Bacterial meningitis in high-risk populations

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Publication date
2024

Document Version
Final published version

Link to publication

Citation for published version (APA):
Sheybani, F. (2024). *Bacterial meningitis in high-risk populations*. [Thesis, fully internal, Universiteit van Amsterdam].

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Fereshte Sheybani

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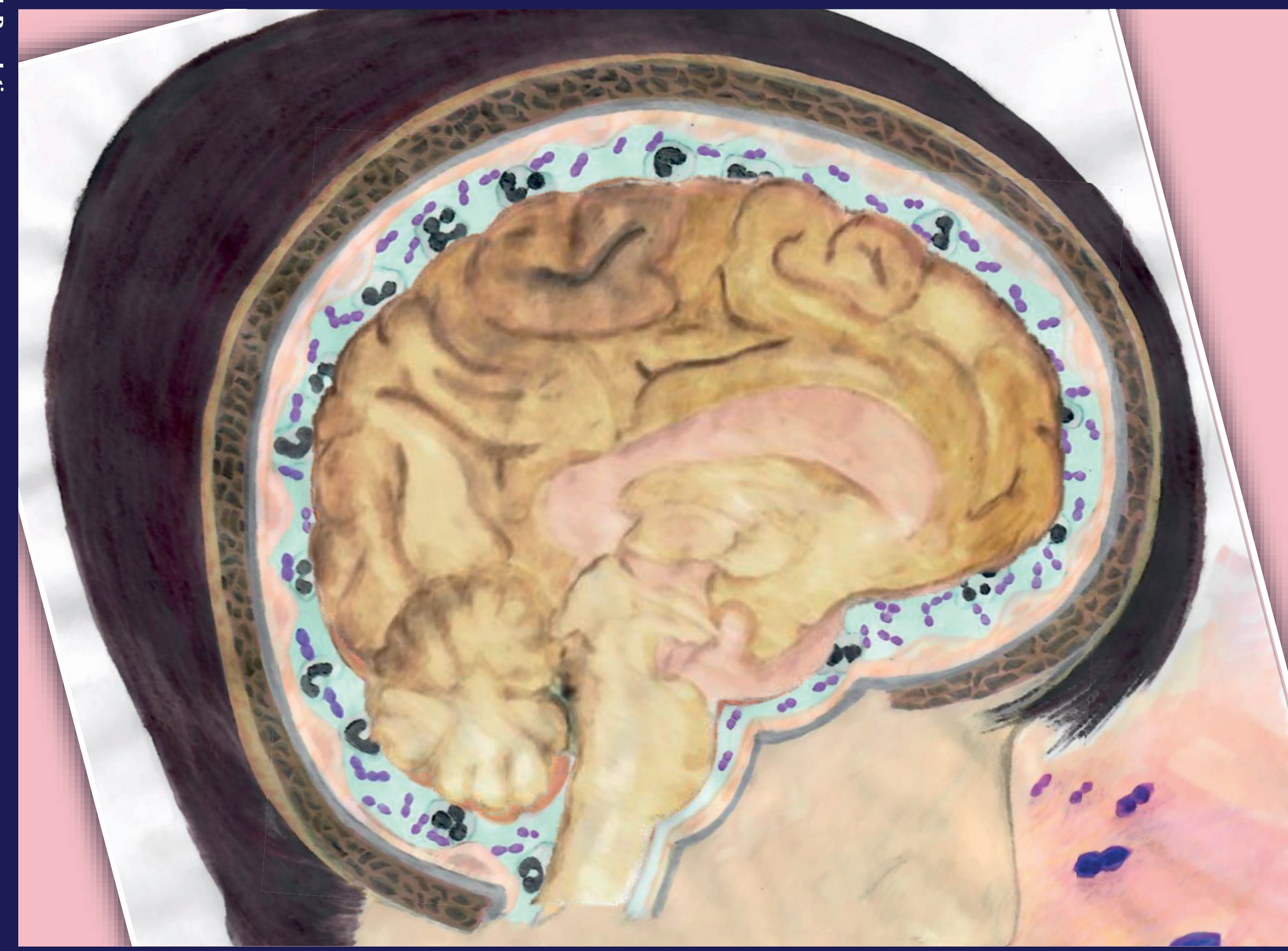

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Colophon

Cover design Fereshte Sheybani

Printed by Print Service Ede

ISBN 9789083402444

Printing of this thesis was financially supported by the department of Neurology of the Academic Medical Center and the University of Amsterdam.

Bacterial meningitis in high-risk populations

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 23 april 2024, te 16.00 uur

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CHAPTER 1

INTRODUCTION

Bacterial meningitis is a life-threatening infection of the meninges, subarachnoid space, and brain (1). Despite the progress that has been made in the prevention and treatment of bacterial meningitis during the past decades, globally the burden of the disease is still high (2). Meningitis remains among the four largest contributors to neurological disability-adjusted life-years (DALYs) worldwide (3). Neurological or neurobehavioral sequelae occur in up to 30% of survivors of bacterial meningitis and cause devastating social, emotional and economic consequences in patients, families, and communities (4). Based on the global burden of disease study (1990-2016), despite a decrease in rates and absolute numbers of deaths and DALYs due to meningitis, the overall number of reported cases has risen (3), and the incidence is strongly related to measures of deprivation (2).

Bacterial meningitis affects all countries of the world (5) but the incidence varies substantially by geographical region (2). In Western countries, the incidence rate of bacterial meningitis has gradually declined to 0.7–0.9 per 100 000 per year in the past 10–20 years, however, it is as high as 20-80 per 100,000 population per year in densely populated low-middle income countries, and still is substantially higher up to 1000 per 100 000 persons per year within the Sahel region of west and central Africa (2, 6).

Over the last decades, the epidemiology of bacterial meningitis has changed significantly (7). Historically, three main bacteria have been responsible for causing community-acquired bacterial meningitis, including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (5). Conjugate vaccines against the most common causes of community-acquired bacterial meningitis have effectively reduced the incidence of *H. influenzae* type b, *N. meningitidis* serogroup C, and several serotypes of *S. pneumoniae* (7). Nevertheless, the prevalence of vaccine escape variants is rising because conjugate vaccines are only effective against serotype/serogroup-specific meningitis (8). Furthermore, the availability of these vaccines in developing countries remains an issue (9). The distribution of the causative pathogens of bacterial meningitis also depends upon the region of the world. For example, *Streptococcus suis* is an emerging zoonotic cause of meningitis in Asia, and epidemics due to non-group A meningococcal meningitis continue to occur in Sub-Saharan Africa (10). Furthermore, some causes of bacterial meningitis such as *Listeria monocytogenes*, Group B Streptococci, and Gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) are more likely to affect specific groups, including neonates, pregnant women, transplant recipients, and other immunocompromised hosts, and older adults (8, 11).

Acute bacterial meningitis is a medical emergency and its mortality rate is considerably high (12). Prompt use of dexamethasone and appropriate antibiotics, together with optimal supportive care, can reduce the mortality and

morbidity associated with bacterial meningitis (13). All these require early recognition of meningitis and appropriate investigation (14). It has been shown that any delay in the diagnosis and the initiation of antimicrobial therapy may lead to a catastrophic outcome, especially in patients with clinical deterioration (15). In spite of this, diagnostic dilemmas often occur in patients with suspected meningitis because the typical clinical characteristics are frequently absent (2). The prevalence of the classic triad of fever, neck stiffness, and an altered mental status is low among patients with community-acquired bacterial meningitis (13), and clinicians must be vigilant and have a high index of suspicion to minimize poor outcomes (14).

Diagnosis of bacterial meningitis is even more challenging in those with underlying comorbidities and immunocompromised patients. Immunocompromised status has been identified as a predictor of poor outcomes in patients with bacterial meningitis (13). Delayed treatment more than two hours from admission has been observed more often in the group with immunosuppression, as compared with the immunocompetent individuals (16). The symptoms of acute bacterial meningitis may differ between immunocompromised and non-immunocompromised patients, and clinical presentation may be more subacute and indolent in the compromised hosts (16). Furthermore, patients with an immunocompromised status more often suffer from meningitis caused by relatively resistant bacteria like *L. monocytogenes* or *P. aeruginosa*. This together with a reduction in bacterial clearance, is probably the reason why the immunocompromised state has been related to the poor outcome in bacterial meningitis (16).

Comorbid and immunocompromising conditions are heterogeneous. So, it does not seem appropriate to consider all patients with underlying comorbidities and immunosuppression in one category of immunocompromised patients or special hosts. The severity and type of immunosuppression due to a variety of underlying comorbidities and their treatment are not similar. As a result, the spectrum of the causative pathogens may be different and bacterial meningitis may present differently in certain high-risk groups. For example, bacterial meningitis in a diabetic patient is more similar to immunocompetent individuals than cancer patients or those receiving immunosuppressive medications (16). Thus, having knowledge regarding the characteristics of bacterial meningitis in certain high-risk groups is potentially helpful for their optimal management and improving their clinical outcomes.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis was to study the presenting characteristics, risk factors, treatment practice, complications and outcome in bacterial meningitis patients in high-risk populations. To do this we used data from two prospective cohort studies from the Netherlands, one on community acquired bacterial meningitis (MeninGene study) and one on patients with suspected meningitis (the PACEM study).

In the MeninGene study, adults (patients older than age 16 years) who had bacterial meningitis in the Netherlands since Jan 1, 2006, and who were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis have been included. Online case-record forms were used to collect data on patients' history, symptoms and signs on admission, laboratory findings at admission, clinical course, outcome and neurological findings at discharge, and treatment. Bacterial meningitis has been defined as a bacterial pathogen isolated in cerebrospinal fluid, or the combination of a positive PCR or antigen test in cerebrospinal fluid (CSF) for *Streptococcus pneumoniae* or *Neisseria meningitidis* with at least one specific CSF finding predictive of bacterial meningitis (according to the criteria of Spanos and colleagues: glucose concentration <340 mg/L, CSF glucose: blood glucose ratio <0·23, protein concentration >220 mg/dL, white cell count >2000 cells per µL, or >1180 polymorphonuclear leucocytes per µL). Episodes of hospital-acquired meningitis, defined as bacterial meningitis that occurred while in hospital or within 1 week after discharge, and bacterial meningitis in patients with head trauma or neurosurgery in the previous month, or those with a neurosurgical device or missing outcome were excluded (17).

In the PACEM study that was performed as a single center study (Academic Medical Center, Amsterdam, The Netherlands), adults (age > 16 years) presenting to the emergency department or inpatients with suspected central nervous system (CNS infection) who underwent CSF examination were prospectively included. Episodes were identified during morning rounds or reported to the investigators by the treating physician. To assure no episodes were missed, an overview of all CSF samples analyzed by the hospital laboratory was checked and all episodes fulfilling the inclusion criteria were also included. Episodes of neurological infections that developed within one month of neurosurgery or traumatic brain injury as well as those who had a neurosurgical device in situ were excluded. Online case record forms were used to collect data on medical history, clinical characteristics on presentation and results of ancillary investigations including blood tests, cerebrospinal fluid analysis, microbiological examination and radiological imaging, and neurological status at discharge (18).

In **Chapter 2** we describe patients with multiple myeloma who develop bacterial meningitis who were included in the MeninGene study. It has previously been described that pneumococcal infections are frequent in patients with multiple myeloma and in otherwise healthy patients, pneumococcal infection may even be the unmasking event, leading to identification of the multiple myeloma. During treatment for multiple myeloma a severe immunocompromised state can occur, which predisposes to infections with opportunistic bacteria. In the study we describe clinical presentation and causative pathogens of bacterial meningitis during different stages of multiple myeloma, complications and outcome. In **Chapter 3** we describe patients from the MeninGene cohort who had a medical history of inflammatory bowel disease. It has previously been described that patients with inflammatory bowel disease have an increased risk of infection, either due to dysfunctional immune system, disrupted bowel function or immunosuppressive treatment. We now look at clinical presentation of bacterial meningitis, its causative pathogens and effect of IBD treatment on meningitis outcome. **Chapter 4** describes HIV-infected patients with suspected central nervous system infections from the PACEM cohort. It has previously been reported that HIV-infected patients are at substantially higher risk of acquiring bacterial meningitis. We now describe the characteristics of HIV-infected patients with CNS infections and discuss the importance of bacterial meningitis in comparison with other CNS infections in HIV-infected patients. We also discuss the value of CD4 lymphocyte count in differentiating between CNS infections and non-infectious syndromes. In **Chapter 5**, patients with community-acquired bacterial meningitis who were simultaneously diagnosed with vertebral osteomyelitis in the MeninGene study are described. Previously, concomitant occurrence of bacterial meningitis and vertebral osteomyelitis has been rarely reported. We now highlight the clinical characteristics, laboratory and imaging features, and clinical outcome of meningitis patients with vertebral osteomyelitis and review meningitis patients with vertebral osteomyelitis reported in the literature.This thesis concludes with a general discussion in **Chapter 8**.

CHAPTER 2

BACTERIAL MENINGITIS IN PATIENTS WITH MULTIPLE MYELOMA: A PROSPECTIVE NATIONWIDE COHORT STUDY AND REVIEW OF THE LITERATURE

Fereshte Sheybani, Matthijs C. Brouwer, Diederik van de Beek

International Journal of Infectious Diseases 2022; 122: 492-6.

ABSTRACT

Objective To study the clinical features of bacterial meningitis in myeloma patients.

Methods We analyzed myeloma patients included in a nationwide cohort of patients >16 years old with community-acquired bacterial meningitis in the Netherlands between 2006 and 2018. Subsequently, we reviewed the literature for articles reporting myeloma patients with bacterial meningitis.

Results A total of 27 of 2306 (1.6%) episodes of bacterial meningitis occurred in myeloma patients. Six of 27 (22%) patients received stem cell transplantation. CSF showed a median leukocyte count of 172/µL and 12 (46%) of 26 patients had a CSF leukocyte count <100/µL. *Streptococcus pneumoniae* was the causative pathogen in 25 (93%) patients. Fourteen (52%) patients had unfavorable outcome of whom 10 (37%) died. Ninety-one myeloma patients with bacterial meningitis were described in the literature. The most common pathogen in these patients was *S. pneumoniae* (35 of 48; 73%) and four (20%) of 20 cases died.

Conclusion Bacterial meningitis in patients with multiple myeloma is a severe disease with high rates of unfavorable outcome. Patients often present with a low CSF leukocyte count compared to bacterial meningitis in patients without multiple myeloma. Physicians should have a low threshold to perform a lumbar puncture in myeloma patients and start antibiotic treatment pending CSF chemistry and culture results.

INTRODUCTION

Multiple myeloma is the second most common hematologic malignancy accounting for 1% of all cancers (19, 20). Despite improvements in the outcome of patients with multiple myeloma as a result of novel treatments, a substantial proportion of patients s die early after diagnosis, and infection accounts for 45-65% of death in myeloma patients (21-24). Infections in multiple myeloma are mainly bacterial and associated with high disease burden, relapsed disease, and treatment with high-dose chemotherapy (22). In addition to the tissue damage and immune-modulating effects of anticancer drugs, multiple myeloma itself increases the chance of infection because of hypogammaglobinemia (25). Other disease-related factors that are related to compromised immune responses against infections in multiple myeloma include defective opsonization, decreased granulocyte adhesiveness, impaired leukocyte migration, and renal function impairment (19, 26).

Bacterial meningitis is a serious infection that occurs relatively often in multiple myeloma and accounts for 1.8-6.8% of all the infectious complications (27, 28). In a population-based study, a 16-fold increase in risk of bacterial meningitis was found in myeloma patients compared to the general population (29). Conversely the diagnosis of pneumococcal meningitis was associated with an increased risk of multiple myeloma during long term follow-up (30) and higher chance of death due to multiple myeloma (31). Among various types of hematological malignancies, multiple myeloma carries the highest risk for development of invasive pneumococcal infection with a relative risk of 61, as compared to the adult population (32).

Although available literature highlighted many features of more common infectious complications of multiple myeloma such as pneumonia and bloodstream infections (29, 33), information regarding characteristics of bacterial meningitis in multiple myeloma is limited. In this study, we describe the clinical and laboratory features and clinical outcome of myeloma patients with bacterial meningitis in a nationwide prospective cohort of community-acquired bacterial meningitis in the Netherlands and provide a review of the literature.

METHODS

Between March 2006 and December 2018, patients >16 years old with community-acquired bacterial meningitis defined by positive CSF culture were included prospectively in a nationwide cohort in the Netherlands. Detailed methods have been published previously (34). Patients with negative CSF cultures or hospital-associated meningitis were excluded. Data on patient history, symptoms and signs on admission, laboratory findings, radiologic examination, treatment, and outcome were prospectively collected using a case record form (CRF). Multiple myeloma is not routinely scored in the CRF but cancer and immunosuppressive therapy are scored and underlying comorbidities recorded. For all patients in whom cancer was described in the CRF, the discharge letter was retrospectively assessed to analyze the type of cancer. From these data patients with multiple myeloma were selected. Furthermore, from the discharge letter interval between diagnosis of multiple myeloma and bacterial meningitis, treatments for multiple myeloma and comorbid conditions were scored.

Outcome was scored using the Glasgow Outcome Scale (GOS) score. A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1 to 4. Informed consent was obtained during admission from all participating patients or their legally authorized representatives. The study was approved by the ethical committee of the Academic Medical Center.

We use the following search strategy in PUBMED for the literature review: (("Infections"[Mesh]) AND ("Multiple Myeloma"[Mesh]) AND (English[lang]). The references of relevant publications were also reviewed, as part of data screening. The following characteristics of reported cases were retrieved, analyzed, and compared with those from our cohort: age, gender, underlying comorbidities, immunomodulatory and immunosuppressive medications, causative pathogen, and source of isolation of pathogen, complications, and clinical outcome.

Continuous data were described with medians and interquartile range and categorical variables with frequency and percentage of the total number of cases the variable was known for. The Fisher's exact test and Chi-square tests were used for categorical variables, and Mann Whitney U test was used for continuous variables, as appropriate. A p-value < 0.05 was considered as statistically significant.

RESULTS

From 2006 to 2018, at total of 27 of 2306 (1.2%) community acquired bacterial meningitis episodes occurred in patients with multiple myeloma (table 1). These accounted for 9.3% of all the 289 episodes of bacterial meningitis in cancer patients in the cohort. The median age of patients was 65 (interquartile range [IQR] 59-71) years and 10 (37%) were female. Six of 27 (22%) myeloma patients underwent stem cell transplantation (SCT) prior to the meningitis episode, including four with autologous SCT, and two with history of autologous and subsequent

allogenic SCT. Three out of six SCT patients were on immunosuppressive and/or immunomodulating treatment when meningitis occurred, of which two experienced relapses of multiple myeloma after SCT.

Overall, 16 of 24 (67%) myeloma patients were taking immunosuppressive or immunomodulating medication at the time of diagnosis of bacterial meningitis. Eleven (46%) were on corticosteroids, eight (33%) on immunomodulators (i.e., thalidomide and lenalidomide), and five (21%) on alkylating agents (i.e., cyclophosphamide and melphalan).

In two (8%) out of 25 patients, bacterial meningitis unmasked the multiple myeloma and the median interval between diagnosis of multiple myeloma and bacterial meningitis was 42 (IQR 17-84) months. Two patients had history of invasive pneumococcal infections, of which one had recurrent episodes. Other risk factors for meningitis besides the multiple myeloma and related immunosuppression were identified in 7 (26%) patients, and consisted of otitis in 3 and pneumonia in 4.

The most common clinical manifestation of meningitis was an impaired level of consciousness in 20 (77%) of 26 patients, followed by fever in 19 (76%) of 25, headache in 11 (58%) of 19 and neck stiffness in 14 (58%) of 24. Neurological deficits were recorded in seven (26%) of 27 patients. Eleven (44%) of 25 patients presented within 24 hours of onset of symptoms of meningitis and seven (35%) out of 20 had classic triad of meningitis at the time of hospital admission. The median of CSF leukocyte counts in patients was 172/μL (IQR, 25-1681) and 12 (46%) of 26 patients had CSF leukocyte counts of less than 100/μL. The most common pathogen that was isolated from 25 (93%) patients was *S. pneumoniae*. Other pathogens were *Listeria monocytogenes* and *Escherichia coli*, each in one patient. The patient with meningitis caused by *E. coli* also had pancreatic cancer and had been treated with both corticosteroids and melphalan. The patient with listeria meningitis had been treated with a combination of corticosteroids, lenalidomide, and cyclophosphamide. However, we had insufficient data on disease course to conclude these patients had advanced or refractory multiple myeloma. The causative pathogen was also isolated from blood in all patients.

Overall, in 17 (48%) of 27 episodes systemic complications occurred. Eleven (42%) out of 26 patients developed respiratory failure and 13 (50%) needed mechanical ventilation. Circulatory shock complicated bacterial meningitis in four (17%) out of 24 patients. Other systemic complications included renal impairment in four (15%) out of 27 patients and nosocomial pneumonia in five (19%). Furthermore, in 21 (81%) of 26 cases neurologic

Table 1. Characteristics of myeloma patients with bacterial meningitis in the cohort and in the literature

Characteristics	Cohort	Literature	Combined
Age- years	65 (59-71)#	59 (54-75)	63 (56-72)
Gender-female	10/27 (37)	9/21 (43)	19/48 (40)
First presentation of multiple myeloma	2/27 (7)	13/31 (42)	15/58 (26)
Stem cell transplantation	6/27 (22)	1/27 (4)	7/54 (13)
Immunomodulating treatment	16/24 (67)	11/24 (46)	27/48 (56)
Clinical manifestations			
Headache	11/19 (58)	5/19 (26)	16/38 (42)
Fever	19/25 (76)	16/20 (80)	35/45 (78)
Impaired level of consciousness	20/26 (77)	13/19 (68)	27/45 (60)
Neck stiffness	14/24 (58)	10/18 (56)	24/41 (59)
Seizure	3/27 (11)	2/18 (11)	5/45 (11)
Focal neurological deficits	7/19 (37)	5/19 (26)	12/42 (29)
Bacteremia	26/26 (100)	14/19 (74)	40/43 (93)
CSF parameters			
Leukocyte count-cells/μL	172 (25-1681)	374 (217-1535)	260 (38-1481)
Granulocyte, %	83 (79-94)	90 (68-94)	85 (76-94)
Protein concentration- mg/dL	385 (260-733)	238 (132-555)	359 (212-608)
Causative pathogens			
Streptococcus pneumoniae	25/27 (93)	18/31 (58)	43/58 (74)
Neisseria meningitidis	0/27 (0)	4/31 (13)	4/58 (7)
Other pathogens	2/27 (8)	9/31 (29)	11/58 (19)
Unfavorable outcome	14/27 (52)	NR	NR
Death	10/27 (37)	4/20 (20)	14/47 (30)

#Numbers are represented by the number of patients with specific characteristics/ the number of patients evaluated (percent) for nominal variables and by median (25th quartile, 75th quartile) for quantitative variables.
* Including 3 cases of otitis media and 4 cases of pneumonia. NR=not reported

complications occurred, which consisted of an altered mental status in 15 (58%), focal neurological deficits in four (20%) out of 20 episodes, cerebrovascular accidents in three (13%) out of 23, hearing impairment in 2 (11%) out of 18, and hydrocephalus in 1 (5%).

Ten (37%) patients died after a median of three days from admission to death (IQR 0-10 days). Causes of death were brain herniation (n=2), respiratory failure (n=2), status epilepticus (n=1) and failure to improve after which the treatment was discontinued (n=1). There were three patients who developed cerebrovascular complications consisting of cerebral infarctions in two and an intracerebral hemorrhage in one. The cause of death was unknown in one patient. Of patients who survived, two were severely disabled (GOS 3) and two moderately disabled (GOS 4) and 13 had a favorable outcome (GOS 5).

Myeloma patients with meningitis were older as compared to non-myeloma episodes in the cohort (65 years [IQR, 59-71] versus 61 years [IQR, 47-70], P=0.037). Multiple myeloma patients had lower CSF leukocyte counts (172 [IQR, 25-1681] versus 2347 [IQR, 597-6730], P<0.001), and more frequently had positive blood cultures (100% versus 72.8%, P=0.003), than other cases with meningitis in the cohort. Myeloma patients with meningitis were at higher risk of death (10 of 27 37%) as compared to 363 of 2252 (16%) non-myeloma episodes in the cohort (P=0.007).

Literature review

A search of the English literature identified 91 episodes of bacterial meningitis in myeloma patients in 24 articles (supplementary 1). Clinical characteristics and outcome were reported in 20 patients and microbiological features in 48. The median age was 59 (IQR 54-75) years and 9 (43%) out of 21 were female. In 13 (42%) of 31 episodes, bacterial meningitis was the unmasking event of multiple myeloma. In 13 (54%) out of 24 episodes, patients were not taking any immunosuppressive medication at the time of diagnosis of meningitis. Immunosuppressive medication included corticosteroids in 8 (36%) of 22 cases, alkylating agents (i.e., busulphan, carmustine, carboplatin, and thiotepa) in 6 of 22 (27%), immunomodulators (i.e., thalidomide and lenalidomide) in 4 (18%) of 22, and other antineoplastic agents (i.e., vincristine and doxorubicin) in 2 (9%) of 22. One patient had received SCT.

The most frequent clinical characteristic of bacterial meningitis reported was fever in 16 (80%) of 20 episodes, followed by impaired consciousness in 13 (68%) of 19 episodes, headache in 5 (26%), and focal neurologic deficits in 4 (21%). The classic triad of meningitis was reported in 6 (33%) of 18 patients. Thirty-five (73%) of 48 episodes of meningitis were caused by *S. pneumoniae*. Other causative pathogens included *Neisseria meningitides* in 3 (6%), and *Haemophilus influenzae*, *Haemophilus quentini*, *Listeria monocytogenes*, *Pasteurella multocida*, *Escherichia coli*, and *Stomatococcus mucilaginosus*, each in one. Overall, 85% of the episodes were caused by gram-positive bacteria. The median of CSF leukocyte counts was 374 (IQR 217-1535) cells/μL. Two (11%) out of 18 cases had CSF leukocyte counts of less than 100/μL and 9 (50%) CSF leukocyte counts of less than 300/μL.

Complications that were reported in patients included circulatory shock in 2 cases, mechanical ventilation in 2, and renal failure, and nosocomial infection, each in one. Death occurred in 4 (20%) of 20 episodes of meningitis.

DISCUSSION

Our study showed that about 1% of episodes of bacterial meningitis occur in patients with multiple myeloma and myeloma patients account for about 10% of all cancer patients with bacterial meningitis. Among all types of cancer, it is the most common underlying active malignancy that has been identified in patients with bacterial meningitis (35). The absolute risk of multiple myeloma following pneumococcal meningitis has been estimated to be 0.9% per patient-year (30). Furthermore, long-term follow up of survivors of pneumococcal meningitis showed about 3% chance of death due to multiple myeloma within the next 10 years after meningitis in those older than 50 years (31).

A previous study showed the incidence of bacterial infections in multiple myeloma has a bimodal pattern of peak; one within a few weeks of diagnosis and the second within 6th year following disease diagnosis (29, 36, 37). It can occur as either a presenting feature in up to 15% of patients (38) or a complication of multiple myeloma (28, 33, 39). In 7% of our patients and 42% of the patients reported in the literature, multiple myeloma was unmasked by meningitis. Differences in the frequency of diagnosis of bacterial meningitis as an unmasking event in our patients and what has been previously reported could be due to several reasons. First, we did not follow our patients beyond their hospital discharge. Therefore, there might be meningitis patients whose underlying malignancies were diagnosed shortly after hospital discharge and we did not include them in the study. Second, because case reports most often described patients with rare, unusual or atypical manifestations of disorders, it is expected that

the episodes of meningitis that unmasked an occult multiple myeloma have been more frequently reported than those occurred in patients who were already diagnosed with multiple myeloma.

Type of infections in multiple myeloma is associated to the disease stadium; infections caused by gram-positive cocci occurs mainly in patients with untreated, active diseases, or in patients responding to administered chemotherapy, whereas gram negative bacteria episodes occur primarily in those with advanced or refractory diseases (39-41). Despite the long interval between diagnosis of multiple myeloma and meningitis in most of our patients with median of 42 months, all but one of the episodes of meningitis were caused by gram-positive bacteria and *S. pneumoniae* was the most common causative pathogen in 93%. The diversity of causative pathogens reported in the literature was substantially higher with 42% of cases being caused by pathogens other than *S. pneumonia*. The difference between the causative pathogens in our patients and those reported previously could be due to differences in local epidemiology, publication bias and different time periods in which the cases occurred. Over time the epidemiology of bacterial meningitis has changed due to vaccination and stochastic changes, but also the treatment of multiple myeloma has changed. In our cohort 20% of patients had a history of SCT, compared to less than 5% in patients reported in the literature.

We found that classic symptoms and signs of bacterial meningitis were frequently absent in myeloma patients. This implies that even in the absence of classic manifestations, bacterial meningitis should be considered and CSF examination is warranted. CSF leukocytes count was found to be less than 100 /μL in half of multiple myeloma patients with bacterial meningitis, which could be misinterpreted as being due to viral infection (42). Therefore, in multiple myeloma patients a low threshold for starting antibiotic treatment for bacterial meningitis should be kept, even with mild abnormalities of the CSF. A low CSF leukocyte count was previously found to be as an independent predictor of poor outcome in bacterial meningitis (43) in other cancer patients with bacterial meningitis (35). The lower CSF leukocyte counts in multiple myeloma patients is probably the result of less effective immune response to the presence of bacteria in the subarachnoid space or a hyperacute course of bacterial meningitis. More than half of the patients in our study were on immunomodulatory or immunosuppressive medications, and corticosteroids were the most common medications used by patients in both cohort and literature. While active multiple myeloma intrinsically affects the humoral arm of the immune system, chemotherapeutic regimens are associated with decrease in cell-mediated immunity, hypogammaglobulinemia and neutropenia (44). Despite these multiple causes of immune system dysfunction, clinical trials on the efficacy and complications of different chemotherapeutic regimens in treatment of multiple myeloma rarely reported central nervous system infection as a complication (45, 46).

Outcome in our cohort and the literature was poor with mortality of 37%, which is considerably higher compared to the 17% in the overall population (34). In most of patients who died, death occurred early after hospital admission. Higher and earlier mortality of bacterial meningitis in multiple myeloma could be related to more fulminant course of meningitis, or complications related to the underlying malignancy in these patients.

Our study has several limitations. First, we selected our patients based on a diagnosis of cancer in the CRF after which we checked discharge letters for the type of cancer. Since these data and letter were not available for all patients, cases of multiple myeloma may have been missed. Furthermore, as bacterial meningitis patients were followed-up until discharge for the meningitis episode, those in whom multiple myeloma was diagnosed after hospital discharge were not included. Finally, in patients with bacterial meningitis who die within short time of admission a diagnosis of multiple myeloma may be missed. Although multiple myeloma could be a possible underlying condition in such situations, it is likely to make up only a small proportion of cases of fulminant meningitis. Nevertheless, this may lead to an underestimation of the incidence of multiple myeloma in bacterial meningitis patients.

In conclusion, bacterial meningitis is a serious complication of multiple myeloma that is associated with high mortality and morbidity. It could present as a complication of multiple myeloma in those already diagnosed with the disease or unmask the occult underlying myeloma. Clinical characteristics and typical CSF abnormalities may be absent and a low threshold for CSF examination and empirical treatment for bacterial meningitis pending CSF cultures should be kept.

Supplementary 1. Characteristics of published papers reporting myeloma patients with bacterial meningitis in the literature

n	Author, year	Country	Age, sex	No. of patients	Previously diagnosed multiple myeloma	Immunomodulators or immunosuppressants	Causative pathogen	CSF parameters	Complication	Outcome
1	Clarke, 1966	UK	46, M	1	No	None	Gram-positive cocci	Purulent CSF	Haemorrhagic retinopathy	Survived
2	Mangi, 1973	US	77, M	1	Yes	Prednisone, melfalan	*S. pneumoniae*	W: 4350, P: 94%, Glc: 14	NS	NS
3	Twomey, 1973	US	NSS	7	NS	NS	NSS	NS	NS	4 out of 7 due to meningitis
4	Baker, 1974	US	52, F	1	No	None	*S. pneumoniae*	W:NS, Glc: 5, Pr: elevated	Bilateral haemorrhagic retinopathy	Died
5	Posner, 1978	US	59, F	1	No	None	*S. pneumoniae,* type 33	NS	Pulmonary edema	Died; autopsy performed
6	Nolan, 1979	US	60, M	1	No	None	*N. meningitis,* group B	W: 1819, P: 75%, GLC: NS, Pr: NS	None	Survived
		US	60, M^	1	Yes	Carmustine, doxorubicin, prednisone, vincristin	*S. pneumoniae* type 23	W: 811, P: 17%,	None	Survived
7	Wagener, 1981	US	55, F	1	Yes	Chemotherapy	*Haemophilus influenza* type f	W: 5, P: 20%, Glc: 150, Pr: 38.1	NS	Died
8	Savage, 1982	US		2	NSS	NSS	*S. pneumoniae, E. coli*	NS	Concomitant pneumonia	NSS
9	Ellison, 1983	US	NSS	1	Yes	NSS	*N. meningitidis*	NS	NS	NSS
10	Schifferli, 1984	Switzerland	57, M	1	No	None	*N. meningitidis,* group B	W: 7300, P: 100%, Glc: 9, Pr: 470	None	Survived

11	Blot, 1994	France	54, F	1	Yes	Chemotherapy	*L. monocytogenes*	NS	Circulatory shock, respiratory distress due to diffuse alveolar haemorrhage, mechanical ventilation, ICU admission	Survived
12	Abraham, 1997	US	48, M	1	Yes, Autologous PBSCT	Busulfan, thiotepa, carboplatin (conditioning regimen)	*Stomatococcus mucilaginosus*	W: 1318, P: 98%, Glc: 1, Pr: 188	NS	Survived
13	Layton, 1999	US	78, F	1	No	None	*Pasteurella multocida*	W: 113, P: 82%, Glc:48, Pr: 260	Septic arthritis	Survived
14	Cesana, 2003	Italy	NSS	1	Yes	Vincristine, Adriamycin, dexamethasone	*L. monocytogenes*	NSS	Brain abscess	NSS
15	Costa, 2004	US	57, M	1	No	None	*S. pneumoniae*	W: 3500, P: 85%, Glc: 22, Pr: 985	tonic-colonic seizure	Survived
16	Bigaillon, 2007	France	88, M	1	No	None	*S. pneumoniae*	W: 12, P: 100%, Glc: 1.8, Pr: 583	Myocardial ischemia, acute renal failure	Died
17	Pasa, 2009	Turkey	77, M	2	Yes	Thalidomide, dexamethsone	*S. pneumoniae*	W: 251, P: 92%, CSF/serum Glc ratio: 0.32, Pr: 216	None	Survived
			55, M		Yes	Thalidomide, dexamethasone	*S. pneumoniae*	W: 459, P: 90%, CSF/serum Glc ration: 0.28, Pr: 124	None	Survived
18	Matano, 2010	Japan	80, F	1	Yes	Melphalan, prednisone	*L. monocytogenes*	W: 222, P: 62%, Glc: 49, Pr: 155	None	Survived
19	Paleiron, 2012	France	64, F	1	No	None	*N. meningitidis*, serotype B	W: 1440, P: 90%, Glc:	Purpura fulminans	Survived

20	Blimark, 2015	Sweden	NSS	51	NSS	NSS	NSS	NSS	NSS	NSS
21	Naderi, 2016	Iran	54, M	1	No	None	*S. pneumoniae*	W: 200, P: 85%, Glc: 14, Pr: 106	Extensive herpes labialis	Survived
22	Dunphy, 2017	UK	64, F	1	No	None	*S. pneumoniae*	W:290, P:90%, Glc < 18.8, Pr: > 600	Pneumocystis pneumonia, *C. difficile* colitis	Survived
23	Noginskiy, 2018	US	72, M	1	No	None	*S. pneumoniae*	W: 275, P: 95%, Glc: 3.93, Pr: NS	Circulatory shock, ICU admission, hospital-acquired candidemia	Survived
24	Cohen, 2019	Israel	56, M	1	No	None	*Haemophilus quentini*	W: 235, P:15%, Glc: 51, Pr: 72	Pneumonia, septic polyarthritis and osteomyelitis, soft tissue abscess	Survived

MM: multiple myeloma; NS: not stated; NSS: not stated specifically; NA: not applicable; CSF: cerebrospinal fluid; OP: opening pressure; W: leukocytes; P: polymorphonuclear leukocyte percentage; GLc: glucose; Pr: protein; ICU: intensive care unit; HTN: hypertension;
^Second episode of bacterial meningitis in the same patient.

There was also one study that conducted to estimate the risk of multiple myeloma subsequent to an episode of serious pneumococcal infection and reported four patients who were diagnosed with multiple myeloma after an interval of several months to years of diagnosis of pneumococcal meningitis (Gregersen et al., 2001). Due to the long interval between diagnosis of meningitis and multiple myeloma, these four patients were not included in the analysis. In another study with the aim of the evaluation of long-term mortality in patients diagnosed with pneumococcal meningitis, only for 6 out of 23 multiple myeloma patients, it has been reported that the diagnosis of underlying hematologic malignancy was made before admission for meningitis (Roed et al., 2010). Given that no information about the interval between diagnosis of multiple myeloma after meningitis was provided regarding other 17 patients, we only included the 6 patients who were known to have multiple myeloma before meningitis in our analysis.

CHAPTER 3

COMMUNITY-ACQUIRED BACTERIAL MENINGITIS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES

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Journal of Infection 2022; 85: 573-607.

INTRODUCTION

Inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease, are chronic inflammatory disorders of the gastrointestinal tract. Higher incidence of common infections has been reported in IBD patients compared to matched controls (47). Here, we report characteristics of IBD patients with community-acquired bacterial meningitis that were identified in a large nationwide observational cohort study and performed a review of the literature.

METHODS

From March 2006 through December 2021, patients of 16 years of age or older with community-acquired bacterial meningitis were included in a prospective nationwide cohort in the Netherlands (MeninGene) (34, 48). In this cohort, community-acquired bacterial meningitis was defined by a positive CSF culture or when CSF showed at least one individual predictor of bacterial meningitis according to the Spanos criteria (49). Detailed study methods have been published previously (34). Outcome was scored using the Glasgow Outcome Scale (GOS) score. A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1 to 4. Informed consent was obtained during admission from all participating patients or their legally authorized representatives. The study was approved by the Medical ethical committee of the Amsterdam University Medical Center, location Academic Medical Center (AMC).

Pubmed was searched up to December 2021 using the following search strategy for the literature review: ("Meningitis"[Mesh]) AND ((("Inflammatory Bowel Diseases"[Mesh]) OR "Crohn Disease"[Mesh]) OR "Colitis, Ulcerative"[Mesh]). As a part of data screening, the references of relevant publications were also reviewed.

Continuous data were described with medians and interquartile range and categorical variables with frequency and percentage. The Fisher's exact test and Chi-square tests were used for categorical variables, and Mann Whitney U test was used for continuous variables, as appropriate. A P-value < 0.05 was considered as statistically significant.

RESULTS

From 2006 through 2022, 27 of 2704 (1%) community acquired bacterial meningitis episodes were recorded in 27 IBD patients, including 13 (48%) patients with Crohn's disease and 14 (52%) with ulcerative colitis (Table). The median age of IBD patients was 56 (interquartile range [IQR] 45-67) years, and 9 (33%) were female.

Ten of 27 (37%) patients received treatment with 5-aminosalicylates, 9 (33%) corticosteroids, 8 (30%) purine analogues (*i.e.*, 6-mercaptopurine, 6-thioguanine or azathioprine), 7 (26%) TNF inhibitors (*i.e.*, infliximab or adalimumab), and cyclosporine in one patient (4%). Eight of 27 patients (30%) used a combination of immunosuppressants. Twelve of 27 patients (44%) did not receive immunosuppressive medication. Median time from diagnosis of IBD to meningitis was 3 years (IQR 2-7). Ten (37%) IBD cases experienced preceding gastrointestinal symptoms (consisting of watery or bloody diarrhea, and vomiting); these symptoms were initially attributed to IBD exacerbation in 8 patients.

Common presenting features of meningitis were fever (24 of 26 patients; 92%), headache (20 of 24; 83%), neck stiffness (19 of 24; 79%), and impaired level of consciousness (14 of 24; 59%). The classic triad of meningitis consisting of fever, neck stiffness and altered mental status was present in 11 of 21 patients (52%). On admission, focal neurological deficits were present in 5 of 25 patients (20%) and seizures in 2 of 24 patients (8%). Neuroimaging was performed in 23 of 27 patients (85%) showing a brain abscess and cerebral infarction, each in one patient (4%). Median cerebrospinal fluid (CSF) leukocyte count was 1432 cells per µL (IQR, 554-3468).

CSF cultures grew *Listeria monocytogenes* in 13 of 27 patients (48%), *Streptococcus pneumoniae* in 9 (33%) and *Neisseria meningitidis* in 2 (7%). All 7 patients using TNF inhibitors had listeria meningitis. All 10 cases with preceding gastrointestinal symptoms were diagnosed with listeria meningitis. IBD patients with bacterial meningitis were at higher risk of listeria infection as compared to patients without IBD (13 of 27 [48%] versus 156 of 2677 [6%]; odds ratio 15.01; 95%CI 6.93-32.47; P<0.001). One patient with pneumococcal meningitis died (4%); all other patients survived. Outcome was unfavorable in 9 of 27 patients (33%).

Table. Characteristics of IBD patients with bacterial meningitis in the cohort and in the literature

Characteristics[a]	**Cohort (N=27)**	**Literature (N=30)**	**Combined (N=57)**
Age- years	56 (45-67)	40 (26-65)	52 (36-66)
Gender-female	9/27 (33)	11/28 (39)	20/55 (36)
Time from IBD to meningitis (yea9rs)	3 (2-7)	4 (2-16)	3 (2-8)
IBD Type			
Crohn's disease	13/27 (48)	19/30 (63)	32/57 (56)
Ulcerative colitis	14/27 (52)	11/30 (37)	25/57 (44)
Anti-inflammatory and immunomodulating treatment			
Corticosteroids	9/27 (33)	23/30 (77)	32/56 (57)
TNF-alpha inhibitors	7/27 (26)	21/30 (70)	24/56 (43)
Purine analogues	8/27 (30)	16/30 (53)	28/56 (50)
5-aminosalicylates	10/27 (37)	12/27 (44)	22/53 (42)
Clinical manifestations			
Headache	20/24 (83)	16/25 (64)	36/49 (73)
Fever	24/26 (92)	22/25 (88)	46/51 (90)
Impaired level of consciousness	14/24 (59)	16/25 (64)	30/49 (61)
Meningeal signs	19/24 (79)	11/25 (44)	30/49 (61)
Seizure	2/24 (8)	1/25 (4)	3/49 (6)
Focal neurological deficits	5/25 (20)	5/25 (20)	10/50 (20)
Bacteremia	11/19 (58)	12/21 (57)	23/40 (58)
CSF parameters			
Leukocyte count (cells/µL)	1432 (554-3468)	763 (106-3499)	1109 (361-3462)
Granulocyte (%)	87 (82-98)	83 (59-92)	84 (71-95)
Protein concentration (mg/dL)	201 (99-547)	150 (73-355)	189 (91-454)
Glucose concentration (mg/dL)	29 (9-56)	27 (20-50)	27 (13-54)
Causative pathogens			
Listeria monocytogenes	13/27 (48)	21/29 (72)	34/56 (61)
Streptococcus pneumoniae	9/27 (33)	1/29 (3)	12/56 (21)
Neisseria meningitidis	2/27 (7)	1/29 (3)	3/56 (5)
Other pathogens	0/27 (0)	5/29[b] (17)	5/56 (9)
No pathogen isolated	1/27 (4)	1/29 (3)	2/56 (4)
Unfavorable outcome[c]	9/26 (35)	NR	NR
Death	1/26 (4)	6/28 (21)	7/55 (13)

[a]Numbers are represented by the number of patients with specific characteristics/ the number of patients evaluated (percent) for nominal variables and by median (25th quartile, 75th quartile) for quantitative variables.
[b]Including *Bordetella bronchiseptica*, *Campylobacter fetus*, *Pseudomonas stutzeri*, Peptostreptococcus, *E. coli*, and Bacteroides. NR=not reported
[c]Unfavorable outcome was defined as a Glasgow Outcome Scale score of 1 to 4.

The literature search revealed 61 IBD cases with meningitis in 50 publications; 31 patients were excluded leaving 30 patients with IBD and community-acquired bacterial meningitis (supplementary table). Nineteen patients (63%) had CD and 11 (37%) UC. All patients but one received immunosuppressive medication: corticosteroids (n=27, 77%), TNF- inhibitors (n=21, 70%), purine analogues (n=16, 53%), and 5-aminosalicylates (n=12; 44%). Fever was reported in 22 of 25 patients (88%), headache in 16 patients (64%), and impaired consciousness in 16 patients (64%). The most common causative pathogen was *L. monocytogenes* occurring in 21 (72%) of 29 patients. Fatal outcome was reported in six (21%) of 28 patients (Table).

DISCUSSION

IBD is an uncommon risk factor for bacterial meningitis patients occurring in 1% of bacterial meningitis cases. *L. monocytogenes* is the most common causative pathogen, especially in those using anti-TNF agents. One single-center laboratory surveillance study estimated an elevated incidence of listerial bacteriemia for IBD patients with an odds ratio of 7.4 compared to the general population, irrespective of anti-TNF therapy treatment (50). Listeriosis is common in biologics-treated patients, especially related to anti-TNF therapy treatment use given concomitantly with other immunosuppressive therapies (51). Indeed, all patients with meningitis using TNF inhibitors were infected with *L. monocytogenes*. TNF is a pro-inflammatory cytokine that plays a key role in IBD pathogenesis (52) and in host resistance against various microorganisms, particularly intracellular pathogens (53).

Meningitis developed concomitantly or shortly after development of gastrointestinal symptoms that were often interpreted as flares of IBD. It remains unclear whether these symptoms were actually due to IBD flares or caused by the intestinal listerial infection preceding invasive disease. Bacterial meningitis in IBD was associated with high rates of unfavorable outcome (33%), but the morality rate was relatively low (4%).

Our study has several limitations. We selected our patients based on patients' underlying conditions in the CRF, after which discharge letters were analyzed for more detailed information. Since these data and letters were not available for all patients, IBD cases may have been missed. Nevertheless, to the best of our knowledge, this is the largest cohort of IBD patients with bacterial meningitis published to date.

Supplementary 1. IBD patients with community-acquired bacterial meningitis in the literature

Author	Year	Country	IBD	IBD to meningitis, years	Drug	Syndrome	Pathogen	Complications	Outcome
Wallace et al.	1995	US	CD	4	Prednisone, Sulfasalazine	Meningitis, epidural abscess, sacral osteomyelitis	None	Epidural abscess, sacral osteomyelitis	Survival
Kamath et al.	2002	US	CD	2	Infliximab, methyl prednisone, 6-MP, mesalamine	Bacteremia, probable meningitis	*Listeria monocytogenes*	Sepsis caused by Candida albicans	Survival
Slifman et al.	2003	Sweden	CD	NR	Infliximab, prednisone, 6-MP	Meningitis, bacteremia	*Listeria monocytogenes*	Residual paralysis of one eye	Survival
	2003	Italy	CD	NR	Infliximab, methyl prednisone, AZT	Meningitis	*Listeria monocytogenes*		Death
Maggiore et al.	2004	US	CD	3	Mesalamine, corticosteroid, infliximab	Meningitis, ileal fistulous communication	Gram-positive cocci	Multiple paraspinous abscesses, lumbar spinal epidural abscess with sinus tract to neural foramina	Survival
Ljung et al.	2004	Sweden	CD	NR	Infliximab	Meningitis	*Listeria monocytogenes*	None	Survival
Williams et al.	2005	Canada	CD	0	Infliximab, prednisone, AZT, 5-ASA	Acute meningoencephalitis	*Listeria monocytogenes*	None	Survival
Ramsay et al.	2007	US	CD	1	Mesalamine, 6-MP, prednisone	Pneumoencephalomeningitis	Peptostreptococcus, *E. coli*, Bacteroides	Intraabdominal abscess, sacrococcygeal bone osteomyelitis	Survival
Izbeki et al.	2008	Hungary	CD	23	Infliximab, Methyl prednisone, 6-MP	Meningoencephalitis	*Listeria monocytogenes*	Residual unilateral weakness of eye movements, sig. diplopia, PTE	Survival
Umehara et al.	2009	Japan	CD	21	Prednisone, mesalamine, Infliximab	Acute meningitis	*Campylobacter fetus*	None	Survival
Almeida et al.	2009	Portugal	CD	0	None	Acute meningitis	NR	Spinal epidural abscess	Survival
Chuang et al.	2010	US	CD	2	Infliximab, prednisolone, 6-MP	Meningitis	*Listeria monocytogenes*	gentamicin ototoxicity	Survival
Triantafillidis et al.	2010	Greece	UC	5	Mesalamine, corticosteroid, AZT	Meningoencephalitis	*Listeria monocytogenes*	None	Survival

Damergis et al.	2010	Rhode Island	CD	NR	AZT	Bacterial meningitis, Otitis media	*Streptococcus pneumoniae*	Bilateral myringotomies, MV, pneumocephalus, intermittent disorientation, amnesia, visual hallucination	Survival
Majumder et al.	2013	US	CD	2	Certolizumab pegol	Acute meningoencephalitis	*Neisseria meningitidis* group C/W135 antigen	None	Survival
Abreu et al.	2013	Portugal	UC	4	5-ASA, Corticosteroid, Infliximab	Acute meningitis	*Listeria monocytogenes*	None	Survival
	2013	Portugal	UC	5	5-ASA, Corticosteroid, Infliximab	Acute meningoencephalitis	*Listeria monocytogenes*	None	Survival
Issa et al.	2013	Lebanon	UC	NR	AZT, prednisone, Infliximab	Acute meningoencephalitis	*Listeria monocytogenes*	Persistent fever, cardiopulmonary arrest, multi-organ failure	Death
			UC	NR	AZT, prednisone, Infliximab	Acute meningoencephalitis	*Listeria monocytogenes*	None	Survival
Rana et al.	2014	UK	UC	42	Corticosteroid, Infliximab	Acute meningitis	*Listeria monocytogenes*	Hydrocephalus, MV	Survival
Miranda-Bautista et al.	2014	Spain	CD	NR	Corticosteroid	Rhombencephalitis	*Listeria monocytogenes*	NR	Death
			CD	NR	Corticosteroid	Meningoencephalitis	*Listeria monocytogenes*	NR	Survival
Boland et al.	2015	US	CD	NR	Certolizumab pegol, AZT, budesonide, Vedolizumab	Acute meningitis	*pseudomonas stutzeri*	None	Survival
Salonga-Reyes et al.	2015	Australia	UC	NR	Mesalamine, AZT, prednisone, Infliximab	Acute meningoencephalitis	*Listeria monocytogenes*	Dense left hemiplegia, aspiration pneumonia	Death
Parihar et al.	2016	Ireland	UC	0	Infliximab, corticosteroid	Acute meningitis	*Listeria monocytogenes*	None	Survival
Stratton et al.	2016	UK	CD	2	Infliximab, corticosteroid, AZT	Rhombencephalitis	*Listeria monocytogenes*	Coma, spastic quadriparesis, tracheostomy, gastrostomy, MV, recurrent episodes of aspiration pneumonia	Death

Inoue et al.	2017	Japan	UC	16	Prednisolone, AZT, 5-ASA	Colitis progressed to septicemia and meningitis	*Listeria monocytogenes*	Concurrent CMV colitis, candida septicemia, pulmonary aspergilloma	Survival
Acewicz et al.	2017	Poland	CD	NR	Methylprednisolone, mesalamine	Rhombencephalitis	*Listeria monocytogenes*	Shock, MV, multiple hypodensity on brain CT	Death
Tsuchiya et al.	2018	Japan	UC	17	5-ASA, 6-MP, Infliximab	Colitis progressed to septicemia and meningitis	*Listeria monocytogenes*		
Radclif et al.	2020	US	UC	NR	Infliximab	Meningitis	*Bordetella bronchiseptica*	Temporary neurosurgical drain placement, worsening encephalopathy, communicating hydrocephalus	

CD: Crohn's disease; UC: ulcerative colitis; NR: not reported; 5ASA: 5-aminosalicylates; AZT: azathioprine; 6-MP: 6-mercaptopurine; PTE: Pulmonary thromboembolism; MV: mechanical ventilation; CSVT: Cerebral sinovenous thrombosis; CMV: cytomegalovirus; CT: computed tomography; BM: bone marrow; EVD external ventricular drain; AKI: acute kidney injury.

CHAPTER 4

VERTEBRAL OSTEOMYELITIS IN BACTERIAL MENINGITIS PATIENTS

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International Journal of Infectious Diseases 2021; 111: 354-9.

ABSTRACT

Objectives: To analyze clinical and laboratory characteristics of vertebral osteomyelitis in community-acquired bacterial meningitis patients

Methods: We analyzed all the episodes of vertebral osteomyelitis included in a cohort study of adult patients with community-acquired bacterial meningitis in the Netherlands. Subsequently, we performed a systematic review of published cases.

Results: Between March 2006 and August 2018, 10 of 1974 (0.5%) meningitis patients were diagnosed with vertebral osteomyelitis. The median age was 70 (interquartile range [IQR] 54-74) and 6 (60%) were male. The median time between diagnosis of bacterial meningitis and vertebral osteomyelitis was 6 days (IQR 1-13). Most common presenting symptoms were back or neck pain occurring in 7 patients (70%); 1 patient presented with neurological deficits due to cauda equina compression. *Streptococcus pneumoniae* was the causative pathogen in 5 patients and *Staphylococcus aureus* in 3. In our literature review 32 additional cases were identified showing similar distribution of age, gender and pathogen. Seven (18%) out of 40 patients from our series and those reported in the literature died.

Conclusions: Concomitant vertebral osteomyelitis in community-acquired bacterial meningitis patients is rare. Persisting back pain is a clue to the diagnosis and should prompt an MRI of the spine because prolonged antibiotic treatment or surgical treatment may be indicated.

INTRODUCTION

Despite recent advances in prevention and treatment of acute bacterial meningitis, it remains a life-threatening disease with significant morbidity and mortality (54, 55). Patients with bacterial meningitis often present with distant foci of infection, such as otitis, sinusitis, pneumonia, or endocarditis which can either precede or complicate clinical course (17, 56-59). Vertebral osteomyelitis has been rarely reported in patients with community-acquired meningitis but the frequency has not been mentioned. It can occur as a result of hematogenous seeding of bacteria to the vertebrae but it may also arise from continuous spread of infection (60). While contiguous spread of microorganisms from the adjacent soft tissue to the vertebrae is a known underlying pathogenesis of vertebral osteomyelitis (61), whether it can also develop from the spinal subarachnoid space in the setting of bacterial meningitis is unknown. There are a few case reports and case series in the literature that have described patients with concomitant bacterial meningitis and vertebral osteomyelitis (62-91). Most of them described vertebral osteomyelitis as a complication of bacterial meningitis (68, 82) but it also reported as a coexistence or predisposing condition for meningitis (65, 84). As vertebral osteomyelitis requires prolonged antibiotic treatment compared to bacterial meningitis and potentially surgical intervention, it is important to diagnose vertebral osteomyelitis in bacterial meningitis patients to prevent further morbidity.

In this study, we report vertebral osteomyelitis concomitant with community-acquired bacterial meningitis identified from a nationwide observational cohort study.

METHODS

In this observational study, we evaluated patients with vertebral osteomyelitis included in a nationwide prospective cohort of adults (patients older than age 16 years) with bacterial meningitis in the Netherlands between January 1, 2006, and August 31, 2018. Methods have been described previously in detail (17). For all patients an electronic case record form (CRF) was filled in by the treating physician and subsequently checked and (if needed) supplemented by the researchers. Vertebral osteomyelitis is not routinely scored in the CRF, but could be extracted from open text fields in which 'other' neurologic or systemic complications of bacterial meningitis could be entered. From all patients with vertebral osteomyelitis the discharge letter and radiological imaging were retrospectively analyzed for specific clinical characteristics (e.g., back pain), which were not routinely scored in the CRF. Surgical and antibiotic treatment was also collected from discharge letters. Vertebral osteomyelitis was defined as a positive culture of biopsy material derived from the vertebrae, intervertebral disk space, or paravertebral or epidural abscess or in the setting of clinical and radiographic findings typical of vertebral osteomyelitis with positive blood or CSF cultures (92, 93).

Outcome was scored according to the Glasgow Outcome Scale (GOS). A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1 to 4. Subsequently, we reviewed the literature on vertebral osteomyelitis in patients with bacterial meningitis. We excluded cases of tuberculous meningitis and osteomyelitis as this is a distinct clinical syndrome (94). PubMed was searched for English language reports of vertebral osteomyelitis preceding or complicating, or diagnosed concomitant with bacterial meningitis. The following search strategy was used: ("Meningitis"[Mesh]) AND ("Discitis"[Mesh] OR "vertebral osteomyelitis" OR "spondylodiscitis" OR "spondylodiskitis" OR "spine infection"). Data were extracted on patient characteristics and underlying comorbidities, causative pathogen, imaging modalities, affected level of spine, associated paravertebral, epidural or psoas abscess(es), antimicrobial and/or surgical treatment, complications, and clinical outcome.

Continuous data were described with medians and interquartile range and categorical variables with frequency and percentage. The Mann Whitney U test was used for continuous variables whereas Fisher's exact test and Chi-square tests were used for categorical variables, as appropriate. A p-value < 0.05 was considered as statistically significant.

Patients or their legal representatives received written information about the study and were asked to give written informed consent for participation. The study was approved by the medical ethical committee of the Academic Medical Centre, Amsterdam, the Netherlands.

RESULTS

We identified 10 patients with vertebral osteomyelitis in a cohort of 1974 episodes of bacterial meningitis (0.5%; table 1). Six of the 10 patients (60%) were male and the median age was 70 years (interquartile range [IQR] 54-74). Four patients (40%) had a history of osteo-articular disorders, mostly lumbar disk herniation. Two patients had underlying malignancies (prostate cancer, chronic leukemia) and two had systemic autoimmune disorders (rheumatoid arthritis, psoriasis). Diagnosis of concomitant infective endocarditis was made in one patient whose illness was also complicated by septic arthritis of the shoulder joint.

The median time between diagnosis of bacterial meningitis and vertebral osteomyelitis was 6 days (IQR 1-13). The presenting sign or symptom of vertebral osteomyelitis was neck or back pain in 7 patients (60%), persisting inflammatory biomarkers in blood in 2 patients (20%), and a cauda equina syndrome in 1 patient (10%). One patient (10%) had severe new-onset back pain two weeks prior to the episode of bacterial meningitis, suggesting that vertebral osteomyelitis preceded bacterial meningitis. In other patients, vertebral osteomyelitis was diagnosed simultaneously or after the diagnosis of meningitis was made. The median of CSF leukocyte counts in patients was 1443/µL (IQR, 256-11602), CSF granulocyte counts 345/ µL (75, 5799) CSF protein 420 mg/dL (193, 615), and CSF glucose 10.8 mg/dL (4.5, 39.6).

Diagnosis of spinal involvement was confirmed using spinal MRI in all patients and 3 patients also underwent positron emission tomography (PET) scan. The osteomyelitis was localized at lumbar level in 8 patients, cervical in 2 patients, and thoracic level and sacrum both in 1 patient. In one patient both thoracic and lumbar vertebrae were affected. Seven (70%) patients had epidural, paravertebral, or psoas abscess as shown by MRI and/or PET imaging. In six patient echocardiography was performed of which one patient with pneumococcal meningitis was diagnosed with concomitant endocarditis.

The causative pathogen was *Streptococcus pneumoniae* in 5 patients (50%), *Staphylococcus aureus* in 3 patients (30%), and *Streptococcus agalactiae* in 2 (20%). All 10 patients received prolonged antimicrobial treatment and in three cases surgical drainage of abscess(es) and/or debridement was performed. Of those undergoing surgery in addition to antimicrobial therapy the treatment consisted of drainage of an infected epidural abscess in two patients and drainage of a psoas abscess and aortic valve replaced because of concomitant endocarditis in the third case.

Four patients had an unfavorable outcome of whom one died. Neurologic sequelae in survivors with an unfavorable outcome included cognitive impairment in 2 cases, and cranial nerve palsies and aphasia, each in one. All 3 patients with staphylococcal meningitis survived but all experienced a complicated course of illness, which included renal failure, respiratory insufficiency, rupture of a mycotic cerebral aneurysm with a sub-arachnoid hemorrhage, psoas abscesses, and nosocomial pneumonia. We did not identify differences in age, gender, medical history, clinical symptoms and signs on admission, persistent fever during admission between meningitis patients with and without osteomyelitis.qZ'

Review of the Literature

The search yielded 65 articles of which 31 studies were relevant to our review (62-91). Thirty-two patients with bacterial meningitis and vertebral osteomyelitis were identified of whom 18 (57%) were male (table 1). The median age of patients was 60 years (IQR 22-80), and 2 children (<18 years) were included. There were two patients with a recent (minor) trauma of the spine (64, 65), one patient with repeated intervertebral disc herniation (95), one with chronic low back pain (63), and one with long-standing history of T4 paraplegia secondary to transverse myelitis (83). Ten out of 29 patients (34%) were immunocompromised due to alcoholism, diabetes mellitus, cancer, organ transplantation, liver cirrhosis, and splenectomy.

Presenting symptoms of vertebral osteomyelitis included cervical or back pain in 24 (83%) of 29 patients and neurological deficits related to cord or nerve root compression was found in 4 (14%). In 16 (55%) out of 29 patients, symptoms of vertebral osteomyelitis started before meningitis, in 9 (31%) after meningitis, and in 4 (14%) simultaneously. Diagnosis of spinal involvement was confirmed using spinal MRI in 22 patients and isotope bone scan in 4 of which 3 patients also underwent MRI. In 7 patients no information was available on the imaging modalities. Diagnosis of vertebral osteomyelitis was made during postmortem examination in one patient for whom there was no imaging performed of the spinal cord and died within days after hospital admission (65). The most common affected level of vertebral column was lumbar in 22 (73%) patients, followed by the cervical spine in 7 (23%). Nineteen (63%) patients had associated abscess(es) in the epidural, paravertebral, and/or psoas compartments. The most common causative pathogen was *S. pneumoniae*, which was identified in 14 of 32 (44%) patients, followed by other streptococcal species in 6 (19%). Two children were reported with *Pasteurella multocida*. Three (10%) out of 27 patients had concomitant endocarditis (81, 90, 96) and two patients had an infected aneurysm of the abdominal aorta (76, 88). Bacteremia was identified in 20 (66%) patients. All patients received antimicrobial treatment and 9 (31%) required surgical interventions. Overall, six (20%) patients died (62-65, 69, 90).

Table 1. Characteristics of patients reported in the literature and in the present study with bacterial meningitis and vertebral osteomyelitis

	Present study	Literature	Total
No. of cases	10	32	42
Age, median	70 (54-74)[1]	60 (22-80)	61 (52.5-71)
Gender, male	6/10 (60)	16/28 (57)	22/38 (58)
History of osteoarticular disorders of spine[2,3]	4/10 (40)	2/30 (7)	6/40 (15)
Concurrent endocarditis	1/10 (10)	3/27 (10)	4/40 (10)
Causative pathogen			
Streptococcus pneumoniae	5/10 (50)	14/32 (44)	19/42 (45)
Staphylococcus aureus	3/10 (30)	3/32 (9)	6/42 (14)
Streptococcal species[4]	2/10 (20)	6/32 (19)	8/42 (19)
Salmonella species	-	2/32 (6)	2/42 (5)
Pasteurella multocida	-	2/32 (6)	2/42 (5)
Other pathogens	-	3/32 (9)	3/42 (7)
No pathogen isolated	-	2/32 (6)	2/42 (5)
Source of isolation of the pathogen			
Blood	6/10 (60)	20/30 (66)	26/40 (65)
CSF	7/10 (70)	19/30 (63)	26/40 (65)
Bone or abscess(s)	-	3/30 (10)	3/40 (8)
Affected level(s) of vertebral column			
Cervical	2/10 (20)	7/30 (23)	9/40 (22)
Thoracic	1/10 (10)	4/30 (13)	5/40 (13)
Lumbar	8/10 (80)	22/30 (73)	30/40 (75)
Sacral	2/10 (20)	5/30 (17)	7/40 (18)
Abscesses			
Epidural	2/10 (20)	11/30 (37)	13/40 (33)
Paravertebral	4/10 (40)	8/30 (27)	12/40 (30)
Iliopsoas	3/10 (30)	6/30 (20)	9/40 (23)
Therapeutic modalities			
Surgical interventions	3/9 (33)	9/29 (31)	12/38 (32)
Hyperbaric oxygen[5]	-	1/30 (3)	1/38 (3)
Mortality rate	1/10 (10)	6/30 (20)	7/40 (18)

[1] Numbers are represented by the number of patients with specific characteristics/ the number of patients evaluated (percent) for nominal variables and by median (25th quartile, 75th quartile) for quantitative variables.

[2] Degenerative disc disease, spondylodesis, spinal disc herniation led to foot drop, degenerative disc disease with root compression, recessus stenosis, and previous spinal surgery.

[3]Difference between cohort and literature statistically significant P<0.05

[4] *Streptococcus agalactiae, Streptococcus suis, Streptococcus tigurinus, Enterococcus faecalis,* and *Enterococcus avium*.

[5] One patient who did not respond to the combination of antimicrobial therapy and surgical intervention (Omori et al., 2008).

DISCUSSION

Our study shows that concomitant occurrence of community-acquired bacterial meningitis and vertebral osteomyelitis is rare, and was found in 0.5% of bacterial meningitis patients. Persisting back or neck pain were found to be clues to the diagnosis and should prompt neuroimaging of the spine and spinal cord. Although rare, diagnosis of this condition is important because of longer duration of antibiotic treatment, possible need for surgical intervention, and risk of concomitant endocarditis and adjacent abscesses, which were identified in 10% and 65% of episodes, respectively. Bacterial infection of the spine requires six or more weeks of intravenous antimicrobial treatment and spinal surgical intervention in those with neurologic deficits, paravertebral abscesses, cord compression, or progressive, persistent, or recurrent diseases (92, 93). Consistent with previous studies on the general population of community-acquired bacterial meningitis (13), *S. pneumoniae* was found as the most frequent causative pathogen in patients with meningitis and vertebral osteomyelitis, causing 45% of cases. Nevertheless, other streptococcal species and *S. aureus* are relatively common in patients with concomitant spondylodiscitis. This could influence the choice of ancillary investigations and empirical antimicrobial regimen for meningitis patients with vertebral osteomyelitis.

Back and neck pain were the most common presenting symptoms of vertebral osteomyelitis in patients with bacterial meningitis. These symptoms, however, are relatively common in patients with meningitis and may be considered as pain due to meningeal irritation or post-lumbar puncture pain. As a result, delayed or missed diagnosis of vertebral osteomyelitis is possible to occur in bacterial meningitis, as frequently occurs in vertebral osteomyelitis in general due to low specificity of presenting symptoms (97, 98). Persistent back or neck pain can be considered as clues to the diagnosis of vertebral osteomyelitis. Other symptoms suggestive of vertebral osteomyelitis in bacterial meningitis patients consist of neurological symptoms localized to the spinal cord, cauda equina or spinal nerve roots, and persistently elevated inflammatory markers without clear focus. Patients with meningitis and vertebral osteomyelitis, especially those with staphylococcal infections, often experienced systemic and neurologic complications during the disease course. This is likely to be due to older age, high frequency of underlying comorbidities, and longer duration of treatment in hospital.

The sequence of infections in bacterial meningitis patients with vertebral osteomyelitis is unclear, as vertebral osteomyelitis can be complicated by bacterial meningitis and vice versa. Hematogenic spread of the pathogens is the most likely mechanism by which both infections are caused (61, 70), and in all patients with vertebral osteomyelitis and patients with *S. aureus* meningitis echocardiography is indicated to rule out coexisting endocarditis (99). On the other hand, a considerable proportion of patients in our cohort and literature had adjacent

infectious foci, such as paraspinal or epidural abscesses that could raise at least two other hypotheses for the pathogenesis of concomitant occurrence of bacterial meningitis and vertebral osteomyelitis. First, during the procedure of lumbar puncture, inadvertent penetration to these infectious foci might cause spread of the infection to the subarachnoid space. However, the osteomyelitis is in all cases ventral to the spinal column, so contamination is unlikely to occur through a lumbar puncture. Second, parameningeal sources might cause an inflammatory reaction in the CSF and symptoms and signs of meningeal irritation. The CSF findings of parameningeal reaction may be confused with concomitant bacterial meningitis. Nevertheless, the inflammatory reactions caused by parameningeal infectious foci are often mild as compared with bacterial meningitis.

In comparison to the meta-analysis of the literature we found the mean age of our patients to be higher (70 vs 60 years) and a statistically significant higher proportion of patients had a history of osteoarticular disorders of the spine. These differences could be explained by publication bias in the literature, as younger patients with no prior spine conditions are more likely to be reported in case reports or series.

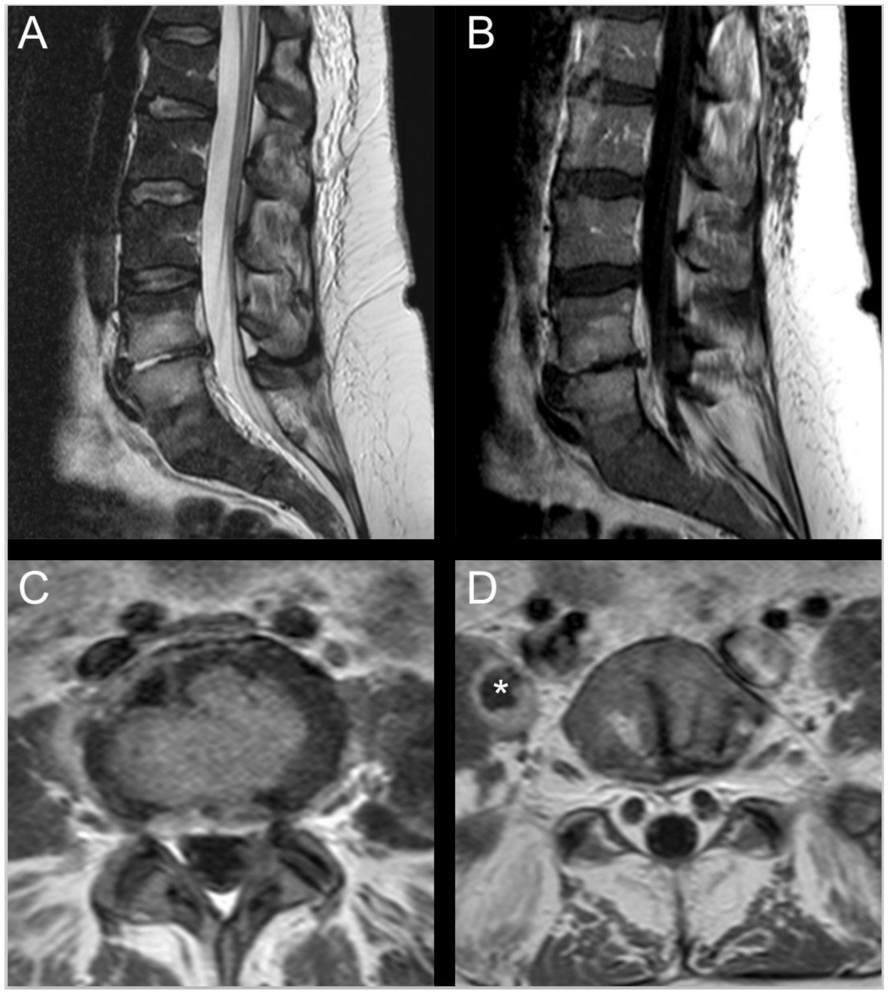
Our study has several limitations. First, vertebral osteomyelitis was not routinely scored on the CRF and cases may have been missed if they were not mentioned by the treating physician in open text field on complications. Furthermore, vertebral osteomyelitis is unlikely to be diagnosed in patients who die due to meningitis in the first week of admission. Finally, we did not routinely follow-up patients after discharge from the hospital and late complications, such as a partially treated vertebral osteomyelitis could have been missed. Therefore, we consider the incidence we found as the minimum incidence, which may be an underestimation. Nevertheless, this is the largest case series of patients with bacterial meningitis and vertebral osteomyelitis described to date. Echocardiography was not performed in all the patients with bacterial meningitis and vertebral osteomyelitis, which may have underestimated the frequency of endocarditis.

In conclusion, vertebral osteomyelitis occurs as rare but serious concurrent infection in patients with bacterial meningitis and is mostly caused by *S. pneumoniae*. In bacterial meningitis patients with persistent back or neck pain, signs of spinal cord or cauda equine compression or radiculopathy, vertebral osteomyelitis should be considered and studied by whole spine MRI. Vertebral osteomyelitis requires prolonged antibiotics and potentially neurosurgical treatment.

FIGURES

Figure 1. Vertebral osteomyelitis of the lumbar spine in bacterial meningitis patients.

MRI of the lumbar spine showing hyperintense signal L5 and S1 on sagittal T2-weighed imaging (a), with gadolinium enhancement of these vertebrae and epidural space on sagittal (B) and axial (C, D) T1-weighted images with an abscess in the right psoas muscle (asterisk).



CHAPTER 5

SUSPECTED CENTRAL NERVOUS SYSTEM INFECTIONS IN HIV-INFECTED ADULTS

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Frontiers in Neurology 2021; 12.

ABSTRACT

Objectives: To study the differential diagnosis of HIV-infected patients with suspected central nervous system (CNS) infections and the association of CD4 counts with the final diagnosis.

Methods: We analyzed HIV-infected patients from a prospective cohort study on the diagnostic accuracy of clinical and laboratory characteristics in adults with suspected CNS infections in an academic hospital in Amsterdam, the Netherlands, who underwent cerebrospinal fluid (CSF) examination.

Results: Thirty-four (9.4%) out of 363 patients with suspected CNS infections were HIV-positive of whom 18 (53%) were diagnosed to have CNS infection, with median CD4 counts of 255 cells/μL. The spectrum of CNS infections consisted of progressive multifocal leukoencephalopathy in 3 patient (17%), cryptococcal meningoencephalitis, toxoplasma encephalitis, angiostrongylus eosinophilic meningitis, and HIV encephalitis, each in 2, (11%), and cytomegalovirus encephalitis, neurosyphilis, tuberculous meningoencephalitis, histoplasma encephalitis, and varicella-zoster virus meningitis, each in one (6%). Clinical characteristics and blood parameters did not differ between HIV infected patients with CNS infections and other diagnoses. The best predictor for CNS infections was the CSF leukocyte count (AUC= 0.77, 95CI% 0.61-0.94). The diagnosis of CNS infection was not associated with the CD4 count (median 205 vs 370, p=0.21). Two patients (11%) with CNS infections died and 2 (11%) had neurological sequelae.

Conclusions: Half of the patients with suspected CNS infections are diagnosed with a CNS infection, and this was not related to CD4 counts. The best predictor for CNS infections was the CSF leukocyte count.

INTRODUCTION

Human immunodeficiency virus (HIV) is a neurotrophic, neuroinvasive and neurovirulent pathogen (100), which can cause direct infection of the central nervous system (CNS) but also predisposes to a variety of other neuroinfections through impaired T-cell mediated immunity (101-103). It has been estimated that in the era before the introduction of combination antiretroviral therapy (cART), around 10% of HIV-infected patients initially presented with neurological disorders, and 30% to 50% of them developed neurological complications during the progression of their diseases (104). Although recent large observational cohorts of HIV-infected patients have reported a significant decrease in the overall incidence of the most frequent HIV-associated neurological disorders in the cART era (105, 106), CNS infections have remained an important cause of morbidity and mortality (107).

Diagnosis of CNS infections in HIV-infected patients can be challenging as a variety of conditions should be considered in the differential diagnosis, and it may be caused by a broad spectrum of pathogens with diverse and overlapping clinical manifestations (108). The causes of CNS infections in HIV have been related to the CD4 lymphocyte count, of which a value below 200 has been described to predispose to cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis (109, 110). HIV patients with higher CD4 counts, on the other hand, are expected to be infected with non-opportunistic pathogens (108). A number of studies have reported the spectrum of CNS infections in patients with low range of CD4 count (106, 111-113), but the distribution of various CNS infections has not addressed in HIV-infected subgroups with higher range of CD4 count.

We describe a population of HIV-infected patients included in a prospective study on the diagnostic accuracy of clinical and laboratory characteristics in patients with suspected CNS infections. We analyzed the causes of CNS infections, the differential diagnosis and the association of CD4 counts with the final diagnosis.

METHODS

We studied HIV-positive patients over 16 years included in cohort of patients with suspected CNS infections in an academic hospital in Amsterdam, the Netherlands, who underwent CSF examination. The methods have been described in detail previously (18). Data collection regarding past medical history, clinical characteristics on presentation and results of ancillary investigations including blood and CSF analysis, microbiological examinations, and imaging studies was done using online case record forms.

The final diagnosis was classified by two researchers based on all available clinical data, including microbiological examination of CSF. The classification was performed sorting each diagnosis into one of the following five categories: 1) CNS infection, 2) nervous system inflammation without infection, 3) non-infectious non-inflammatory neurological disorder, 4) non-neurological infection and 5) other systemic disorder. Outcome was scored using the Glasgow outcome score (GOS). A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1 to 4.

Continuous data were described with medians and interquartile range and categorical variables with frequency and percentage. The Mann Whitney U test was used for continuous variables whereas Fisher's exact test and Chi-square tests were used for categorical variables, as appropriate. The area under curve (*AUC) was measured using the Receiver Operating Characteristic curve (ROC*). A p-value < 0.05 was considered as statistically significant. The study was approved by the medical ethical committee of the Academic Medical Centre, Amsterdam, the Netherlands.

RESULTS

Between February 2012 and May 2015, 363 patients with suspected CNS infections were included of whom 34 were HIV-infected (9.4%). Overall, out of 363 cases with suspected CNS infections, 88 (24%) had CNS infection, 38 (11%) non-infectious non-inflammatory neurological disorders, 121 (33%) non-neurological infections, 108 (30%) non-infectious non-neurological disorders, and 8 (2%) non-infectious neuro-inflammatory disorders. The median age of included HIV-infected patients was 44 years and 24 of 34 (70%) were male. On admission, 19 (55%) patients were on cART, one (3%) stopped treatment shortly before admission, and 10 (29%) were not taking cART despite being diagnosed with HIV infection. In 4 (11%) patients, HIV infection was newly diagnosed during the workup of neurological manifestations.

Presenting signs and symptoms included fever in 10 patients (29%), headache in 16 (47%), neck stiffness in 2 (5%), altered mental status (defined as Glasgow coma scale of less than 14) in 5 (14%) and focal neurological deficits in 3 (8%). Median CD4 counts was 255 (interquartile range [IQR] 92-480). Fifteen of 34 (44%) patients

had a CD4 count below 200, 11 between 200 and 500 (32%), and 8 above 500 (24%). CSF examination showed an elevated leukocyte count (>5/mm^3) in 20 of 34 (59%) patients (Table 1).

Table 1. Characteristics of 34 HIV-infected patients with suspected central nervous system infection

Characteristic	CNS infections	Other diagnoses	Total
Age-years	44 (37-51)†	45 (38-59)	44 (37-53)
Men	13/18 (72)	11/16 (68)	24/34 (70)
New HIV diagnosis	3/18 (17)	1/16 (6)	4/34 (12)
Other underlying comorbidities			
Diabetes mellitus	1/18 (5)	3/16 (18)	4/34 (12)
Cancer	1/18 (5)	1/16 (6)	2/34 (6)
Alcoholism	0/18 (0)	3/16 (18)	3/34 (9)
CD4 count-cells/μL,	205 (55-455)	370 (150-500)	255 (93- 480)
Anti-retroviral therapy	9/17 (50)	10/16 (62)	19/33 (56)
Clinical manifestations			
Presentation < 24 hours	5/18 (28)	2/16 (12)	7/34 (20)
Headache	9/18 (50)	7/16 (43)	16/34 (47)
Fever	4/17 (22)	6/16 (37)	10/33 (30)
Impaired level of consciousness	5/18 (27)	0/16 (0)	5/34 (15)
Neck stiffness	0/18 (0)	2/16 (12)	2/34 (6)
Seizure	2/18 (11)	1/16 (6)	3/34 (9)
Focal neurological deficits	5/18 (28)	2/16 (12)	7 (21)
Blood parameters			
Leukocyte count >12000/μL	2/18 (11)	5/16 (31)	7/34 (21)
CRP, mg/L	5 (1-16)	27 (5-69)	11 (2-34)
CSF parameters			
Opening pressure - mm H_2O	27 (11- 38)	17 (11.5- 20.5)	18.5 (11.7- 27)
Leukocyte count - cells/μL	78 (6-247)	5 (2-9)	8 (3- 107)
Leukocyte count >5/ μL	14/18 (78)	6/16 (38)	20/34 (59)
Leukocyte count >100/ μL	8 (44)	0 (0)	8 (24)
CSF-blood Glucose ratio	0.51 (0.36- 0.61)	0.62 (0.55- 0.84)	0.56 (0.41- 0.67)
Protein concentration- mg/dL	91 (53- 157)	44 (30- 64)	58 (36- 102)
Unfavorable neurological outcome (GOS <5)	4/18 (22)	4/16 (25)	8/34 (23)
Death	2/18 (11)	0/16 (0)	2/34 (6)

CNS: central nervous system; CRP: C-reactive protein; CSF: cerebrospinal fluid; GOS: Glasgow outcome scale
† Numbers are represented by the number of patients with specific characteristics/ the number of patients evaluated (percent) for nominal variables and by median (25th quartile, 75th quartile) for quantitative variables.

Out of 34 HIV-infected patients, 18 (53%) were categorized as having a CNS infection, 7 (21%) with non-infectious non-inflammatory neurological disorders, 6 (18%) with non-neurological infections, 2 (6%) with non-infectious non-neurological disorders, and one (3%) with non-infectious neuro-inflammatory disorders. Of those who were finally diagnosed with CNS infection, 13 (72%) were male and 5 (28%) females with median age of 43 years. Eight (44%) patients with CNS infections were on cART and one discontinued treatment one month before. Their median CD4 was 205 (IQR 55-455). Four (22%) out of 18 patients with CNS infection had normal CSF leukocyte count. Only one (6%) out of 18 patients with CNS infection and 3 (19%) out of 16 with other diagnoses had completely normal CSF. CSF leukocyte count was higher in patients with CNS infections (78 [IQR 6-247] vs. 5 [IQR 2-9]; P-value: 0.002) as was protein concentration (91 [IQR 53-157] vs. 44 [IQR 30-64]; P-value: 0.04), and CSF-to-blood glucose ratio was lower (0.5 [IQR 0.3-0.6] vs. 0.6 [IQR 0.5-0.8]; P-value: 0.01). ROC analysis showed an AUC of 0.77 (95%CI 0.61-0.94) for CSF leukocyte count and 0.75 (95%CI 0.57-0.93) for CSF protein concentration in diagnosing CNS infections. Other clinical or laboratory features, including CD4 count were not associated with diagnosis of CNS infection (median CD4 count 205 [IQR 55-455] in CNS infection group vs 370 [IQR 150-500] in non-CNS infection groups, P-value = 0.21).

The spectrum of CNS infections included PML in 3 (17%) cases, cryptococcal meningoencephalitis, toxoplasma encephalitis, angiostrongylus eosinophilic meningitis, and HIV encephalitis, each in 2 (11%), and cytomegalovirus encephalitis, syphilitic meningitis, tuberculous (TB) meningoencephalitis, histoplasma encephalitis, and varicella-zoster virus (VZV) meningitis, each in one (6%). Final diagnoses were microbiologically confirmed in all but two patients which were classified diagnosed as probable viral CNS infection by the assessors. Both of them were on cART and had CD4 count of more than 200/µL. Two patients who were diagnosed with *Angiostrongylus cantonensis* eosinophilic meningitis were young, male, on cART, and had relatively high CD4 counts (430 and 1020/µL) and marked CSF pleocytosis (441 and 814/µL). In three (16%) patients who were diagnosed with cerebral toxoplasmosis, cryptococcal meningitis and neurosyphilis, the CNS infection was their first manifestation of HIV-infection (Table 2 and 3).

Overall, eight of 34 (24%) patients had an unfavorable outcome, four in each group of CNS infection and other diagnoses (22% and 25%, respectively). Of these, two (11%) patients with CNS infections died. The causes of cause of death were nosocomial sepsis and post-anoxic encephalopathy following resuscitation, and were deemed not be not related to the CNS infection.

Table 2. Final diagnosis based on CD4 counts in HIV-infected patients and associated pathogens in episodes of central nervous system infections

CD4+ count/µL	Final diagnosis				
	CNS infection (53%)	Nervous system inflammation without infection (3%)	Non-infectious non-inflammatory neurological disorder (21%)	Non-neurological infection (21%)	Other systemic disorder (3%)
<200	3 PML (23%) 2 toxoplasma encephalitis (15%) 1 cryptococcal meningitis (8%) 1 EBV-CMV co-infection (8%) 1 histoplasma encephalitis (8%) 1 HIV encephalitis (9%)		2 migraine (15%)	1 pneumonia (8%) 1 systemic viral infection (8%)	1 B-cell lymphoma (8%)
200-500	2 presumed viral meningitis/encephalitis (18%) 1 TB meningoencephalitis (9%) 1 Angiostrongylus eosinophilic meningitis (9%) 1 HIV encephalitis (9%)	1 GBS (9%)	1 Toxic/metabolic encephalopathy (9%) 1 idiopathic cranial nerve palsy (9%)	1 pneumonia (9%) 1 systemic bacterial infection (9%) 1 systemic viral infection (9%)	
>500	1 cryptococcal meningitis (13%) 1 Angiostrongylus eosinophilic meningitis (13%) 1 syphilitic meningitis (13%) 1 VZV meningitis (13%)		2 stroke (25%)	1 leptospirosis (13%)	1 psychiatric condition (13%)

CNS: central nervous system; PML: progressive multifocal leukoencephalopathy; EBV: Epstein - Barr virus; CMV: cytomegalovirus; TB: tuberculous; HIV: human immunodeficiency virus; VZV: varicella-zoster virus; GBS: Guillain-Barré syndrome

Table 3. HIV-infected cases with CNS infections

	Age, gender	CD4, per µL	cART	Initial presentations	GCS	Neuroimaging findings	CSF parameters				Causative pathogen	Diagnosis	Outcome, GOS
							Leucocyte count, per µL	Protein, mg/dL	CSF to blood Glucose ratio	Opening Pressure, mmHg			
1	48, M	70	TDF, Darunavir, 3TC, Ritonavir	Fever, Bradyphrenia, dysphasic, right-sided weakness	15	Widespread non-enhancing white matter abnormalities; Multiple hypodensities in basal ganglia, internal capsule, left cerebral peduncle, and pons	6	54	0.55	-	JCV	PML	1
2	26, M	10	De novo HIV infection	H/A, fever	14	Multiple ring-enhancing lesions with central enhancing nodule and surrounding edema suggestive of toxoplasmosis	6	104	0.48	40	Toxoplasma gondii	Cerebral toxoplasmosis	5
3	50, M	0	None	Cranial nerve palsy, ataxia	14	Multiple hypodensities; T2/FLAIR hyperintensity in left parieto-temporal region, right thalamus, and pons	6	52	0.56	-	JCV	PML	3
4	34, M	110	De novo HIV infection	H/A, confusion, ataxia	11	Normal	651	206	0.41	50	Cryptococcus neoformans	Cryptococcal meningitis	5
5	43, M	230	Receiving cART for 2 years but discounted it for one year before	H/A, nausea	14	Normal	21	81	0.98	13	HIV-1 virus	HIV-1 encephalitis	5
6	34, F	650	TDF, emtricitabine, ritonavir, atazanavir (inconsistent use)	Seizure, aphasia, attention deficit	14	Generalized edema	246	102	0.60	-	VZV	VZV encephalitis	1
7	50, M	530	TDF, emtricitabine, darunavir	H/A, nausea	15	Normal	654	180	0.22	11	Cryptococcus neoformans	Cryptococcal meningitis, IRIS with encephalopathy	5
8	44, M	430	TDF, 3TC, Nevirapine	Confusion, recent episode of painful skin and myalgia	13	T2 hyper intense lesions in tegmentum of pons without contrast enhancement	1323	153	0.37	37	Angiostrongylus cantonesis	Angiostrongylus cantonesis eosinophilic meningitis	5
9	48, M	1020	cART (unknown regimen)	H/A, hyperpathy in the left arm with diminished sense of vibration and position	15	Normal	2442	91	0.37	-	Angiostrongylus cantonesis	Angiostrongylus cantonesis eosinophilic meningitis	5
10	37, M	330	None	H/A, nausea, bradyphrenia, fluctuating aggressive behavior	14	Normal	1131	169	0.43	38	Mycobacterium tuberculosis	Tuberculous meningitis	5
11	52, M	630	De novo HIV infection	??, anisocoria due to left pupillary dilatation	15	Normal	222	42	0.54	-	Treponema pallidum	Syphilitic meningitis and ocular syphilis	5
12	70, M	370	TDF, emtricitabine, efavirenz	Confusion, bradyphrenia, hemianopia, Babinski sign	13	Normal	27	35	0.63	15	No pathogen isolated	Mononuclear (Presumptive viral) meningoencephalitis	5

13	37, M	180	None	Fever, bradyphrenia, Babinski sign	14	Generalized edema, hypodensities in left basal ganglia	9	19	0.67	27	Toxoplasma gondii	Cerebral toxoplasmosis	5
14	37, F	250	3TC, ZDV, nevirapine but discontinued for one month before	Fever, H/A	14	Normal	546	91	0.60	39	No pathogen isolated	Mononuclear (presumptive viral) meningitis	5
15	56, M	7	Prednisone, TDF, emtricitabine, ritonavir	Cognitive deficits, agitation, disorientation	14	Generalized atrophy, areas of increased signal intensity in the pons and right lateral mesencephalon	81	62	0.17	10	EBV, CMV	EBV-CMV encephalitis and CMV retinitis	5
16	57, F	70	None	Episodes of confusion and disorientation, attention deficit, Babinski sign	15	Multiple hypodensities in both frontal lobes; New white matter lesions	93	63	0.70	7	JCV	PML	4
17	43, F	0	cART non-adherent	H/A, nausea, confusion	3	White matter lesions suggestive of HIV encephalitis, small intracerebral hematoma, ischemic lesions in the pons	954	216	0.27	27	Histoplasma capsulatum	Histoplasma capsulatum encephalitis	5
18	42, F	180	3TC, ZDV, lopinavir/ritonavir	H/A, nausea, seizure	8	White matter lesions and leptomeningeal enhancement	672	111	0.33	-	HIV-1	HIV-1 encephalitis	5

cART: combination anti-retroviral therapy; GCS: Glasgow Coma Scale; CSF: cerebrospinal fluid; GOS: Glasgow Outcome Scale; TDF: Tenofovir; 3TC: Lamivudine; JCV: John Cunningham virus; PML: progressive multifocal leukoencephalopathy; H/A: headache; ZDV: Zidovudine; EBV: Epstein–Barr virus; CMV: Cytomegalovirus.

DISCUSSION

Our study shows that half of HIV infected patients with suspected CNS infections are indeed diagnosed with a CNS infection. Our population included patients with relatively high median CD4 count (255 cells/µL), and presence of CNS infection was not associated to CD4 count. Most of the previous studies, even after introduction of cART, reported the spectrum of neurologic complications or CNS infections in HIV-infected patients with median CD4 count in a range between 30 to 90 cells/µL (106, 112-118). Higher median CD4 count in HIV-infected patients in our study might be related to high access to HIV-related health services in the Netherlands with 89% of HIV-infected patients linked to care 92% and treated with cART % in 2017 (119).

We found that CNS infections in HIV-infected patients had many different causes, of which most were opportunistic pathogens, even though the CD4 count was relatively high. This finding, despite relatively high median CD4 count in our patients, could be partly attributed to unmasking of occult opportunistic infections as a result of immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients. Unmasking IRIS is manifested by a robust, inflammatory immune response against the infective pathogen while deteriorating the clinical condition of the patient who recently started taking cART and was previously unable to respond to the opportunistic infection because of immunosuppression (120).

The best predictor for CNS infections was the CSF leukocyte count. This is comparable with findings in HIV negative patients with suspected CNS infections (18). Clinical characteristics had previously been found to have low predictive value in patients with suspected CNS infections (18). Typical clinical characteristics for meningitis, such as neck stiffness, headache, fever and an altered mental status was low among HIV patients with CNS infections (<50%). Therefore, there should be a low threshold for CSF examination in HIV-positive patients with neurological symptoms. Because of the risk of space occupying lesions, cranial imaging should be performed in these patients prior to the lumbar puncture (121). If patients have suspected bacterial meningitis, antibiotics and dexamethasone if indicated should be administered before sending them to the CT scanner (122).

We identified a broad range of causative pathogens. PML, cryptococcal meningoencephalitis, and cerebral toxoplasmosis were the most common opportunistic neurological infections. Studies from other European countries, including Spain (114), France (109), and United Kingdom (123) also reported similar findings and identified these three opportunistic infections among the four most common causes of CNS involvement in HIV-infected patients. However, the population of HIV-infected individuals in these studies had lower CD4 counts, as compared with our cohort. Although tuberculous meningoencephalitis has been reported as one of the most frequent cause of neurological syndromes in HIV-infected patients in the countries endemic for tuberculosis (106, 111, 117, 118, 124-127), it was diagnosed in only one of our patients.

Although about one third of all patients with CNS infection in the whole cohort were diagnosed to have bacterial meningitis, none of the HIV-infected patients were diagnosed with bacterial meningitis. Previous studies on bacterial meningitis show the incidence is 8-19 times increased in HIV infected patients, but the absolute risk is still small (128, 129). In resource rich countries, other cause of CNS infections have been reported to be more prevalent in HIV-infected patients. (130)

Our study had several limitations. First, the number of HIV-infected patients in this study is relatively small, which makes it difficult to draw firm conclusions about the spectrum of HIV-infected patients with CNS complications. Second, only patients who underwent lumbar puncture were included in the study. As a result, we did not study HIV-infected patients whose diagnoses were confirmed by stereotactic or open surgical biopsy or were not candidate for lumbar puncture. This may influence the frequency distribution of the diagnoses because neurological disorders that manifest as single or multiple CNS mass lesions may require brain biopsy for confirmation of the diagnosis. However, recent advances in neuroimaging and molecular-based laboratory tests on CSF have increased the yield of diagnostic tests in patients with CNS infections, decreasing the need for more invasive diagnostic procedures (131).

CONCLUSION

In conclusion, half of the patients with suspected CNS infections are diagnosed with a CNS infection. While CD4 count is not a good predictor for diagnosis of CNS infection versus other diagnosis in HIV-infected patients, specific CSF white cell counts are essential in the making the diagnosis. Therefore, if a CNS infection is suspected cerebrospinal fluid examination indicated in all patients in whom lumbar puncture can be performed safely (132).

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CHAPTER 6

DISCUSSION

Several predisposing factors may increase the susceptibility to bacterial meningitis, including age (133), weakened immune system, anatomical and structural defects (134), and underlying comorbidities such as diabetes mellitus (135). Accordingly, certain groups are at higher risk of acquiring bacterial meningitis. About one-third of the episodes of community-acquired bacterial meningitis occur in immunocompromised patients, making this an important subgroup of patients (16, 17). Certain conditions that cause immunosuppression are specifically associated with an increased risk of bacterial meningitis. These include iatrogenic immunosuppression (e.g., use of immunosuppressive medication or splenectomy), diseases influencing the immune system (e.g. cancer, diabetes mellitus, alcoholism, HIV infection), or hereditary deficiencies of the immune system (136).

Diagnosis and management of bacterial meningitis in these high-risk populations can be a significant challenge. The typical symptoms and signs of meningitis might be masked due to the underlying comorbidities or weakened immune responses. In addition, the spectrum of causative pathogens that needs to be considered is different when the patient has certain specific medical conditions (136). Having knowledge regarding the responsible pathogens, clinical presentations, and optimal diagnostic and therapeutic management in these high-risk groups is necessary for improving their clinical outcomes. In spite of that, our knowledge about bacterial meningitis in high-risk groups mostly comes from case reports and small case series. Furthermore, most practical guidelines on the diagnosis and management of acute meningitis have focused on immunocompetent patients (137) or briefly discussed the immunocompromised hosts as a single group (138). Because survival is directly related to the rapidity with which the diagnosis is made and therapy instituted, and as the etiology of bacterial meningitis may greatly differ from what is observed in the general population, diagnostic and treatment guidelines should be reconsidered in the specific high-risk populations with bacterial meningitis to improve the care of this population.

Bacterial Meningitis in Multiple Myeloma

Cancer patients are at increased risk for meningitis. Between 3% to 12% of patients with community-acquired bacterial meningitis had either active or past cancer (139, 140). Among all types of cancer, multiple myeloma was the most common underlying malignancy. It accounted for 1% of patients with bacterial meningitis and about 10% of all cancer patients with bacterial meningitis (141).

Our findings uncovered the atypical presentation and poor outcome of bacterial meningitis in myeloma patients. Classic symptoms and signs of bacterial meningitis were frequently absent in myeloma patients. Instead, patients most frequently presented with impaired consciousness (141). Also, the increase in the cerebrospinal fluid (CSF) leukocytes was less marked in myeloma patients with bacterial meningitis. This finding commonly leads to misclassification of the disease as viral meningitis. To prevent delayed or misdiagnosis, physicians should be aware of the atypical clinical and laboratory characteristics of bacterial meningitis in myeloma patients, and a low threshold should be kept for starting empirical antimicrobial treatments in myeloma patients in whom meningitis is considered, even in the absence of classic manifestations.

A bimodal peak in the incidence of bacterial infections has been identified in myeloma patients: one within a few weeks of diagnosis and the second within 6th year following disease progression (29, 36, 37). Gram-positive pathogens cause the majority of early-onset sepsis and Gram-negative pathogens account for late-onset sepsis in myeloma patients (39-41). Bacterial meningitis, although a relatively late complication in multiple myeloma, was almost always caused by *Streptococcus pneumoniae* (141). Multiple myeloma is known to be associated with acquired hypogammaglobulinemia (142). This might explain the higher incidence of pneumococcal meningitis in patients with multiple myeloma. Only few studies evaluated the role of immunoglobulin replacement in patients with multiple myeloma and hypogammaglobulinemia. A randomized, double-blind, placebo-controlled, multicenter trial showed protective role of IVIG against life-threatening infections and a significant role in reducing the risk of recurrent infections (143). Accordingly, it has been suggested that regular immunoglobulin substitution should be considered in myeloma patients who suffer from life-threatening or recurrent infections that are reasonably thought to be caused by low levels of polyclonal immunoglobulin (144). Nevertheless, similar benefit was not achieved by use of IVIG to reduce infectious complications in hypogammaglobulinemic patients with multiple myeloma undergoing autologous stem cell transplantation (145). Further studies to determine the immunoglobulin level of myeloma patients with bacterial meningitis and the benefit of immunoglobulin replacement in these patients are warranted. Also, clinical trials investigating the addition of IVIG to the standard treatments of bacterial meningitis in myeloma patients may yield promising results.

About half of myeloma patients with bacterial meningitis experienced unfavorable outcomes, with a rate of about twice the rate in the overall population of adults with community-acquired bacterial meningitis. Death occurred frequently and early in the course of bacterial meningitis in myeloma patients; more commonly within the first 3 days of hospital admission. Higher mortality rate and earlier mortality in myeloma patients with bacterial meningitis might be related to a more fulminant course of meningitis or to the complications related to the underlying malignancy in these patients. Systemic and neurologic complications frequently occurred in patients with multiple myeloma and bacterial meningitis. The older age, higher rate of bacteremia, and lower CSF leukocyte counts were associated with a higher chance of death in this population (141). Further studies are needed to better stratify myeloma patients into risk categories for unfavorable outcomes due to bacterial meningitis, possibly based on host factors, immunoparesis, disease characteristics and complications, and treatments for underlying malignancy.

Bacterial Meningitis in Patients with Inflammatory Bowel Diseases

A number of autoimmune and chronic inflammatory disorders, and their treatments increase the risk of invasive bacterial infections, including bacterial meningitis. In the prospective nationwide cohort of the Netherlands (2006-2014), among patients with community-acquired bacterial meningitis who were taking immunosuppressive and immunomodulatory medications, autoimmune disorders were the most common underlying conditions, among them rheumatoid arthritis and inflammatory bowel diseases (IBD) ranked first and second (146). An overall higher incidence of meningitis has been reported in the population of IBD patients (147) and these patients accounted for 1% of the episodes of community-acquired bacterial meningitis.

A notable finding in our study on IBD patients with bacterial meningitis was an important role of *Listeria monocytogenes* as the most common causative pathogen of meningitis in IBD patients, especially in those using anti-TNF agents (148). Previously, an odds of 7.4 has been reported for the incidence of listeria bacteremia in IBD patients compared to the general population (149). We also highlighted a higher risk of listeria infection in IBD patients with bacterial meningitis with an odds ratio of 15.01 compared to patients without IBD (148). Since *L. monocytogenes* DNA has been found in the intestine of both IBD patients and the control subjects (51), the increased risk for listeria infections in IBD might be explained by mucosal damage in the gut and the use of immunosuppressive therapies. Furthermore, patients with IBD commonly exhibit other risk factors for opportunistic infections, including malnutrition, older age, and chronic medical diseases (150). The most common underlying comorbidities in IBD patients with bacterial meningitis were diabetes mellitus and cancer (148).

IBD are characterized by relapsing and remitting disease courses and treatment goals include induction and maintenance of remission and avoiding complications of the disease (151). Therefore, the cornerstone of therapy for IBD is immunosuppressive agents that dampen the host inflammatory response (150). Anti-TNF agents are among the biologicals that are used in IBD patients (151). TNF is a pro-inflammatory cytokine that plays a key role in IBD pathogenesis (52) and in host resistance against various microorganisms, particularly intracellular pathogens (53). An important finding in our study was that all IBD patients with meningitis using TNF inhibitors were infected with *L. monocytogenes*. The increased risk of acquiring listeriosis in biologicals-treated patients has been also reported in other patient series, especially related to anti-TNF therapy and combination immunosuppressive therapies (51). Physicians and IBD patients should be aware of this increased risk of listeria meningitis, and IBD patients receiving anti-TNF therapy should be advised to avoid foods such as unpasteurized dairy products, unwashed vegetable, and uncooked meet (148). Future studies investigating listeria infection in IBD patients may uncover whether IBD patients who are taking immunosuppressive agents have higher rate of GI colonization with *L. monocytogenes*. Also studies are warranted to determine whether screening for GI colonization with *L. monocytogenes* should be included in the pre-treatment evaluation of IBD patients who are candidate for anti-TNF therapy.

Bacterial meningitis was a relatively late complication in the IBD course, often presenting 3-4 years after diagnosis of IBD. Although patients with bacterial meningitis using immunosuppressive medications are less likely to present with headache or neck stiffness (146), IBD patients often presented with classic features of bacterial meningitis (148). Bacterial meningitis frequently developed concomitantly or shortly after development of gastrointestinal symptoms that were often interpreted as flares of IBD. All IBD cases with preceding gastrointestinal symptoms were diagnosed with listeria meningitis (148). It remains unclear whether these symptoms were actually due to IBD flares or caused by the intestinal listeria infection preceding invasive disease. Having knowledge about the cause of preceding gastrointestinal symptoms might help to hypothesize a possible predisposing role of immunosuppressive agents in developing neurolisteriosis or progression of listeria gastroenteritis to neurolisteriosis.

Despite a high rate of unfavorable outcome of bacterial meningitis in IBD (33%), the mortality rate was relatively low (4%). This finding is not consistent with previously reported high mortality rate of listeria meningitis that is as high as 36% (152). It could possibly be explained by relatively younger age of IBD patients, earlier seeking of medical attention, or less robust inflammatory response in the subarachnoid space due to extensive immunosuppressive treatment used in IBD patients. Larger cohorts of IBD patients with bacterial meningitis are warranted to validate the findings of our study.

Bacterial Meningitis in HIV/AIDS

HIV-infected patients are another high-risk population for bacterial meningitis. Bacterial meningitis, although not one of the most common bacterial infections in HIV-infected patients, has been reported much more frequently in HIV than the general population (153). The global epidemiology of bacterial meningitis has been affected by HIV infection at two key points over the last four decades. First in the 1980s that the incidence of bacterial meningitis increased with the start of the HIV-1 epidemic, and subsequently in the 1990s that a decrease occurred in the incidence of bacterial meningitis after the introduction of antiretroviral treatments (2). Despite increased susceptibility to bacterial meningitis in HIV-infected individuals, the absolute risk is small (154, 155). Our study showed that half of the HIV-infected patients with suspected central nervous system (CNS) infections are indeed diagnosed with CNS infections, and bacterial meningitis is not one of the main causes of neurologic complications (156). The risk of developing bacterial meningitis is related to the CD4 lymphocyte count. A CD4 count less than 200/μL has been reported as the strongest predictor for acquiring bacterial meningitis (157). Similar to previous report of HIV-infected patients with community-acquired bacterial meningitis in the Netherlands (2006-2013) (158), the median CD4 lymphocyte count of HIV-infected patients in our study was relatively high (255 cells/μL) which could affect the number of patients with bacterial meningitis. A higher median CD4 count in HIV-infected patients with bacterial meningitis in the Netherlands could be related to the high access to HIV-related health service with 89% of HIV-infected patients linked to care and 92% treated with cART in 2017 (159). Nevertheless, low rates of bacterial meningitis in HIV-infected patients have been also reported in HIV populations with low median CD4 ranges (30-90 cell/ μL), with bacterial meningitis accounts for only 0-7% of neurological infectious diseases in HIV-infected populations in different clinical settings (106, 109-118, 124-127, 160-164).

Similar to other European countries (i.e., Spain (114), France (109), and the United Kingdom (110)), we found most CNS infections in HIV-infected patients were caused by opportunistic pathogens. PML, cryptococcal meningoencephalitis, and cerebral toxoplasmosis were the most common opportunistic neurological infections in HIV-infected patients with CNS infections. Although the cause of CNS infections in HIV has been related to the CD4

count (165, 166), CD4 lymphocyte count was not a good predictor for differentiating between CNS infections and other neurological disorders in HIV-infected patients (156). The best predictor for CNS infection in HIV-infected patients was the CSF leukocyte count (156). The finding that is consistent to what has been reported about HIV-negative patients with suspected CNS infections (42).

Vertebral Osteomyelitis in Bacterial Meningitis

Patients with bacterial meningitis is often present with distant foci of infection which can either precede or complicate the clinical course (17, 167-170). Vertebral osteomyelitis occurred in 0.5% of episodes of community-acquired bacterial meningitis (171). Initial complaints of vertebral osteomyelitis in patients with bacterial meningitis were nonspecific and mainly included back or neck pain. As a result, it might be missed or subject to delay in diagnosis (172), as frequently occurs in vertebral osteomyelitis in general (97, 98). Backache could be due to an array of other conditions as well as secondary to meningeal irritation or post-lumbar puncture pain that makes the decision regarding the best approach more difficult. Therefore, persistent back or neck pain can be considered as clues to the diagnosis of vertebral osteomyelitis. Other findings suggestive of vertebral osteomyelitis in bacterial meningitis were neurological symptoms localized to the spinal cord, cauda equina or spinal nerve roots, and persistently elevated inflammatory markers without a clear focus (171). Meningitis patients with vertebral osteomyelitis were frequently old and had a history of osteoarticular disorders of the spine. The osteomyelitis was mostly localized at the lumbar level and less frequently at the cervical vertebrae. Although pneumococcal spondylodiscitis is rare, we found *S. pneumoniae* is the most common causative pathogen in about half of patients with meningitis and vertebral osteomyelitis. Other streptococcal species and *Staphylococcus aureus*, however, were relatively common causes of infection in patients with concomitant meningitis and vertebral osteomyelitis. The findings that could influence the choice of ancillary investigations and the empirical antimicrobial regimen for meningitis patients with vertebral osteomyelitis (171).

The sequence of infections in meningitis patients with vertebral osteomyelitis has remained unknown. Hematogenous spread of infection, spread of infection from the subarachnoid space or para meningeal foci, and osteomyelitis as a complication of diagnostic lumbar puncture have been proposed as the possible underlying pathogenesis for development of vertebral osteomyelitis in patients with bacterial meningitis. Of these, hematogenous spread of the pathogens is the most likely mechanism through which both infections are caused (61, 70). Furthermore, vertebral osteomyelitis might serve as a portal of entry for bacterial meningitis, or it may cause meningeal inflammation even in the absence of subdural or epidural abscess. However, the inflammatory reactions caused by para-meningeal infectious foci are often mild as compared with bacterial meningitis.

Despite the overall rarity of concomitant occurrence of bacterial meningitis and vertebral osteomyelitis, the diagnosis of this condition is important because of the longer duration of antimicrobial treatment required, possible need for neurosurgical treatment, and risk of concomitant endocarditis and adjacent abscesses, which were identified in 10% and 65% of episodes of our cohort, respectively (171). Therefore, in patients with bacterial meningitis who experience persistent back or neck pain, signs of spinal cord or cauda equina compression or radiculopathy, vertebral osteomyelitis should be considered and investigated. Bacterial infection of the spine requires ≥ 6 weeks of intravenous antimicrobial treatment and a spinal surgical intervention in those with neurological deficits, paravertebral abscesses, cord compression, or progressive, persistent, or recurrent disease (93).

FUTURE DIRECTIONS

Patients with bacterial meningitis are not a homogeneous group and differences in risk factors, comorbidities, clinical presentation, causative pathogens and complications during admission are all important to study to enable optimal treatment. Using large prospective cohorts, preferably nation-wide or international, provides us the opportunity to study all these subgroups and work towards personalized medicine. Validation of such results internationally will extend the generalizability of these findings and increase the impact of new discoveries.

In this thesis we studies several of the subgroups, including multiple myeloma patients in whom meningitis often lead to early death or significant complications during clinical course. Given the possible role of immunosuppression particularly hypogammaglobulinemia in the poor outcome of bacterial meningitis in myeloma patients, future studies should evaluate the type and severity of immunoparesis in myeloma patients with bacterial meningitis and whether immunoglobulin replacement in addition to antibiotic and corticosteroid treatment could potentially improve patients' outcomes. Better stratification of myeloma patients into risk categories for unfavorable outcomes due to bacterial

meningitis, possibly based on host factors, immunoparesis, underlying disease characteristics and complications, and treatments for underlying malignancy may help in prognostication.

For patients with IBD we showed *L. monocytogenes* is the main cause of bacterial meningitis in patients with IBD, particularly those receiving TNF-alpha inhibitors. Studies evaluating the rate of GI colonization with *L. monocytogenes* in IBD patients before and after immunosuppressive therapy may uncover the role of immunosuppressives in the pathogenesis of listeria meningitis in IBD patients. Almost all IBD patients with listeria meningitis experience an episode of GI symptoms before development of meningitis. GI symptoms frequently assumed to be the sign of IBD flare and is tried to be managed by increasing immunosuppression. Identification of the cause of preceding GI symptoms, whether it is actually due to IBD flare or caused by GI listeria infection, might help to hypothesize whether increasing immunosuppression is responsible for development of invasive listeria infection or IBD intrinsically increase the risk for listeria invasion to the bloodstream and CNS. It is also remained to be studied whether screening for GI colonization with *L. monocytogenes* should be included in the pre-treatment evaluation of IBD patients who are candidate for anti-TNF therapy. Potentially gut microbiome studies of IBD patients may be of use to identify those at risk for invasive listeriosis.

These are some examples of how prospective cohort studies may identify clinically relevant findings for subpopulations with bacterial meningitis, but also identify new research questions that need further investigation. The larger such cohorts will become, the better we can answer these new research questions. International cooperation between our Dutch research group and a Danish nationwide study on CNS infections already showed that combining forces provides even better data for looking at patients with rare causes of bacterial meningitis (e.g., *Escherichia coli* and *Staphylococcus aureus*). Setting up a (initially regional) prospective cohort study in Northeast Iran as next step in my research will further help the international research community on CNS infections to extrapolate research findings to a broader population.

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SUMMARY

Bacterial meningitis is a life-threatening condition, particularly in populations with underlying comorbidities and immunocompromised hosts. Diagnosis and management of bacterial meningitis in these high-risk populations is challenging. Not all immunocompromised individuals are at the equal risk of acquiring bacterial meningitis, and the clinical presentations, spectrum of causative pathogens, and clinical outcome of meningitis may greatly differ among specific high-risk groups. Having knowledge regarding the characteristics of bacterial meningitis in certain high-risk groups is potentially helpful for their optimal management and improving their clinical outcomes. In this thesis, we describe the characteristics of community-acquired bacterial meningitis in specific high-risk populations.

In **Chapter 2**, we describe multiple myeloma patients with community-acquired bacterial meningitis from a prospective Dutch nationwide cohort performed from March 2006 to August 2018. Subsequently, we present the result of our review of the literature yielding 91 additional cases. Bacterial meningitis is a serious complication of multiple myeloma that is associated with high mortality and morbidity. It could present as a complication of multiple myeloma in those already diagnosed with the disease or unmask an occult underlying multiple myeloma. Clinical characteristics and typical CSF abnormalities may be absent in these patients and a low threshold for CSF examination in myeloma patients and empirical treatment for bacterial meningitis pending CSF cultures should be kept.

In **Chapter 3**, we present inflammatory bowel disease (IBD) patients with community-acquired bacterial meningitis from a prospective Dutch nationwide cohort performed from March 2006 to December 2021. Subsequently, we review the literature yielding 30 additional cases. Most IBD patients with a bacterial meningitis present with typical features of bacterial meningitis and despite a relatively low case fatality rate in IBD patients with bacterial meningitis, many patients have an unfavourable outcome. *L. monocytogenes* is the most common causative pathogen, especially in those using anti-TNF agents both with or without co-treatment with immunosuppressive agents, and those presenting with gastrointestinal symptoms. Avoidance of foods that are potential source of *L. monocytogenes* should be emphasized to IBD patients, particularly those who are receiving TNF inhibitors.

In **Chapter 4**, we present HIV-infected patients with suspected CNS infections from a prospective single center cohort from February 2012 and May 2015. Half of HIV-infected patients with suspected CNS infections were

diagnosed to have CNS infection, with median CD4 counts of 255 cells/μL. Bacterial meningitis was not a main cause of CNS infection in HIV-infected patients with suspected CNS infections. The spectrum of CNS infections consisted of progressive multifocal leukoencephalopathy, cryptococcal meningoencephalitis, toxoplasma encephalitis, angiostrongylus eosinophilic meningitis, HIV encephalitis, cytomegalovirus encephalitis, neurosyphilis, tuberculous meningoencephalitis, histoplasma encephalitis, and varicella-zoster virus meningitis. Clinical characteristics and blood parameters did not differ between HIV infected patients with CNS infections and other diagnoses. The best predictor for CNS infections was the CSF leukocyte count. The diagnosis of CNS infection was not associated with the CD4 count.

In **Chapter 5**, we describe patients with community acquired bacterial meningitis who were simultaneously diagnosed with vertebral osteomyelitis from a prospective Dutch nationwide cohort performed from March 2006 to August 2018. Subsequently, we performed a review of the literature yielding 32 additional cases. Vertebral osteomyelitis is a rare but serious complication of bacterial meningitis that most commonly affects the elderly and those with a history of osteoarticular disorders of the spinal column. *Streptococcus pneumoniae* was found as the most common causative pathogen and the lumbar spine was most frequently affected. Early diagnosis of vertebral osteomyelitis in patients with bacterial meningitis is important because it requires longer duration of antibiotic therapy and potentially surgical intervention.

SAMENVATTING

Bacteriële meningitis is een levensbedreigende aandoening, vooral bij mensen met onderliggende comorbiditeit en stoornissen van het immuunsysteem. De diagnose en behandeling van bacteriële meningitis bij deze risicogroepen is een uitdaging. Niet alle immuungecompromitteerde personen lopen hetzelfde risico om bacteriële meningitis te krijgen, en de klinische presentaties, het spectrum van causale pathogenen en de klinische uitkomst van meningitis kunnen sterk verschillen tussen specifieke risicogroepen. Kennis van de kenmerken van bacteriële meningitis bij deze risicogroepen is zinvol om de behandeling te optimaliseren en de uitkomst te verbeteren. In dit proefschrift beschrijven we de kenmerken van door ‘community acquired’ bacteriële meningitis in specifieke hoogrisicogroepen.

In **hoofdstuk 2** beschrijven we multipel myeloompatiënten met community-acquired bacteriële meningitis uit een prospectief Nederlands landelijk cohort, uitgevoerd van maart 2006 tot augustus 2018. Vervolgens presenteren we het resultaat van ons literatuuronderzoek dat 91 aanvullende gevallen opleverde. Bacteriële meningitis is een ernstige complicatie van multipel myeloom en gaat gepaard met een hoge mortaliteit en morbiditeit. Het kan zich voordoen als een complicatie van multipel myeloom bij mensen bij wie de ziekte al is vastgesteld of kan leiden tot de ontdekking van een multipel myeloom. Klinische kenmerken en typische afwijkingen van de liquor kunnen bij deze patiënten afwezig zijn en er moet een laagdrempelig liquoronderzoek worden gedaan bij myeloompatiënten met verdenking meningitis. In afwachting van liquorkweken wordt geadviseerd empirische behandeling voor bacteriële meningitis te starten.

In **hoofdstuk 3** beschrijven we een serie patiënten met community-acquired bacteriële meningitis met inflammatoire darmziekten (IBD) in de voorgeschiedenis uit een prospectief Nederlands landelijk cohort, uitgevoerd van maart 2006 tot december 2021. Vervolgens beschrijven we beschreven casus uit de wetenschappelijke literatuur, waaruit 30 aanvullende gevallen werden geidentificeerd. De meeste IBD-patiënten met een bacteriële meningitis vertonen typische kenmerken van bacteriële meningitis en ondanks een relatief laag sterftecijfer bij IBD-patiënten met bacteriële meningitis, hebben veel patiënten een slechte uitkomst vanwege restverschijnselen. *Listeria monocytogenes* is de meest voorkomende verwekker, vooral bij patiënten die anti-TNF-middelen gebruiken, al dan niet in combinatie met andere immunosuppressiva, en bij patiënten met gastro-intestinale symptomen. Het vermijden van voedsel dat een potentiële bron van *L. monocytogenes* is, moet worden benadrukt bij IBD-patiënten, vooral bij degenen die TNF-remmers krijgen.

In **hoofdstuk 4** presenteren we HIV-geïnfecteerde patiënten met de verdenking op een neurologische infectieziekte uit een prospectief single center cohort, uitgevoerd tussen februari 2012 en mei 2015. Bij de helft van de Hiv-geïnfecteerde patiënten met de verdenking op een neurologische infectieziekte werd een infectie vastgesteld. Het mediane CD4-getal bij deze patiënten was 255 cellen/µL. Bacteriële meningitis werd in dit cohort niet gevonden bij HIV-geïnfecteerde patiënten. Het spectrum van CNS-infecties bestond uit progressieve multifocale leukoencefalopathie, cryptokokkenmeningoencefalitis, toxoplasma encefalitis, angiostrongylus eosinofiele meningitis, HIV encefalitis, cytomegalovirus encefalitis, neurosyfilis, tuberculose meningoencefalitis, histoplasma encefalitis en varicella-zostervirus meningitis. Klinische kenmerken en bloedparameters konden niet gebruikt worden om te differentiëren tussen Hiv-geïnfecteerde patiënten met en zonder neurologische infectie. De beste voorspeller voor CNS-infecties was het aantal leukocyten in de liquor. Het hebben van een neurologische infectie was niet geassocieerd met het CD4-getal.

In **hoofdstuk 5** beschrijven we patiënten met 'community-acquired' bacteriële meningitis die tegelijkertijd werden gediagnosticeerd met spondylodiscitis of vertebrale osteomyelitis uit een prospectief Nederlands landelijk cohort uitgevoerd van maart 2006 tot augustus 2018. Vervolgens hebben we een literatuuronderzoek uitgevoerd wat nog 32 extra casus opleverde. Spondylodiscitis of vertebrale osteomyelitis is een zeldzame maar ernstige complicatie van bacteriële meningitis die vooral voorkomt bij ouderen en mensen met een voorgeschiedenis van osteoarticulaire aandoeningen van de wervelkolom. *Streptococcus pneumoniae* werd gevonden als de meest voorkomende verwekker en de infectie was het vaakst in de lumbale wervelkolom gelokaliseerd. Een vroege diagnose van wervel-osteomyelitis bij patiënten met bacteriële meningitis is belangrijk omdat dit een langere duur van de antibioticatherapie en mogelijk een chirurgische ingreep vereist.

CURRICULUM VITAE

Fereshte Sheybani was born on February 15, 1984, in Mashhad, Iran. She graduated from high school in 2002 and received her high school diploma from The National Organization for Development of Exceptionally Talents (NODET) in Mashhad, Iran. She studied Medicine at Mashhad University of Medical Sciences and obtained her medical degree in 2009. She completed the Infectious Diseases residency training program at Mashhad University of Medical Sciences in 2013. She received board certification in Infectious Diseases and Tropical Medicine from the Iranian National Board of Infectious Diseases and Tropical Medicine in 2013.

In December 2019, Fereshte had the opportunity to join the Neuroinfections Amsterdam research group. As a Ph.D. candidate, she worked on her thesis, entitled "Bacterial Meningitis and its Complications in High-Risk Populations" under the supervision of Prof. Dr. Diederik van de Beek and Prof. Dr. Matthijs C. Brouwer.

She is currently working as an associate professor in Infectious Diseases and Tropical Medicine at Mashhad University of Medical Sciences, Iran. Her main research interest is focused on Neurological Infectious Diseases. She is also interested in doing research about diagnostic errors in infectious diseases, infectious granulomatous disorders, and antimicrobial resistance and stewardship. In 2019, She set up an online registry system for patients with community-acquired central nervous system (CNS) infections in Mashhad, Iran. Over the last three years, she and her colleagues have successfully recorded the clinical characteristics and outcomes of hundreds of patients with community-acquired CNS infections.

She is married to her job, loves rock and mountain climbing, enjoys painting, and lives with her lovely parents in Mashhad, Iran.

PORTFOLIO

Name PhD student: Fereshte Sheybani

PhD period: December 2019 - TBD

Name PhD supervisors: Prof. Dr. D. van de Beek

Prof. Dr. M. C. Brouwer

1. PhD training	Year	Workload (ECTS)
General courses		
Systematic review and meta-analysis	2017-2019	
Scientific writing		
Controlled trials and randomization		
Survival analysis		
Specific courses		
Seminars, workshops and master classes		
Weekly Department Seminars	2019 - 2020	
Presentations		
Vertebral osteomyelitis in bacterial meningitis: Research meeting at AMC		
Suspected CNS infections in HIV-infected patients: : Research meeting at AMC		
(Inter)national conferences		
Central Nervous System Infections in Iran: The Need for A Clinical Data Registry, oral presentation at *14th Professor Alborzi International Clinical Microbiology Congress & 3rd International Congress on Prevention Strategies for Healthcare-associated Infections, Mashhad, Iran*	2020	

3. Parameters of Esteem	Year
Grants	

LIST OF PUBLICATIONS

Haddad M, **Sheybani F**, Olfati N, Nahayati MA, Boostani R, Layegh P, Rashid-Nejad A. Central nervous system reactivation of herpesviridae family in patients with COVID-19. Journal of Neurovirology. **2023** Apr;29(2):211-217.

Khajavinia F, **Sheybani F**, Nazeri N, Haddad M. *Mycobacterium simiae* pulmonary disease: A Report of 17 Cases and Long-Term Follow-up. Infectious Diseases in Clinical Practice. **2023** Jan 1;31(1): e1196.

Naderi H, **Sheybani F**, Parsa A, Haddad M. Neurobrucellosis: report of 54 cases. Tropical Medicine and Health. **2022** Dec;50(1):1-6.

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Sheybani F, Brouwer MC, van de Beek D. Bacterial meningitis in patients with multiple myeloma: a prospective nationwide cohort study and review of the literature. International Journal of Infectious Diseases. **2022** Sep 1; 122:492-6.

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Poorzand H, Hamidi F, **Sheybani F**, Ghaderi F, Fazlinezhad A, Alimi H, Bigdelu L, Bizhaem SK. Infective Endocarditis: Clinical Characteristics and Echocardiographic Findings. Frontiers in Cardiovascular Medicine. **2022**;9.

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Haddad M, **Sheybani F**, Olfati N, Azhdari Y. Steroid-Responsive Post-Traumatic Persistent Neutrophilic Meningitis. Case Reports in Medicine. **2022** Jan 12;2022.

YaddolahiFar M, **Sheybani F**, Eslami S, Taherzadeh Z, Naderi H, Mohseni M, Zakeri E, Khosravi N. Why Vancomycin Is Overly Prescribed Despite the Lack of Supporting Microbiological Data: To Design a Concept Map. Infectious Diseases in Clinical Practice. **2021** Mar 1;29(2): e101-4.

Sanei Z, **Sheybani F**, Eslami S, Naderi H, Taherzadeh Z, Vatanchi AM, Varzandeh M. Physicians' Counseling on Toxoplasma gondii Prepregnancy Screening Tests: A Simulation-Based Study. Infectious Diseases in Clinical Practice. **2020** Nov 1;28(6):380-4.

Vakilzadeh MM, Heidari A, Mehri A, Shirazinia M, **Sheybani F**, Aryan E, Naderi H, Najaf Najafi M, Varzandeh M. Antimicrobial resistance among community-acquired uropathogens in Mashhad, Iran. Journal of Environmental and Public Health. **2020** Oct 5;2020.

Mohseni M, **Sheybani F**, Eslami S, Taherzadeh Z, Naderi H, YaddolahiFar M, Khosravi N, Tayefi M. Investigation of the Efficacy of an Intervention on Vancomycin Use in a Country with High Rate of Vancomycin Prescription: A Before-After Study. Infectious Diseases in Clinical Practice. **2020** Sep 1;28(5):281-4.

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Miradi M, **Sheybani F**, Sarvghad MR, Allahyari A, Arian M, Nooghabi MJ. Microbiological Spectrum of Infection-Related Febrile Episodes in Adult Patients with Hematologic Malignancies: A Prospective Cohort from a Tertiary Center in Iran. Infectious Diseases in Clinical Practice. **2019** Sep 1;27(5):278-82.

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A word of thanks

First and foremost, with a deep sense of gratitude and indebtedness, my heartful thanks go to my dear promotors, Professor Diederik van de Beek and Professor Matthijs C. Brouwer. No words can express my gratitude and appreciation for all they have done for me. Thank you for believing in me and helping me get through this journey.

Dear Diederik and Matthijs
Thank you for your invaluable guidance, constructive criticism, and encouragement. I truly appreciate your scientific, methodical, focused, and positive approach.

I thank my dear friend, Doctor Shahrzad S. Deliran who has always been there for me through thick and thin.

Dear Shahrzad
I truly believe that without your support it would have been impossible for me to accomplish the goal! Thank you for all your kindness.

My deep gratitude goes to my lovely parents for all their kind support and all the sacrifices that they have made for me.

پدر و مادر عزیز و مهربانم

دستتون رو می بوسم و برای همه چیز ازتون سپاسگزارم.

I am also extremely grateful to my dear mentors Professor Mohammadreza Sarvghad and Professor Hamidreza Naderi, and to my dear friends Dr Mahboubeh Haddad, Ms. Marjan Varzandeh, Mr. Mohammad Sattari and Ms. Marzieh Sattari for all their help and support.