitis in intensive care: a 10-year retrospective study and literature review. Acute Crit Care 37:61–70
35. Zhu J, Qiu X, Ji C, Wang F, Tao A, Chen L (2023) Frailty as a predictor of neurosurgical outcomes in brain tumor patients: A systematic review and meta-analysis. Front Psychiatry 14:1126123