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Differences in the courses of meningococcal and pneumococcal cerebrospinal meningitis

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ABSTRACT

Neisseria meningitidis and *Streptococcus pneumoniae* are the most common pathogens causing cerebrospinal meningitis (CSM) in adults. The mortality rate and the number of complications remain high. In our study, retrospective evaluations were conducted on data concerning 98 adult patients with bacterial cerebrospinal meningitis caused by *Neisseria meningitidis* (n = 42) and *Streptococcus pneumoniae* (n = 56), hospitalised at the Regional Specialistic Hospital in Wroclaw (Poland) within the period 1998–2018.

Compared to the group infected with *S. pneumoniae*, patients infected with *N. meningitidis* were younger and were less often affected by an additional disease burden; they presented more frequently with haemorrhagic rashes. Compared to the *S. pneumoniae* group, in patients with meningococcal CSM, cytosis in cerebrospinal fluid measuring < 1,000 cells/ mL was less frequent; intravascular coagulation syndrome appeared more frequently; the hospitalisation time was shorter and the rate of mortality was lower. Meningococcal meningitis occurs more frequently among young people with no history of disease. It is characterised by the rapid development of symptoms, which results in earlier diagnosis and more favourable prognosis compared to cases of *S. pneumoniae*. Irrespective of the pathogen, advanced age and a level of cytosis in cerebrospinal fluid of < 1,000 cells /µl indicate an unfavourable prognosis.

Key words: neuroinfection, pneumococcal meningitis, meningococcal meningitis

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Introduction

Bacterial cerebrospinal meningitis is an acute life-threatening infection of the central nervous system (CNS) which poses serious diagnostic and therapeutic problems. These infections require urgent diagnostics and therapy, interdisciplinary and multidirectional medical care, often including hospitalisation in critical care units and long-term treatment of complications.

In Poland, about 3,000 cases of meningitis (of all aetiologies) are recorded every year, of which about one-third are infections of bacterial aetiology; thus, the incidence of this disease is estimated at approximately 2–2.5/100,000 inhabitants [1]. Children up to four years of age are particularly susceptible to infection (incidence of 7/100,000) [2]. The incidence of bacterial CNS infections may be underestimated, despite mandatory reporting of infections. According to reports from Regional Sanitary-Epidemiological Stations 121 cases of cerebrospinal meningitis (CSM) of *N. meningitidis* aetiology occurred in Poland in 2015, whereas the National Reference Centre for the Diagnosis of Bacterial Infections of the Central Nervous System reported 200 cases of invasive meningococcal disease [3, 4].

Of bacterial CSM cases, 35–45% were caused by encapsulated bacteria — *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* — with the share of the last-named being marginal, constituting < 5% of cases [1, 2]. Despite widespread and easy access to anti-microbial

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treatment, the rate of mortality due to bacterial CSM in Poland remains at 20–30%, reaching 50% in patients over 65 years of age [5, 6]. This is associated not only with the virulence of the pathogens, but frequently with delayed treatment.

Despite the effectiveness of antibiotic therapy, many patients develop serious complications, including tissue necrosis, amputation of limbs, organ damage and permanent neurological consequences such as intellectual disabilities, personality changes, hearing loss, paresis, etc. [7, 8]. The adverse consequences of infections significantly reduce patients' quality of life and may be responsible for re-hospitalisation.

There are some studies from Sweden, Finland and from the Netherlands suggesting that *S. pneumoniae* infection is associated with higher mortality and higher rates of unfavourable outcome, also affecting older patients with disease burden [9–13]. On the other hand, researchers from Portugal have linked *N. meningitidis* with a higher probability of neurological sequelae than *S. pneumoniae* [14].

The clinical course, especially mortality, of infectious diseases may be geographically diverse, which is the result of the local spread of serotypes, differences in hosts' susceptibility (i.e. genetic factors), but also differences in the organisation of healthcare systems. Especially this last element influences mortality and sequelae rates as it affects the timing of medical assistance, diagnosis and the prompt implementation of proper treatment [15].

Clinical rationale for the study

Our work is the first Polish study to investigate differences between clinical courses of these two aetiologies. Also the period of time (20 years) is significant. It is worth underlining that only confirmed cases of meningitis of these two aetiologies were analysed, and therefore the results of this study should be reliable.

Other researchers from Poland have focused on epidemiological studies (i.e. the occurrence of meningitis in different age groups, bacterial serotypes isolated from cerebrospinal fluid and their susceptibility to antibiotics, etc.) or analysis distinguishing between suppurative and aseptic meningitis, and have not noticed changes in the clinical course related to these two aetiologies [16–18].

Materials and methods

Data from adult patients (≥ 18 years old) hospitalised in the period 1998–2018 at the J. Gromkowski Regional Specialistic Hospital in Wroclaw (Poland) with confirmed cerebrospinal meningitis (defined as changes in cerebrospinal fluid with general symptoms) of known aetiology (i.e. *N. meningitidis* or *S. pneumoniae*) were analysed.

The following were subjected to evaluation: demographic factors (age, gender), the month in which the disease occurred, department of hospitalisation (Infectious Diseases and/or Anaesthesiology and Intensive Care), duration of symptoms up to the moment of hospital admission, presence of disease burden and other risk factors reported in literature, reported complaints and clinical symptoms found in patients, results of cerebrospinal fluid examinations, blood test results, organ failure, presence of pneumonia at any time during hospitalisation (defined as a new chest X-ray finding with general symptoms), duration of hospitalisation, presence of complications, and mortality.

The following were used in the analysis: for qualitative data - Fisher's exact test; for quantitative data - the Mann-Whitney test. Analysis of the relationship between cytosis < 1,000 cells /µl and complications as well as mortality was performed using Fisher's exact test.

Multiple factor analysis of the impact of the studied groups, age and cytosis on mortality and complications was carried out by means of multiple logistic regression. The entire analysis was carried out using the statistical package R for Windows (version 3.5) [19].

Results

Among adult patients hospitalised at the J. Gromkowski Regional Specialistic Hospital because of bacterial CSM, 42 cases (28 men, 67%) of *N. meningitidis* aetiology and 56 cases (36 men, 64%) of *S. pneumoniae* aetiology were identified.

Patients infected with *N. meningitidis* ranged from 19–74 years (average 34 ± 16), including 30 (71%) patients aged < 40 years; five (12%) patients had been diagnosed with chronic diseases, e.g. hypertension, type 2 diabetes, alcoholism, sideropenic anaemia, paroxysmal atrial fibrillation, grade 3 obesity, fatty liver disease and polyneuropathy; 11 (26%) patients were characterised by at least one risk factor for CSM (Tab. 2).

The time elapsed from the onset of the first symptoms to admission to hospital is summarised in Table 1.

The general condition of 29 (69%) patients upon admission was defined as serious. Assessments of general condition were carried out by a clinician on the basis of state of consciousness, physical symptoms, and a physical examination. The classic 'triad' of symptoms in the form of neck stiffness, fever, and disturbances of consciousness occurred in seven (17%) patients.

No evidence of seasonal incidence was observed.

The results of laboratory tests are listed in Table 1. In the examination of cerebrospinal fluid collected at admission, segmental cells were dominant in the smear in each case. In the morphology of peripheral blood, thrombocytopaenia, which appeared in 20 (48%) cases, drew attention. Concentration of C-reactive protein (CRP) showed a significant range of values, from 2 to 443 mg/L (average 204). Procalcitonin concentration was determined in only eight patients (due to the unavailability of the test until 2010); the results were in the range of 7.02–78 ng/mL (average 24.96).

Table 1. Results

	N. meningitidis **(n = 42)**	***S. pneumoniae*** **(n = 56)**	**Statistical difference**
Age (avg. ± SD)	34 ± 16 years	51 ± 16 years	p = 2.1 × 10–6
Presence of chronic diseases (n)	5 (12%)	43 (77%)	**p = 2.1 × 10–5**
Time elapsed to admission to hospital (n):			
• < 24 h	• 23 (50%)	• 17 (30%)	• none
• 24–72 h	• 10 (24%)	• 10 (18%)	• none
• > 72 h	• 0 (0%)	• 17 (30%)	• **p = 8.3 × 10–5**
• No data	• 11 (26%)	• 12 (21%)	• n/d
Accompanying symptoms (n):			
• neck stiffness	• 37 (88%)	• 47 (84%)	• none
• other meningitis symptoms	• 24 (57%)	• 33 (59%)	• none
• consciousness disturbances	• 24 (57%)	• 41 (73%)	• none
• fever	• 20 (48%)	• 49 (89%)	• **p = 3.5 × 10–5**
• headache	• 31 (74%)	• 28 (50%)	• **p = 0.022**
• vomiting	• 33 (79%)	• 12 (21%)	• **p = 9 × 10–9**
• haemorrhagic rash	• 26 (62%)	• 2 (4%)	• **p = 10–10**
PMR results (avg./range):			
• cytosis (cells/μL)	• 6,846/10–25,000	• 4,293/10–40,000	• **p = 0.018**
• cytosis < 1,000 cells/μL (n)	• 7 (24%)	• 22 (39%)	• **p = 0.013**
• protein (mg/dL)	• 472/30–926	• 597/45–6,000	• none
• glucose (mg/dL)	• 16/0–72	• 11/0–54	• none
• chlorides (mmol/L)	• 117/106–134	• 114/89–135	• none
Peripheral blood count (n):			
• Anaemia	• 7 (17%)	• 24 (43%)	• **p = 0.004**
• Leucocytosis	• 34 (81%)	• 48 (86%)	• none
• Leucopaenia	• 1 (2%)	• 2 (4%)	• none
• Thrombocytopaenia	• 20 (48%)	• 16 (29%)	• none
DIC (n)	13 (31%)	1 (2%)	**p = 4.5 × 10–5**
Pneumonia (n)	4 (10%)	16 (29%)	**p = 0.024**
Time of hospitalisation (avg./range)	18/9–55 days	27/4–122 days	**p = 0.036**
Mortality (n)	0 (0%)	12 (21%)	**p = 0.001**

Seven patients (17%) were diagnosed with septic shock, respiratory failure occurred in one-third of patients, and acute kidney injury (AKI) in 10 (24%) patients. Hepatic failure was found in one patient (2%). Ten (24%) patients required hospitalisation in the Department of Anaesthesiology and Intensive Care. In 11 (26%) patients additional organ complications appeared in the form of hydrocephalus, cerebral oedema, hemiparesis, upper limb paresis, neuropathy of the median nerve, endophtalmitis, eyeball haemorrhage, cardiac arrhythmia and reactive arthritis.

Adjunctive corticosteroid therapy was administered to all patients.

Patients infected with *S. pneumoniae* ranged from 22 to 81 years (average 51 ± 16), of whom 14 (25%) were < 40 years. In 43 patients (77%) chronic diseases were present, including: hypertension, coronary heart disease, cardiac arrhythmias, bronchial asthma, chronic bronchitis, peptic ulcer disease, chronic gastritis and oesophagitis, toxic liver damage, fatty liver disease, chronic hepatitis B or C, liver cirrhosis, chronic pancreatitis, type 2 diabetes, alcoholism, drug addiction, epilepsy, post-inflammatory encephalopathy, hypothyroidism, systemic lupus erythematosus, HIV infection, and plasma cell myeloma. At least one risk factor of infection was present in 39 (70%) patients (Tab. 2).

Table 2. Distribution of risk factors of CSM in study population [6, 7, 8]

Risk factors	*N. meningitidis* (n = 42)	*S. pneumoniae* (n = 56)
Crowding, including:	4	N/A
– prison term	1	
– stay in a boarding school	1	
– work in a pre-school or greenhouse	2	
Low socio-economic status	n/a	3
Previous history of CSM	4	7
Splenectomy	0	2
Liver cirrhosis	1	2
Sinusitis	1	11
Alcoholism	2	10
Diabetes	1	6
Emaciation	n/a	2
Cancer	n/a	1 (plasma cell myeloma)

Time elapsed until admission to the hospital is presented in Table 1.

In 46 (82%) patients, the general condition upon admission was defined as serious. Assessments of general condition were carried out in the same way as in the group infected with *N. meningitidis*. The classic triad of symptoms occurred in 33 (59%) patients.

No evidence of seasonal incidence was observed.

Demographic, clinical and laboratory data on these patients is also presented in Table 1. In the cerebrospinal fluid, in each case, the smear was dominated by segmental cells. In the morphology of peripheral blood, anaemia, which appeared in 24 (43%) cases, drew attention. CRP concentration averaged 197 mg/L and fluctuated within the range of 16–500 mg/L. Procalcitonin was performed in 16 patients; the average concentration was 17.6 ng/mL (range 0.3–100).

Septic shock occurred in 15 (27%) patients, circulatory failure in 17 (30%), respiratory failure in 27 (48%), acute kidney injury in 21 (38%), and hepatic failure in two (4%). A total of 33 (59%) patients required hospitalisation in critical-care conditions.

23 (43%) patients developed complications, including: ischaemic stroke, haemorrhagic stroke, hydrocephalus, limb paresis, epilepsy, polyneuropathy, cranial nerve palsy, post-inflammatory encephalopathy, hearing loss, infective endocarditis, and gastrointestinal bleeding.

Adjunctive corticosteroid therapy was administered to 53 patients (95%).

Statistical analysis

The differences, including assessments of statistical significance, between groups in terms of demographic factors, occurrence of associated symptoms, length of hospitalisation and mortality are presented in Table 1.

No significant differences were noted in the frequency of complications and ICU (intensive care unit) hospitalisation between the two groups of patients.

Regardless of the aetiological factor, cytosis < 1,000 cells/μl was correlated with a higher rate of mortality ($p = 0.0058$) and more frequent ICU hospitalisation ($p = 0.0039$), while age > 60 years was a factor increasing the risk of death ($p = 0.02$).

In the process of multiple factor analysis, it was shown that along with increasing age, irrespective of CSM aetiological factor, the need for ICU hospitalisation and risk of death increased; the risk of organ-related complications also increased.

Similarly, regardless of the group, it was found that cytosis < 1,000 cells/μl in cerebrospinal fluid was associated with a greater risk of severe disease course, as well as greater risks of hospitalisation in ICU and of death.

Discussion

In a series of clinical observations it has been demonstrated that many factors influence the course of meningitis, including: age, sex, the patient's disease burden and general condition (including state of consciousness) upon admission to hospital, mean arterial pressure, leucocyte and platelet counts, cerebrospinal fluid cytosis, and aetiological factors [7, 20, 21].

In the analysed material, CSM caused by *N. meningitidis* occurred more frequently in the group of younger patients than did CSM caused by *S. pneumoniae.* This is in agreement with epidemiological data on invasive meningococcal disease in Poland and throughout the world, according to which the frequency of its occurrence decreases with age, whereas the incidence of invasive pneumococcal disease is highest in the groups < 4 and > 65 years of age [3, 22, 23]. This age distribution may be due to pathogen exposure: asymptomatic carriage of *N. meningitidis* initially increases with age, peaking (at 24–37%) in the group of 15 to 24-year-olds, and subsequently falling to less than 10% at more advanced ages [24]. Another risk factor for invasive meningococcal disease is crowding in places such as barracks, prisons, and boarding schools [25], which most typically house young populations. Considering the percentage of carriers in this age group, crowding additionally increases their exposure to the pathogen.

Irrespective of bacteria, a higher rate of mortality and a greater risk of death in patients > 60 years have been demonstrated in both groups, which accords with other reports [26]. This may be an expression of a progressive qualitative and quantitative deterioration of the immune system with age [27].

The population with pneumococcal CSM was characterised by a greater disease burden in terms of internal disease and that risk factors for meningitis were more likely to be present, as a result of the fact that the incidence of chronic diseases and medical interventions increases along with age, which is consistent with global epidemiological data [28].

The time elapsed from the onset of the first symptoms to hospital admission also varied. Patients with pneumococcal disease were hospitalised more frequently after 72 hours since the appearance of the first symptoms compared to the group with meningococcal infections (Tab. 1). In 18 cases (32%), pneumococcal CSM was preceded by a localised infection (otitis, sinusitis, pneumonia) with a milder course. CSM was most likely a complication of the primary infection. This may explain the delay in seeking help and the longer time to develop symptoms. In our study, patients with meningococcal infections were admitted after a shorter period of time elapsed from the onset of symptoms than those with pneumococcal infections. *N. meningitidis* infection was definitely characterised by a more dynamic course than *S. pneumoniae*. In accordance with the data from the literature, the median time elapsed from the onset of symptoms to hospital admission for invasive meningococcal disease is in the range of 12–24 h, depending on the course of the disease [24], as well as on the patient's age: for the group of 15- to 16-year-olds, the median was 22 h, for children < 1 year of age, it was 13 h [29].

There was no significant difference in general condition upon admission between the groups; however, it should be remembered that this is a subjective and imprecise criterion. More sudden development of the disease, which is undoubtedly associated with a more urgent need for hospitalisation, may hasten the implementation of empirical antibiotic therapy in the *N. meningitidis* group, early inclusion of which is of key significance for the prognosis [15].

Headache and vomiting were significantly more common in the *N. meningitidis* group, and fever in the *S. pneumoniae* group. The classic triad of symptoms — neck stiffness, fever and disturbed consciousness — rarely occurred in the group with meningococcal infection in contrast to the pneumococcal CSM group, which is consistent with the observations of other clinicians. The literature indicates an approximate sensitivity rate of 60% for this constellation of symptoms in disease diagnosis [30, 31].

In our material, haemorrhagic rashes were found in 62% of patients with meningococcal infection, which falls within the 28–78% range described by other authors, and in only 4% of patients with CSM in the course of *S. pneumoniae* infection [20, 32]. The more frequent presence of haemorrhagic rashes in the *N. meningitidis* group is not a surprising phenomenon, as it is part of the picture of the disease described in the literature; the bacterium itself is one of the most common infectious agents causing such changes [22, 30, 33]. However, haemorrhagic rash is not pathognomonic for invasive meningococcal disease; it also occurs, although less frequently, in the course of invasive infections due to *S. pneumoniae*, *S. aureus*, *H. influenzae* and other pathogens [34].

In both groups, the result of cerebrospinal fluid analysis was similar and typical of bacterial CSM [7]. One statistically significant difference was the pleocytosis: the total number was lower in the pneumococcal group. According to the data in the literature, relatively low cytosis (< 1,000 cells/μl) is associated with an unfavourable course of the disease [35].

In our study, we showed that cytosis of < 1,000 cells/μl is associated (regardless of the pathogen) with a significantly higher mortality rate and more frequent hospitalisation in intensive care units. According to Weisfelt et al., low pleocytosis is associated with an inadequate or moderate immune response, and is described as a factor associated with a poor prognosis [26], which we observed as well in our material. Low pleocytosis also appears in the early stages of infections, especially meningococcal ones [36].

It appears that the greater incidence of anaemia in the pneumococcal group compared to that infected with *N. meningitidis* may be associated with the greater incidence of other systemic diseases in this group and is more likely a manifestation of these diseases, the more so given that a higher percentage of patients with DIC or haemolysis was not observed in this group. On the contrary, intravascular coagulation syndrome occurred significantly less frequently than in the meningococcal group. There is no precise data in the literature on the incidence of anaemia in bacterial CSM. In both groups, leucocytosis was found in the vast majority of patients. Our analysis showed no differences between groups in terms of the incidence of leucocytosis and leucopaenia. Total values were not analysed.

In the group of patients with pneumococcal infections, pneumonia was found with significantly greater frequency compared to the meningococcal group. This can be explained by three mechanisms: the presence of pneumonia upon admission as the primary source of the infection; blood-borne pneumonia as a result of the dissemination of pathogens; and secondary pneumonia associated with hospitalisation (prolonged stay in a supine position, colonisation by hospital pathogens, poor ventilation due to serious overall condition, respiratory therapy, etc.).

Another factor conducive to the occurrence of pneumonia is duration of hospitalisation [37], which is significantly greater in the pneumococcal group. This is the result of all of the features of the group in question: the age of the patients, risk factors, comorbidities, and the pathogen itself, which constitutes an independent unfavourable prognostic factor.

In accordance with the relevant definition, the diagnosis of DIC cases in our study was made by a clinician on the basis of symptoms of bleeding diathesis and (often multiple) laboratory assays of coagulation system parameters, which, however, were not always supported by the point scale [38]. *N. meningitidis* possesses significant potential for the development of DIC, due, among other factors, to the presence of lipopolysaccharide (LPS), which is absent in *S. pneumoniae*; this may explain differences between the groups [38–41].

In both meningococcal and pneumococcal CSM, neurological complications develop in 12–41% of patients (depending on the pathogen), among which the most common is hearing impairment, affecting 24% of patients with pneumococcal

infections and 8% with meningococcal infections [42–44]. Neurological complications also predominated in our observations. However, given the retrospective nature of our study and the lack of thorough neurological or audiometric evaluation upon discharge from hospital or during convalescence, we cannot precisely compare our data to the observations of other authors.

In our study we did not find statistical differences between groups in terms of the frequency of ICU hospitalisation, the occurrence of organ failure (except for the occurrence of DIC syndrome), or the occurrence of complications. In the process of conducting multivariate analysis, however, we showed that, regardless of the aetiology of meningitis, the risk of the necessity for ICU hospitalisation, complications and death increased along with the age of patients.

The use of corticosteroids has been recommended in bacterial meningitis since the beginning of the 21st century. It is proven that adjuvant corticosteroid therapy reduces the rates of hearing loss and neurological sequelae regardless of aetiology in high income countries. The use of steroids also reduces mortality rate in pneumococcal (risk ratio 0.84 with 95% confidence interval from 0.72 to 0.98), but not in meningococcal, meningitis or in bacterial meningitis overall [45]. In our study, all patients with meningococcal, and nearly all with pneumococcal, meningitis received corticosteroids during treatment. Therefore it is not possible to determine if their impact was significant for survival and complications.

The mortality rate for pneumococcal CSM was 21%, significantly higher than that of the group infected with *N. meningitidis*, which is consistent with data from the literature (range 10–30%) [5, 35]. The mortality rate of meningococcal infections, at the level of 0%, was below the range of 3–10% found in the literature. This may result from the fact that our study did not take unconfirmed cases into account. During the collection of material the authors found isolated cases of death (shortly after admission to hospital) in which the clinical picture was very likely to indicate a meningococcal disease, although no microbiological confirmation was obtained. In addition, the result of our observations may be explained by the younger age of patients with CSM of meningococcal aetiology, a lesser internal diseases burden, and the sudden onset of the disease leading to quicker diagnosis and treatment. It should also be noted that the centre in which the patients were hospitalised is experienced in diagnosing and treating CNS infections.

Conclusions

Bacterial cerebrospinal meningitis is a life-threatening disease associated with a high risk of death as well as with serious complications. Meningococcal infections occur more frequently in young people, as opposed to pneumococcal infections, the incidence of which increases markedly with patients' age. CSM triggered by *Neisseria meningitidis* is characterised by the sudden and rapid development of symptoms, which allows earlier diagnosis; haemorrhagic rashes also occur more frequently and prognosis is more favourable compared to infections caused by *Streptococcus pneumoniae*. Regardless of the pathogen, older age and cerebrospinal fluid pleocytosis < 1,000 cells/μl are factors increasing the need for critical care procedures as well as the risk of death.

Given that our findings, especially time of admission and mortality rates, are in line with other studies, we conclude that the therapeutic setting of bacterial meningitis in specialistic hospitals in Poland is comparable with that of other hospitals in Western Europe.

Clinical Implications/Future directions

Since bacterial meningitis is a severe disease, establishing screening tools and risk factors for unfavourable outcomes, as well as identifying the pathogen, is crucial for management. There is a need to collect data regarding complications and patient histories after hospitalisation because there is a lack of such information in Poland.

Limitations

Our paper is characterised by several limitations. It is a single-centre retrospective analysis, which means that not all data regarding the course of the disease was available in each case. Given the 20-year timespan of data collection, the results of some laboratory tests were missing e.g. procalcitonin concentration because this parameter could not be measured until 2010, or chloride anion concentration in cerebrospinal fluid, because it was not always requested. Moreover, the number of patients in both groups was relatively low.

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