Listeria monocytogenes meningitis in the elderly: epidemiological, clinical and therapeutic findings

Pasquale Pagliano[1], Tiziana Ascione[1], Giovanni Boccia[2], Francesco De Caro[2], Silvano Esposito[3]

[1]AORN dei Colli, D. Cotugno Hospital, Department of Infectious Diseases, Naples, Italy;
[2]Institute of Hygiene, University of Salerno, Italy;
[3]Department of Infectious Diseases, University of Salerno, Italy

SUMMARY

Listeria monocytogenes is a Gram-positive bacillus and facultative intracellular bacterium whose transmission occurs mainly through the consumption of contaminated food, *L. monocytogenes* invades the host cells using various protein and can escape to the human T-cell immune system by cell-to-cell spreading. If the infection is not controlled at the stage in which the bacterium is in the liver, for instance, due to a severe immunodepression, a secondary bacteraemia can be developed and *L. monocytogenes* reaches the preferred sites transgressing the blood-brain barrier or the placental barrier. Individuals with T-cell dysfunction, such as pregnant women, the elderly, and those receiving immunosuppressive therapy are at the highest risk of contracting the disease. Average life expectancy throughout developed countries has rapidly increased during the latter half of the 20th century and geriatric infectious diseases have become an increasingly important issue.

L. monocytogenes meningitis in young previously healthy adults has been reported only in anecdotal observations. Differently, *L. monocytogenes* is the third most common cause of bacterial meningitis in the elderly population, after *Streptococcus pneumoniae* and *Neisseria meningitidis*. Patients with *L. monocytogenes* meningitis presented with signs and symptoms that were similar to those of the general population with community-acquired bacterial meningitis, but reported a longer prodromal phase. According to literature data, the prevalence of the classic triad of fever, neck stiffness, and altered mental status is 43%, and almost all patients present with at least 2 of the 4 classic symptoms of headache, fever, neck stiffness, and altered mental status.

On the basis of our published data, in patients aged over 50 years, diagnosing *L. monocytogenes* meningitis was more challenging than pneumococcal meningitis, as demonstrated by the lower percentage of cases receiving a correct diagnosis within 48 hours from the onset of symptoms. No significant difference was observed in respect to the presenting symptoms, but progression to respiratory failure was not as rapid as pneumococcal meningitis. Findings of cerebrospinal-fluid (CSF) analysis demonstrated higher glucose concentration and a less evident neutrophil prevalence in patients with *L. monocytogenes* meningitis. Meningitis sustained by *L. monocytogenes* is reported with a higher frequency in elderly, clinical findings cannot support a presumptive diagnosis, but findings of CSF analysis have to be considered.

Keywords: *Listeria monocytogenes*, *Streptococcus pneumoniae*, meningitis, elderly, diagnosis.

■ INTRODUCTION

The average life expectancy in developed countries has rapidly increased during the latter half of the 20th century, and elderly people now account for a growing percentage of the population [1]. The susceptibility of ageing people to infectious diseases is multifactorial and includes both a greater propensity for underlying acute and chronic diseases and immunosenescence, defined as a decline in the immune function related to ageing (both humoral and cellular immunity) [2, 3]. In ageing people, infections are not only more frequent compared to the younger population, but they also have a distinct epidemiological

Corresponding author
Pasquale Pagliano
E-mail ppagliano@libero.it

and clinical presentation, treatment and outcome [4-6]. These findings are explained by a variety of factors, including the ageing process itself, comorbidities (pneumonia and chronic pulmonary diseases, metabolic diseases such as diabetes, renal and hepatic failure and malignancy) and sociological and environmental factors [7]. The most common infections encountered are due to pyogenic bacteria, urinary tract infections, pneumonia, diverticulitis, endocarditis, bacteraemia and skin and soft tissue infection, including those complicating prosthetic implant placement, are those reported with the highest frequency. Susceptibility to bacterial meningitis may be sustained on the basis of epidemiological studies [8-13].

After widespread diffusion of vaccination against *Haemophilus influenzae* b and *Streptococcus pneumoniae* in infancy, bacterial meningitis changed to become a disease largely of adults and was reported with an increasing incidence in ageing people. Current epidemiological investigations report that in people aged 50 years or more, the incidence of *Neisseria meningitidis* is lower compared to younger people, and the main agent responsible for bacterial meningitis is *S. pneumoniae,* which accounts for over 60% of the cases. *Listeria monocytogenes* is reported in about 9% of bacterial meningitis cases, regardless of the presence of comorbidities conditioning a depression of immunity, and *Escherichia coli* and *Klebsiella pneumoniae,* the other 2 most common agents reported, account for about 3% [14-19].

Listeria monocytogenes meningitis

L. monocytogenes is a gram-positive bacillus and facultative intracellular bacterium, it can be found throughout the environment in soil, vegetation and animals [20]. Listeriosis is considered among the most common bacterial foodborne infections, it reports a fatality rate of up to 30% when neurological involvement occurs [21].

The large majority of cases of listerioris are sporadic, but outbreaks occur after contamination of soft cheese or ready to eat food. Transmission occurs through the consumption of contaminated food such as meat (sausages, pate, ham, salami, and chicken), vegetables, ready-to-eat seafood (such as smoked fish or mussels), raw seafood, unpasteurized milk, soft-serve ice creams, and soft cheeses. In a multistate population-based study, *L. monocytogenes* grew from at least one food specimen in the refrigerators of 64% of 123 patients with *L. monocytogenes* infection. In recent years, an increasing rate of listeriosis has been reported particularly in ageing people and in patients receiving immunosuppressive treatment [22, 23].

Intracellular cycle of *L. monocytogenes* and immune response have been largely investigated, but the lack of an animal model makes some pathophysiological aspects of neurolisteriosis still unclear. *L. monocytogenes* invades the host cells using various host proteins to adhere. In the infected hosts, binding of *L. monocytogenes* to host cells involves a bacterial protein (Internalin) and a cell receptor (E-Cadherin) at the intestinal epithelium level [24].

After cell invasion, adjacent cells are invaded through plasma membrane protrusions and therefore cell-to-cell spread occurs without exposition to the extracellular environment so that, through this cycle, *L. monocytogenes* can escape to the human immune system [25]. The invaded cells can cross the intestinal epithelium barrier and also other tissues and organs such as the liver. Bacteria circulating in the blood, either free or associated with leucocytes, spread to the preferred sites of the *L. monocytogenes* transgressing the blood-brain barrier or the placental barrier [26].

Immunity to *L. monocytogenes* is mediated by T-cell limphokine activation of macrophage, which clears *L. monocytogenes* from the blood. Individuals with T-cell dysfunction, such as pregnant women, the elderly, patients living with diabetes mellitus, transplant recipients, and those receiving immunosuppressive therapy based on drugs such as steroids or tumor necrosis factor (TNF)-α inhibitors are at risk of contracting an invasive form of listeriosis such as meningitis. HIV positive patients have a 10-100 fold increase of the risk of listeriosis on the basis of theoretical investigations and on the basis of clinical studies considering patients observed before current anti-HIV drugs availability. The increased risk of *L. monocytogenes* could be lowered by Cotrimoxazole prophylaxis. In considering the actual risk of *L. monocytogenes* meningitis in HIV positive we have to underline that no case is reported in a recent study investigating bacterial meningitis in HIV positive patients. Also patients living with splenectomy can be considered at risk for listeriosis, although it is not clear how splenectomy

predispose to an infection with an intracellular pathogen such as *L. monocytogenes* [27-32].

The infection by *L. monocytogenes* in healthy individuals usually causes self-limited febrile diarrhea or can be asymptomatic; instead, in at risk individuals, it can cause clinical episodes of invasive listeriosis. The disease has three major invasive clinical presentations: bloodstream infection, infection of the central nervous system, and maternal fetal listeriosis. In adults, the most common clinical form of listeriosis is meningitis, due to the bacterial tropism to the central nervous system [33].

Listeria monocytogenes **meningitis in elderly**

L. monocytogenes meningitis in young previously healthy adults has been reported only in anecdotal observations, but its incidence approach to 9% in elderly on the basis of epidemiological data. Table 1 reports the epidemiological findings of bacteria meningitis in elderly on the basis of 4 major studies [16-19].

Presentation of bacterial meningitis in elderly may be troublesome as clinical findings are not always suggestive of meningitis and main clinical symptoms such as neck stiffness or fever may be absent. In fact, when we attempt to diagnose meningitis in elderly patients, we have to consider that fever may be absent at the time of presentation in the emergency room in a variable percentage of patients, headache and nuchal rigidity are noted in a proportion of cases approaching to

60% and a depressed status of conscience may be related to a number of non-infective causes [34]. Studies on meningitis in elderly rarely enrolled a sufficient number of cases to establish the peculiar characteristics of *L. monocytogenes* meningitis in this age.

On the basis of a study comparing the finding of meningitis presentation in respect to age, we can affirm that older patients with meningitis frequently are comatose, but report in a percentage below 50% nuchal rigidity or other signs of meningeal irritation such as Kernig's or Brudzinski's sign and that a linear correlation occurs between age and coma severity [34]. According to literature data, the prevalence of the classic triad of fever, neck stiffness, and altered mental status is below 50%, and almost all patients present with at least 2 of the 4 classic symptoms of headache, fever, neck stiffness, and altered mental status. In these patients only the absence of all the three classic elements supporting meningitis diagnosis (fever, nuchal rigidity and an impaired conscience status) has a relevant predictive value in excluding *L. monocytogenes* meningitis [34]. It is important to underline that nuchal rigidity has a relatively low accuracy in diagnosing bacterial meningitis in ageing patients as non-infective diseases such as cerebrovascular accident, Parkinson's disease or cervical arthritis may cause it. All these conditions may be frequently present in ageing patients requiring admission in an emergency department [33-35].

Table 1 - Main studies involving an ageing population with bacterial meningitis.

Author	Cases included	Bacteria isolated in elderly (%)		Bacteria isolated in adults (%)	
Cabellos [18]	675 cases in 31 years	*S. pneumoniae*	39	*S. pneumoniae*	30
		N. meningitidis	26	*N. meningitidis*	39
		L. monocytogenes	9	*L. monocytogenes*	5
		Other/unknown	26	Other/unknown	26
Weisfelt [17]	696 cases in 42 months	*S. pneumoniae*	68	*S. pneumoniae*	40
		N. meningitidis	14	*N. meningitidis*	50
		L. monocytogenes	7	*L. monocytogenes*	3
		Other/unknown	11	Other/unknown	7
Domingo [19]	635 cases in 28 years	*S. pneumoniae*	38	*S. pneumoniae*	26
		N. meningitidis	16	*N. meningitidis*	16
		L. monocytogenes	19	*L. monocytogenes*	19
		Other/unknown	29	Other/unknown	39
Erdem [16]	159 cases in an unreported period (all over 50 years)	*S. pneumoniae*	69	No data	
		N. meningitidis	3		
		L. monocytogenes	9		
		Other/unknown	19		

In a recent study attempting to investigate the difference of clinical presentation of *L. monocytogenes* and pneumococcal meningitis in patients aged over 50 years consecutively observed during a ten-year period, we reported that *L. monocytogenes* meningitis has distinctive findings that have to be considered in evaluating every ageing patient with meningitis (Table 2). In the cases investigated, diagnosing *L. monocytogenes* meningitis was more challenging than pneumococcal meningitis, as demonstrated by the lower percentage of cases receiving a correct diagnosis within 48 hours from the onset of symptoms, but the clinical findings of *L. monocytogenes* meningitis at the time of our diagnosis were similar. *L. monocytogenes* was frequently observed in comatose patients without a rapid progression to respiratory failure, suggesting that the disease is severe, but it is not as rapidly progressive as pneumococcal meningitis [36]. The absence of extrameningeal infection or basal leak, the presence of an adjunctive condition causing immunocompromission were equally more suggestive of *L. monocytogenes* than pneumococcal meningitis [36].

Given the lack of specificity or sensitivity of symptoms and signs, the basis for the diagnosis of meningitis is the lumbar puncture whose decision to perform in elderly has to be tempered by consideration of the risk of complications from the procedure. Indeed, in this age an altered mental status and fever may be due to intracranial mass lesions such as brain abscess, tumor subdural hematoma, and cerebral infarction or hemorrhage which report a significant risk of brain herniation [37]. While for other age groups the main distinction is between viral and bacterial meningitis, in the geriatric population a more common problem is distinguishing between bacterial meningitis and infection at another site as the cause of fever and acutely depressed mental status [38].

Cerebro-spinal fluid (CSF) examination in adults with bacterial meningitis frequently shows pleocytosis associated to an increase of protein concentration and low CSF glucose as compared to the blood concentration [39]. Gram staining the test with the higher specificity and the lower cost in patients with bacterial meningitis has an accuracy related to pathogen involved in meningeal disease. Atypical findings of CSF analysis and low yield of Gram staining have been described previously in *L. monocytogenes* meningitis [40]. A less evident increase in blood neutrophils and an equally not evident reduction of CSF glucose can be observed in patients with *L. monocytogenes* meningitis, suggesting that the evaluation of these parameters in elderly patients with bacterial meningitis may support a presumptive etiological diagnosis of *L. monocytogenes* meningitis before blood and CSF cultures are available, particularly when CSF Gram stain and the search of bacterial antigen within the CSF are negative [40]. The characteristics reported in CSF examination reflect the different growth rates of *L. monocytogenes* and *S. pneumoniae* and the aspects of the pathway of the immune system activation after pneumococcal or *L. monocytogenes* meningitis. In fact pneumococcal immunity is related to an IgM-mediated complement activation that results in a greater neutrophil activation, and *L. monocytogenes* immunity is associated with a cell-mediated response and a relatively low activation of complement mediated immunity [41].

In our case-series (Table 3), we reported that ageing patients with *L. monocytogenes* meningitis did not show any significant difference in term of CSF cells and protein analysis, but we demonstrated

Table 2 - Clinical and neurological findings of 131 ageing patients with bacterial meningitis.

	Streptococcus pneumoniae (109 cases)	*Listeria monocytogenes* (22 cases)	*P*
Extrameningeal infection (%)	72 (66)	1 (5)*	<0.0001
Respiratory failure within 48 hours from admission (%)	55 (50)	2 (10)	<0.001
Fever (%)	96 (88)	22 (100)	0.12
Neck stiffness (%)	86 (79)	15 (68)	0.45
GCS <11 (%)	77 (71)	21 (95)	<0.05
Motor deficit	9 (8)	1 (5)	0.99
Seizure before admission	9 (8)	2 (9)	0.99

Table 3 - Laboratory findings of 131 ageing patients with bacterial meningitis.

	Streptococcus pneumoniae (109 cases)	*Listeria monocytogenes* (22 cases)	P
White Blood Cells (x10^3 cells /µL)*	18.3 (12.8-23.6)	15.9 (8.6-18.6)	<0.05
Neutrophils (x10^3 cells /µL)*	16.4 (9.9-20.9)	12.7 (6.8-14.8)	<0.01
Platelets (x10^3 cells /µL)*	167 (137-238)	146 (106-170)	0.06
CSF glucose (mg/dl)	10 (4-33)	39 (10-92)	<0.0001
CSF cells (x10^3 cells /µL)*	1.7 (0.4-8.4)	1.2 (0.5-2.7)	0.24
CSF protein (mg/dl)*	551 (206-999)	370 (270-481)	0.09
Erythrocyte sedimentation rate*	86 (64-97)	70 (62-88)	0.91

*data are expressed as median (interquartile range).

that CSF-glucose was significantly higher when *L. monocytogenes* was the causative agent. Furthermore, when we considered blood examination, both white blood cells and blood neutrophils were higher when pneumococcal meningitis was diagnosed. This finding, although achieved statistical significance, had a low practical impact due to the wide range of the values reported [36].

Treatment of bacterial meningitis in elderly is complicated by a number of factors including the increased frequency of resistance of *S. pneumoniae* to penicillin, the increased frequency of *L. monocytogenes*, and the increased rate of resistance to third generation cephalosporin (IIIGC) of *Escherichia coli*. On the basis of current guidelines, empiric treatment of elderly patients with bacterial meningitis has to be based on administration of IIIGC coupled with ampicillin to cover the risk of *L. monocytogenes*. In this age, the Gram stain and the search of bacterial antigen have a pivotal role in guiding empirical choice considering that coverage with drugs active against multi-resistant bacteria may be suggested in some cases at risk to harbor resistant bacteria such those requiring frequent antibiotic treatment or recently hospitalized [42, 43].

Although coverage of *L. monocytogenes* is generally provided by ampicillin administration, a number of other drugs show activity against *L. monocytogenes* and can be employed in the treatment of meningitis [21]. With the exception of natural in vitro resistance to older quinolones, fosfomycin, and expanded-spectrum cephalosporins, *L. monocytogenes* is widely susceptible to clinically relevant classes of antibiotics active against Gram-positive bacteria. Rifampin and vancomycin show an in vitro activity against *L. monocytogenes*, but clinical data are not sufficient

for both the drugs. *L. monocytogenes* meningitis was reported during treatment with vancomycin in a neutropenic patient receiving the drug due to staphylococcal infection, demonstrating that the drug has not sufficient activity against *L. monocytogenes*, at least in severely immunodepressed patients [44]. Instead, rifampin has bacteriostatic activity against *L. monocytogenes* and resistant strains have been reported in patients with extrameningeal infection [45]. Levofloxacin has been proposed as empiric therapy of bacterial meningitis to ensure *L. monocytogenes* coverage on the basis of pharmacological data, but its use has to be evaluated in larger series [46]. Only a few data can support use of Linezolid for the treatment of *L. monocytogenes* meningitis. Cotrimoxazole could be a valuable alternative for the treatment of *L. monocytogenes* meningitis due to its good penetration of CSF and antibacterial activity. Cotrimoxazole and amoxicillin demonstrated to be effective in a case series of 15 patients with *L. monocytogenes* meningitis [47].

Meropenem could be a valuable choice on the basis of in vitro data, but clinical evidences are not conclusive [42].

Elderly patients are considered at the highest risk of an unfavourable outcome after bacterial meningitis being deaths associated to bacterial meningitis itself or to cardiovascular or other comorbidities [48]. Mortality of *L. monocytogenes* meningitis in elderly approaches to 30% but patients with a history of *L. monocytogenes* meningitis report a higher long-term mortality due to death from cancer, suggesting that ageing patients have to be screened for the predisposing conditions after *L. monocytogenes* meningitis [49]. In our case-series comparing patients with *L. monocytogenes* meningitis to those with pneumococcal meningitis, we

reported that despite a lower percentage of cases affected by *L. monocytogenes* meningitis received an appropriate therapy within 48 h from the onset of symptoms, mortality rate was lower than pneumococcal meningitis on the basis of multivariate analysis and patients surviving after *L. monocytogenes* meningitis did not show neurological sequelae.

■ CONCLUSIONS

Bacterial meningitis is a serious and life-threatening disease. *L. monocytogenes* is the third most frequent cause of bacterial meningitis in immunocompromised patients and elderly individuals. Clinical and laboratory findings of *L. monocytogenes* meningitis are similar to those of the general population with bacterial meningitis, including those immunocompromised [50]. Presumptive diagnosis of *L. monocytogenes* meningitis should be based on the anamnestic findings (i.e. current immunosuppressive therapy), on the search for other infective foci, clinical status (i.e. comatose status, rapid progression to respiratory failure) and CSF characteristics. The associated mortality is relatively low, but careful evaluation for relevant comorbidity has to be warranted.

■ REFERENCES

[1] Gavazzi G., Krause K.H. Ageing and infection. *Lancet Infect. Dis.* 2, 659-666, 2002.
[2] Fulop T, Le Page A, Fortin C, Witkowski JM, Dupuis G, Larbi A. Cellular signaling in the aging immune system. *Curr. Opin. Immunol.* 29, 105-111, 2014.
[3] Liang S.Y., Mackowiak P.A. Infections in the elderly. *Clin. Geriatr. M*ed. 23, 441-456, 2007.
[4] High K.P., Bradley S.F., Gravenstein S., *et al.* Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. *J. Am. Geriatr. Soc.* 57, 375-394, 2009.
[5] Malani P.N., Rana M.M., Banerjee M., Bradley S.F. Staphylococcus aureus bloodstream infections: the association between age and mortality and functional status. *J. Am. Geriatr. Soc.* 56, 1485-1489, 2008.
[6] Mody L., Sun R., Bradley S.F. Assessment of pneumonia in older adults: effect of functional status. *J. Am. Geriatr. Soc.* 54, 1062-1067, 2006.
[7] Yoshikawa T.T. Epidemiology and unique aspects of

aging and infectious diseases. *Clin. Infect. Dis.* 30, 931-933, 2000.
[8] Steens A., Eriksen H.M., Bystad H. What are the most important infectious diseases among those ≥65 years: a comprehensive analysis on notifiable diseases, Norway, 1993-2011. *BMC Infect. Dis*. 14, 57, 2014.
[9] Matthews S.J., Lancaster J.W. Urinary tract infections in the elderly population. *Am. J. Geriatr. Pharmacother.* 9, 286-309, 2011.
[10] Kish T.D., Chang M.H., Fung H.B. Treatment of skin and soft tissue infections in the Elderly: a review. *Am. J. Geriatr. Pharmacother.* 8, 485-513, 2010.
[11] Burlaud A., Mathieu D., Falissard B., Trivalle C. Mortality and bloodstream infections in geriatrics units. *Arch. Gerontol. Geriatr.* 51, e106-e109, 2010.
[12] Ascione T., Pagliano P., Mariconda M., et al. Factors related to outcome of early and delayed prosthetic joint infections. *J. Infect.* 70, 30-36, 2015.
[13] Thigpen M.C., Whitney C.G., Messonnier N.E., et al. Bacterial meningitis in the United States, 1998-2007. *N. Engl. J. Med.* 364, 2016-2025, 2011.
[14] Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century; global analysis of the disease burden 25 years after the use of polysaccharide vaccine and a decade after the advent of conjugates. *Clin. Microbiol. Rev.* 13, 302-317, 2000.
[15] Williams C., Masterton R. Pneumococcal immunisation in the 21st century. *J. Infect.* 56, 13-19, 2008.
[16] Erdem H., Coskun O., Ersoy Y., et al. Community-acquired acute bacterial meningitis in the elderly in Turkey. *Clin. Microbiol. Infect.* 16, 1223-1229, 2010.
[17] Weisfelt M., van de Beek D., Spanjaard L., Reitsma J.B., and de Gans J. Community-acquired bacterial meningitis in older people. *J. Am. Geriatr. Soc.* 54, 1501-1507, 2006.
[18] Cabellos C., Verdaguer R., Olmo C., et al. Community-acquired bacterial meningitis in elderly patients: experience over 30 years. *Medicine* (Baltimore), 88, 115-119, 2009.
[19] Domingo P., Pomar V., de Benito N., Coll P. The spectrum of acute bacterial meningitis in elderly patients. *BMC Infect. Dis.* 13, 108. doi: 10.1186/1471-2334-13-108, 2013.
[20] Vázquez-Boland J.A., Kuhn M., Berche P., et al. *Listeria* Pathogenesis and Molecular Virulence Determinants. *Clin. Microbiol. Rev.* 14, 584-640, 2001.
[21] Arslan F., Meynet E., Sunbul M., et al. The clinical features, diagnosis, treatment, and prognosis of neuroinvasive listeriosis: a multinational study. *Eur. J. Clin. Microbiol. Infect. Dis*. 34, 1213-1221, 2015.
[22] Swaminathan B., Gerner-Smidt P. The epidemiology of human listeriosis. *Microbes Infect.* 9, 1236-1243, 2007.
[23] Pinner R.W., Schuchat A., Swaminathan B., et al. Role of foods in sporadic listeriosis. II. Microbiologic and epidemiologic investigation. The Listeria Study

Group. *JAMA.* 267, 2046-2050, 1992.

[24] Disson O. and Lecuit M. Targeting of the central nervous system by *Listeria monocytogenes. Virulence.* 3, 213-221, 2012.

[25] Freitag N.E., Port G.C., Miner M.D. *Listeria monocytogenes*-from saprophyte to intracellular pathogen. *Nat. Rev. Microbiol.* 7, 623-628, 2009.

[26] Ruan Y., Rezelj S., Bedina Zavec A., Anderluh G., Scheuring S. Listeriolysin O membrane damaging activity involves arc formation and lineaction - Implication for *Listeria monocytogenes* escape from phagocytic vacuole. *PLoS Pathog.* 12, e1005597, 2016.

[27] Regan T., MacSharry J., Brint E. Tracing innate immune defences along the path of *Listeria monocytogenes* infection. *Immunol. Cell Biol.* 92, 563-569, 2014.

[28] Porturas T.P., Sun H., Buchlis G., et al. Crucial roles of TNFAIP8 protein in regulating apoptosis and Listeria infection. *J. Immunol*. 194, 5743-5750, 2015.

[29] Pagliano P., Attanasio V., Fusco U., Mohamed D.A., Rossi M., Faella F.S. Does etanercept monotherapy enhance the risk of *Listeria monocytogenes* meningitis? *Ann. Rheum. Dis.* 63, 462-463, 2004.

[30] Mylokanis E., Hohmann E.L., Calderwood S.B. Central nervous system infection with *Listeria monocytogenes*. 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine* (Baltimore). 77, 313-335, 1998.

[31] van Veen K.E., Brouwer M.C., van der Ende A., van de Beek D. Bacterial meningitis in patients with HIV: A population-based prospective study. *J. Infect.* 72, 362-368, 2016.

[32] Perobelli S.M., Alves C.C., Rezende A.B., Farias R.E., Nunes S.I., Teixeira H.C. Splenic autotransplantation reverses interferon-gamma and nitric oxide production and resistance to *Listeria monocytogenes* in splenectomized mice. *Transpl. Infect. Dis.* 13, 154-160, 2011.

[33] Maertens de Noordhout C., Devleesschauwer B., Angulo F.J., et al. The global burden of listeriosis: a systematic review and meta-analysis. *Lancet Infect. Dis.* 14, 1073-1082, 2014.

[34] Magazzini S., Nazerian P., Vanni S., et al. Clinical picture of meningitis in the adult patient and its relationship with age. *Inter. Emerg. Med.* 7, 359-364, 2012.

[35] Waghdhare S., Kalantri A., Joshi R., Kalantri S. Accuracy of physical signs for detecting meningitis: a hospital-based diagnostic accuracy study. *Clin. Neurol. Neurosurg.* 112, 752-757, 2010.

[36] Pagliano P., Attanasio V., Rossi M., et al. *Listeria monocytogenes* meningitis in the elderly: distintive characteristics of the clinical and laboratory presentation. *J. Infect.* 71, 134-136, 2015.

[37] Glimåker M., Johansson B., Bell M., et al. Early lumbar puncture in adult bacterial meningitis-rationale

for revised guidelines. *Scand. J. Infect. Dis.* 45, 657-663, 2013.

[38] Chee C.E. and Mohr D.N. 71 year-old woman with fever and altered mental status. *Mayo Clin. Proc.* 82, 237-240, 2007.

[39] van de Beek D., de Gans J., Spanjaard L., et al. Clinical features and prognostic factors in adults with bacterial meningitis. *N. Engl. J. Med.* 1849-1859, 2004.

[40] Brouwer M.C., van de Beek D., Heckenberg S.G.B., Spanjaard L., de Gans J. Community-acquired *Listeria monocytogenes* meningitis in adults. *Clin. Infect. Dis.* 43, 1233-1238, 2006.

[41] Dupont A., Mohamed F., Salehen N., et al. Septicaemia models using *Streptococcus pneumoniae* and *Listeria monocytogenes*: understanding the role of complement properdin. *Med. Microbiol. Immunol.* 203, 257-271, 2014.

[42] van de Beek D., Cabellos C., Dzupova O., et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis *Clin. Microbiol. Infect*. 22 (Suppl. 3): S37-S62, 2016.

[43] van der Steen M., Leenstra T., Kluytmans J.A., van der Bij A.K.; ISIS-AR study group. Trends in Expanded-Spectrum Cephalosporin-Resistant Escherichia coli and *Klebsiella pneumoniae* among Dutch Clinical Isolates, from 2008 to 2012. *PLoS One*. 10, e0138088, 2015.

[44] Arsene O., Linassier C., Quentin R., Legras A., Colombat P. Development of listeriosis during vancomycin therapy in a neutropenic patient. *Scand. J. Infect. Dis.* 28, 415-416, 1996.

[45] Chenal-Francisque V., Charlier C., Mehvish S., et al. Highly rifampin-resistant *Listeria monocytogenes* isolated from a patient with prosthetic bone infection. *Antimicrob. Agents Chemother.* 58, 1829-1830, 2014.

[46] Viale P., Scudeller L., Pea F., et al. Implementation of a Meningitis Care Bundle in the Emergency Room Reduces Mortality Associated With Acute Bacterial Meningitis. *Ann. Pharmacother.* 49, 978-985, 2015.

[47] Merle-Melet M., Dossou-Gbete L., Maurer P., et al. Is amoxicillin-cotrimoxazole the most appropriate antibiotic regimen for listeria meningoencephalitis? Review of 22 cases and the literature. *J. Infect*. 33, 79-85, 1996.

[48] McMillan D.A., Lin C.Y., Aronin S.I., Quagliarello V.J. Community-acquired bacterial meningitis in adults: categorization of causes and timing of death. *Clin. Infect. Dis.* 33, 969-975, 2001.

[49] Roed C., Engsig F.N., Omland L.H., Skinhoj P., Obel N. Long-term mortality in patients diagnosed with *Listeria monocytogenes* meningitis: a Danish nationwide cohort study. *J. Infect.* 64, 34-40, 2012.

[50] Pagliano P., Attanasio V., Rossi M., et al. Pneumococcal meningitis in cirrhotics: distinctive findings of presentation and outcome. *J. Infect*. 65, 577-579, 2012.