Neuroendocrinology Letters Volume 40 No. 2 2019
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

The clinical course and outcome of *Listeria monocytogenes* meningitis: A retrospective single center study

Marcin Paciorek[1], Carlo Bieńkowski[1], Agnieszka Bednarska[1], Monika Kowalczyk[1], Dominika Krogulec[1], Michał Makowiecki[1], Dominik Bursa[1], Joanna Puła[1], Joanna Raczyńska[1], Dawid Porowski[1], Agata Skrzat-Klapaczyńska[1], Magdalena Zielenkiewicz[2], Marek Radkowski[3], Tomasz Laskus[1], Andrzej Horban[1]

1 Medical University of Warsaw, Department of Adult Infectious Diseases, Warsaw, Poland
2 Institute of Mathematics, University of Warsaw, Poland
3 Medical University of Warsaw, Department of Immunopathology of Infectious and Parasitic Diseases, Warsaw, Poland

Correspondence to: Marcin Paciorek, MD, PhD
Medical University of Warsaw, Department of Infectious Diseases for Adults
Ul. Wolska 37, 02-091 Warszawa, Poland
tel.: +48 505 075 853; fax: +48 22 33 55 210; e-mail: mpaciorek@op.pl

Submitted: 2019-07-12 Accepted: 2019-08-12 Published online: 2019-09-08

Key words: **meningoencephalitis; outcome; bacterial meningitis; *Listeria monocytogenes*; Gram-positive bacteria; immunocompromised; immunosuppressive therapy; cerebrospinal fluid**

Neuroendocrinol Lett 2019; **40**(2):79–84 **PMID:** 31785214 NEL400219A06

Abstract

BACKGROUND: The aim of the study was to determine clinical manifestations and outcome of *Listeria monocytogenes* meningitis (LM) and to compare with other forms of bacterial meningitis (BM).

MATERIAL AND METHODS: We analyzed records of all adult patients with BM who were hospitalized between January 2010 and December 2017 in the largest neuroinfection center in Poland.

RESULTS: Out of 343 analyzed patients with BM 24 were diagnosed to have LM. Patients with LM were older compared to patients with other forms of BM (62 years vs. 57 years, p=0.039), were more likely to have cancer (16.7% vs. 4.7%, p=0.045), receive immunosuppressive treatment (45.8% vs. 10.7%, p<0.001), or be immunocompromised in any way (62.5% vs. 35.5%, p=0.016). Blood tests showed lower WBC (10.7×10^3 cells/µl vs. 15.5×10^3 cells/µl, p=0.004), C-reactive protein (150 mg/L vs. 221 mg/L, p=0,019) and procalcitonin (1.27 ng/mL vs. 3.78 ng/mL, p=0.003) in LM group. Analysis of cerebrospinal fluid showed lower cell count (531.5 cells/µL vs. 1100 cells/µL, p<0.001) and lower chloride (113 mmol/L vs. 117 mmol/L, p=0.036) in patients with LM. In the multiple logistic regression analysis, immunosuppressive therapy was the only variable independently associated with LM (OR:8.72, CI 95%:1.41–64.34, p=0.024).

CONCLUSIONS: LM is associated with older age, cancer and immunosuppressive therapy. However, in multivariate analysis only immunosuppressive therapy turned out to be an independent risk factor for LM.

INTRODUCTION

Listeria monocytogenes can invade Central Nervous System (CNS) involving subarachnoid space and meninges (meningitis) but also brain parenchyma (meningoencephalitis). The latter is responsible for such symptoms as impaired consciousness, seizures, nerve palsies, increased intracranial pressure (ICP) and makes LM a life-threatening medical emergency with a high mortality rate (Charlier *et al.* 2017). The annual incidence rate of listeriosis in Poland in 2017 was 0.32/100000 (National Institute of Public Health, 2017) and *Listeria monocytogenes* meningitis accounted for approximately one third of all listeriosis cases between 2011 and 2016 (The national reference center for the diagnosis of bacterial infections of the central nervous system, 2017). Due to the resistance of *Listeria monocytogenes* to third generation cephalosporins commonly used for empirical treatment of community acquired bacterial meningitis (BM) (Streharova *et al.* 2007 it is important to determine which patients have an increased risk of LM infection so that therapy could be appropriately modified.

The aim of the study was to determine predisposing factors to Listeria monocytogenes meningitis its clinical course and outcome as compared to other forms of BM.

MATERIAL AND METHODS

We evaluated medical records of adult (≥ 18 years old) patients with community-acquired BM who were admitted to the Hospital for Infectious Diseases in Warsaw from January 1st, 2010 to December 31st, 2017. Only patients who underwent diagnostic lumbar puncture were included in the analysis. The diagnosis of BM was based on fulfilling at least one of the following criteria: positive cerebrospinal fluid (CSF) culture, positive CSF Gram staining, typical CSF findings (pleocytosis ≥ 100 cells/μl with≥ 90% neutrophils or decrease of CSF glucose level < 2.2 mmol/L). All cases of LM were confirmed by a culture. Patients with CSF findings typical for BM but negative blood and CSF culture and negative microscopic CSF examination were considered to have BM of unknown etiology. Patients with positive blood culture but negative CSF culture and negative CSF microscopic examination were considered to have BM caused by the pathogen cultured from blood.

Initial antimicrobial treatment followed current guidelines (National antibiotic protection program, 2011) and included vancomycin and a third – generation cephalosporin in patients below 50 years old and a combination of ampicillin and vancomycin together with a third generation cephalosporin in those ≥50 years or likely to be immunocompromised (patients with cancer, diabetes mellitus, HIV infection, liver cirrhosis, alcoholics, patients receiving immunosuppressive therapy). Diagnosis of tuberculosis meningitis was based on positive culture and/or positive nucleic acid amplification and/or positive Ehrlich-Ziehl-Nielsen staining of CSF. Patients with tuberculosis meningitis were treated with rifampicin, isoniazid, pyrazinamide and ethambutol or streptomycin. Patients with meningitis secondary to head trauma, neurosurgical procedures as well as hospital-acquired infections were excluded from analysis.

The Glasgow Coma Scale (GCS) and Sequential Organ Failure Assessment (SOFA) score were assessed during admission, Glasgow Outcome Score (GOS) was calculated at hospital discharge.

Normality of continuous variables was tested using Kolmogorov-Smirnov test. The U Mann Whitney test was used to compare continuous variables and the Fisher exact test was used to evaluate nominal variables. A p value of <0.05 was considered significant. Logistic regression was used to calculate adjusted odds ratios and to determine variables independently associated with LM. Statistical analysis were performed using program R version 3.5.2 (program R, 2019).

RESULTS

The final analysis included 343 patients with BM (213 men and 130 women, median age: 57 years , interquartile range [IQR]: 41,5–69). Patients with LM were older compared to those with other etiology of BM (62 years vs. 57 years IQR: 56–71 years vs. 40–69 years, p=0.016) (Table 1). An etiological factor was identified in only 65% of patients with BM. However, in 47% of patients antibiotic treatment initiation preceded diagnostic lumbar puncture. *Streptococcus pneumoniae* was the most common causative organism (n=66, 19.24%) followed by: *Staphylococci* (n=41, 11.95%), *Neisseria meningitidis* (n=30, 8.74%), *Listeria monocytogenes* (n=24, 7.0%), *Mycobacterium tuberculosis* (n=20, 5.83%), other Gram-positive bacteria (n=23, 6.71%), other Gram-negative bacteria (n=12, 3.5%), *Haemophilus influzenzae* (n=4, 1.17%). Etiology remained unknown in 117 patients (34.11%).

There were no statistically significant differences in symptoms and signs between the groups (Table 1). Fever was the most common symptom and occurred in 78.4% of all patients included in the study, 46.1% of all patients had headache, in 29.7% patients nausea or vomiting occurred. Meningeal signs were the most frequent symptom and occurred in 76.4% of all patients with BM. 15.5% of the patients had seizures in the course of the disease (Table 1). There were no statistically significant differences in disease severity at admission, mortality, or outcome measured by GOS and the frequency of Intensive Care Unit hospitalization was also similar (Table 1). Analysis of risk factors (Table 1) revealed that patients with LM were more likely to have cancer (16.7% vs. 4.7%, p=0.045) and receive immunosuppressive treatment (45.8% vs. 10.7%, p<0.001) However, 3 patients with LM did not have any form of immunodeficiency and were less than 50 years old.

Tab. 1. Demographic characteristic, symptoms and signs, comorbidities, disease severity, outcome in Listeria meningitis and non–Listeria patients with bacterial meningitis. Data are presented as median (interquartile range)* or n/N (%).

Demographic characteristic, signs and symptoms	Listeria meningitis n=24	non-Listeria bacterial meningitis n=319	*p*-value
Age (years)*	62 (56 - 71)	57 (40 - 69)	0.016
Male (%)	15/24 (62.5)	198/319 (62.1)	1
Pyrexia > 37.8 C (%)	21/24 (87.5)	248/309 (80.25)	0.55
Glasgow Coma Scale score*	12/24 (9.25 – 13.75)	4/317 (3 - 5)	0.871
Headache (%)	11/23 (47.83)	147/301 (47.57)	1
Skin rash (%)	1/24 (4.17)	23/309 (7.44)	0.851
Back pain (%)	2/23 (8.7)	32/304 (10.52)	1
Cranial nerves palsy (%)	2/24 (8.33)	20/317 (6.31)	1
Peripheral nerves palsy (%)	4/24 (16.67)	37/317 (11.67)	0.69
Nausea/vomiting (%)	6/23 (26.09)	96/312 (30.76)	0.813
Impaired hearing (%)	0/23 (0)	28/308 (9.09)	0.261
Meningeal signs (%)	20/24 (83.33)	242/307 (78.83)	0.835
Aphasia (%)	3/22 (13.64)	27/312 (8.65)	0.686
Ataxia (%)	2/23 (8.7)	14/314 (4.46)	0.679
Seizures (%)	2/24 (8.33)	51/318 (16.03)	0.476
Comorbidities			
Diabetes (%)	8/24 (33.33)	65/318 (20.44)	0.219
Lymphoma/Leukemia (%)	3/24 (12.5)	15/318 (4.72)	0.241
Cancer (%)	4/24 (16.67)	15/318 (4.72)	**0.045**
Immunosuppressive therapy (%)	11/24 (45.83)	34/317 (10.73)	**< 0.001**
Organ transplant recipients (%)	0/24 (0)	1/318 (0.31)	1
Hepatic cirrhosis (%)	2/24 (8.33)	8/319 (2.51)	0.314
Alcoholism (%)	0/24 (0)	45/316 (14.24)	0.094
Any immunodeficiency (%)	15/24 (62.5)	113/318 (35.53)	**0.016**
Disease severity/outcome			
ICU admission (%)	9/24 (37.5)	125/318 (39.3)	1
SOFA score on admission*	3 (1 - 5)	2 (1 - 4)	0.19
Glasgow outcome score*	4 (3 - 5)	4 (3 - 5)	0.871
Mortality (%)	5/23 (21.74)	51/316 (16.14)	0.684

Abbreviations: ICU – Intensive Care Unit, SOFA – Sequential Organ Failure Assessment score

Blood laboratory tests (Table 2) showed a lower WBC (10.7×10^3 cells/μl vs. 14.6×10^3 cells/μl, IQR: 8.5–14.4 $\times 10^3$ cells/μl vs 10.3–20.3 $\times 10^3$ cells/μl, $p<0.001$), lower C-reactive protein (CRP) (150 mg/L vs. 221 mg/L, IQR: 64–228.8 mg/L vs. 71–330 mg/L, $p=0{,}019$) and lower procalcitonin (PCT) level (1.27 ng/mL vs. 3.78 ng/mL, IQR: 0.32–4.7 ng/mL vs. 0.41–13.26 ng/mL, $p=0.003$) in the LM group. Analysis of cerebrospinal fluid (CSF) results revealed lower cell count (531.5 cells/μL vs. 1100 cells/μL, IQR: 165.3–909.3 cells/μL vs. 243–4460 cells/μL, $p<0.001$) and lower chlorides (113 mmol/L vs. 117 mmol/L, IQR: 110–118 mmol/L vs. 112–121.25 mmol/L $p=0.036$) in patients with LM compared to patients with BM.

In multiple logistic regression analysis immunosuppressive therapy was the only variable independently associated with LM (OR: 8.72, CI 95%: 1.41–64.34, $p=0.024$), (Table 3).

DISCUSSION

Listeria monocytogenes was the causative agent in 7.0% of all cases of BM. This percentage is higher than in other studies in the developed countries. In a review of 696 cases of bacterial meningitis in adults in the Neth-

Tab. 2. Laboratory blood and CSF findings in Listeria meningitis compared to other forms of bacterial meningitis. Data are presented as median (interquartile range).

Blood test results	Listeria meningitis n=24	non-Listeria bacterial meningitis n=319	*p*-value
CRP (mg/L)	150 (64 - 228.75)	221 (71 - 330)	**0.019**
Lactic acid (mmol/L)	2.025 (1.475 - 2.33)	2.0 (1.573 - 2.93)	0.323
WBC (1000 cells/μL)	10.7 (8.45 - 14.35)	14.6 (10.3 - 20.3)	**<0.001**
PLT (1000 cells/μL)	154.5 (113.8 - 195.8)	191 (139 - 254)	0.142
PCT (ng/mL)	1.265 (0.32 - 4.7)	3.775 (0.413 - 13.263)	**0.003**
d-dimers (ug/L)	1624.58 (1323.845 - 3039)	2435.31 (1226.92 - 4349)	0.934
Creatinine (umol/L)	63 (53.8 - 82.5)	68 (55 - 86)	0.239
Urea (mmol/L)	5.69 (4.36 - 7.1)	6.54 (4.4 - 10.7)	0.051
CSF test results			
Cytosis (cells/uL)	531.5 (165.25 - 909.25)	1100 (243 - 4460)	**<0.001**
Granulocytes (%)	62 (42.25 - 78.75)	88 (70.75 - 95)	0.056
Protein (g/L)	1.768 (1.155 - 3.783)	2.995 (1.5 - 6.63)	0.099
Glucose (mmol/L)	1.36 (0.97 - 3.3)	1.79 (0 - 3.29)	0.836
Lactic acid (mmol/L)	7.415 (3.21 - 8.773)	6.18 (3.46 - 10.99)	0.609
Chlorides (mmol/L)	113 (110 - 118)	117 (112 - 121.25)	**0.036**

Abbreviations: CRP – C-reactive protein, WBC – white blood cells, PLT – platelets, PCT – procalcitonin, CSF – cerebrospinal fluid

erlands (van de Beek *et al.* 2004), *L. monocytogenes* accounted for 4% and similar numbers were reported in the cohort study from Denmark (Bodilsen 2014) and in a large surveillance study in the United States (Thigpen *et al.* 2011). One of possible explanations of high incidence of LM could be a changing pattern of BM etiology. In a single center study from Spain the frequency of bacterial meningitis caused by Listeria monocytogenes increased more than double fold from 5.9% to 14.2% in years 1996–2010 when compared to previous 1982–1996 period (Domingo *et al.* 2013).

Another plausible explanation for frequent LM in our investigation could be high percentage of immunocompromised patients who accounted for 36% of all studied group, which is more than in studies from Netherlands (16%) (van de Beek *et al.* 2004) and USA (22%) (Thigpen *et al.* 2011). Patients with LM were more likely to be immunocompromised than patients with BM (63% vs. 36%, p=0.016) which is in line with other studies (Amaya-Villar *et al.* 2010; Koopmans *et al.* 2013) were neurolisteriosis was associated with immunosuppressive state.

Tab. 3. Results of multiple logistic regression analysis of factors independently associated with Listeria monocytogenes aetiology in patients with bacterial meningitis.

Variable	*p*-value	OR	95%CI
Cancer	0.7609	0.633	0.02 - 9.332
Immunosuppressive therapy	0.0238	8.723	1.407 - 64.336
Any Immunodeficiency	0.632	1.489	0.272 - 7.723
Age	0.1498	1.035	0.99 - 1.09
CRP	0.4387	1.003	0.996 - 1.009
WBC	0.366	1.06	0.923 - 1.198
PCT	0.1157	0.659	0.326 - 0.956
CSF cytosis	0.1531	1	0.999 - 1.0
CSF chlorides	0.1925	0.947	0.871 - 1.03

Results are presented as odds ratio (OR) and confidence interval (CI). CRP: C-reactive protein, WBC: white blood cells, PCT: – procalcitonin, cytosis: cytosis in the cerebrospinal fluid, chlorides: concentration of chlorides in the cerebrospinal fluid.

Patients from LM group were older compared to BM (median 62 years vs. median 57 years, p=0.016). Similar findings were reported in a three-year multicenter surveillance study of community-acquired *Listeria monocytogenes* meningitis in which only age, immunosuppression and CSF / blood glucose ratio were independently associated with a LM (Amaya-Villar *et al.* 2010). Mook *et al.* found that listeriosis is more common in patients with underlying diseases such as: malignancies (especially of the blood), kidney disease, liver disease, diabetes, alcoholism, and age ≥60 years (Mook *et al.* 2011). In our study it was the immunosuppressive therapy that was the most common (46%) coexisting predisposing factor to LM and was the only variable independently associated with LM in logistic regression analysis. Similarly high prevalence of immunosuppressive therapy (53%) among patients with LM was also reported in a 11 year long retrospective analysis (Muñoz-Gallego *et al.* 2017). These results indicate the necessity to suspect *Listeria monocytogenes* etiology in patients with BM receiving such treatment.

Unexpectedly, *Listeria monocytogenes* was not found to in any alcoholic patients in our study, despite it was a common pathogen constituting 7% of all BM. These results are in contrast to some other studies, in which alcoholism was identified as one of the predisposing factors for listeriosis (Mook *et al.* 2011; van de Beek *et al.* 2004; Weisfelt *et al.* 2010). The reasons for this finding are unclear. However, this difference was not statistically significant (p=0.09). The explanation could be less frequent alcohol abuse among elderly patient with bacterial meningitis (Cabellos *et al.* 2009) who have higher risk of LM or among those receiving immunosuppressive therapy which we demonstrated to be independent risk factor highly predisposing for LM (OR 8.7).

Analysis of blood tests revealed lower WBC (10.7×10^3 cells/μl vs. 15.5×10^3 cells/μl, p=0.0036), PCT (1.27 ng/mL vs. 3.78 ng/mL, p=0.003) and CRP concentration (150 mg/L vs. 230 mg/L, p=0,02) in the LM group. However, these findings could be directly related to coexisting immunosuppression. It was reported that cancer patients with BM have lower WBC than their cancer free counterparts (Pomar *et al.* 2017) and in the multicenter study by Amaya-Villa *et al.* (Amaya-Villar *et al.* 2010) WBC was lower in immunocompromised patients with LM compared to LM patients without any obvious immunodeficiencies.

Elderly age could be another variable coexisting with lower WBC: in the analysis of elderly patients with BM (Pagliano *et al.* 2016) it was demonstrated that patients with LM had lower WBC in blood analysis compared to the patients with pneumococcal BM, concentration of CRP and PCT were not analyzed in these studies (Amaya-Villar *et al.* 2010; Pomar *et al.* 2017; Pagliano *et al.* 2016). Similar to our findings values of CRP (mean 113 mg/L) and lower PCT (median 1.4 ng/mL) concentration was demonstrated in the large national prospective cohort study from France (Charlier *et al.* 2017).

CSF analysis revealed lower cytosis in LM patients which is line with other studies showing lower cytosis in CSF in LM patients compared to patients with pneumococcal meningitis (Lim *et al.* 2017) or to patients with BM caused by pathogen other than *Listeria monocytogenes* (Amaya-Villar *et al.* 2010). However, low CSF cytosis could be due to immune affecting comorbidities which are common in LM – in the study of Costerus JM *et al.* patients with BM and active cancer had lower CSF leukocyte count than cancer-free patients (Costerus *et al.* 2016).

Our study has a few important limitations. First of all, it was a single center study and the group of patients with LM was relatively small. Finally the analysis was carried out retrospectively.

In conclusion LM is associated with older age, cancer and immunosuppressive therapy. However, in multivariate analysis only immunosuppressive therapy turned out to be an independent risk factor for LM.

ACKNOWLEDGEMENTS / FUNDING

Marcin Paciorek was supported by The Research Development Foundation Hospital for Infectious Diseases, FRN 004/2019.
Magdalena Zielenkiewicz was supported by The Research Development Foundation Hospital for Infectious Diseases, FRN 004/2019.
Tomasz Laskus was supported by The National Science Center Grant 2017/25/B/NZ6/01463.

REFERENCES

1 Amaya-Villar R, García-Cabrera E, Sulleiro-Igual E, Fernández-Viladrich P, Fontanals-Aymerich D, Catalán-Alonso P et al. (2010). Three-year multicenter surveillance of community-acquired Listeria monocytogenes meningitis in adults. BMC Infect Dis. Nov 11; **10**: 324.
2 Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H (2014). Dexamethasone treatment and prognostic factors in community-acquired bacterial meningitis: a Danish retrospective population-based cohort study. Scand J Infect Dis. Jun; **46**(6): 418–25.
3 Cabellos C, Verdaguer R, Olmo M, Fernández-Sabé N, Cisnal M, Ariza J, et al. (2009). Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine (Baltimore). Mar; **88**(2): 115-9.
4 Charlier C, Perrodeau É, Leclercq A, Cazenave B, Pilmis B, Henry B, et al. (2017). Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. Lancet Infect Dis; **17**: 510–19.
5 Costerus JM, Brouwer MC, van der Ende A, van de Beek D, (2016). Community-acquired bacterial meningitis in adults with cancer or a history of cancer. Neurology. Mar 1; **86**(9): 860–6.
6 Domingo P, Pomar V, Benito N, Coll P, (2013). The changing pattern of bacterial meningitis in adult patients at a large tertiary university hospital in Barcelona, Spain (1982–2010). J Infect: **66**: 147–54.

7 Koopmans MM, Brouwer MC, Bijlsma MW, Bovenkerk S, Keijzers W, van der Ende A et al. (2013). Listeria monocytogenes sequence type 6 and increased rate of unfavorable outcome in meningitis: epidemiologic cohort study. Clin Infect Dis. Jul; **57**(2): 247–53.
8 Lim S, Chung DR, Kim DS, Sohn KM, Kang SJ, (2017). Predictive risk factors for Listeria monocytogenes meningitis compared to pneumococcal meningitis: a multicenter case-control study. Infection **45**: 67–74.
9 Mook P, O'Brien SJ, Gillespie IA, (2011). Concurrent conditions and human listeriosis, England, 1999-2009, Emerg Infect Dis. Jan; **17**(1): 38–43.
10 Muñoz-Gallego I, Candela Ganoza G, Chaves F, San Juan R, Orellana MA, (2017). Listeria monocytogenes bacteraemia over an 11-year period: Clinical and epidemiologic characteristics in the south area of Madrid. J Infect. Sep; **75**(3): 276–278.
11 National antibiotic protection program, Recommendations for the management of bacterial infections of the central nervous system, http://antybiotyki.edu.pl/wp-content/uploads/Rekomendacje/rekomendacje-ukl-nerwowy_2011.pdf, Accessed April 20, 2019.
12 National Institute of Public Health - National Institute of Hygiene, Department of Epidemiology of Infectious Diseases and Surveillance Chief Sanitary Inspectorate, Department of Prevention and Control of Infectious Diseases and Diseases in People, Infectious diseases and poisoning in Poland, http://wwwold.pzh.gov.pl/oldpage/epimeld/2017/Ch_2017_wstepne_dane.pdf, Accessed June 6, 2019.
13 Pagliano P, Ascione T, Boccia G, De Caro F, Esposito S, (2016). Listeria monocytogenes meningitis in the elderly: epidemiological, clinical and therapeutic findings, Infez Med. Jun 1; **24**(2): 105–11.
14 Pomar V, Benito N, López-Contreras J, Coll P, Gurguí M, Domingo P (2017). Characteristics and outcome of spontaneous bacterial meningitis in patients with cancer compared to patients without cancer. Medicine (Baltimore). May; **96**(19): e6899.
15 Streharova A, Babjakova A, Moravcikova A, Harnicarova A, Holeckova K, Lesnakova A, et al. (2007). Neuroinfections due to Listeria monocytogenes. Neuro Endocrinol Lett. Nov; **28** Suppl 3: 20–1.
16 The national reference center for the diagnosis of bacterial infections of the central nervous system, http://koroun.edu.pl/wp-content/uploads/2017/10/ListeriozawPolscewlatach2011-2016.pdf, Accessed April 20, 2019.
17 The R Project for Statistical Computing, https://www.r-project.org, Accesed March 15, 2019.
18 Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, (2011). Bacterial meningitis in the United States, 1998-2007. N Engl J Med; **364**: 2016.
19 van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeuelen M, (2004). Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med; **351**:1849.
20 Weisfelt M, de Gans J, van der Ende A, van de Beek D (2010). Community-acquired bacterial meningitis in alcoholic patients. PLoS One ; **5**(2): e9102.