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PRINCIPLES OF DIAGNOSIS AND TREATMENT OF BACTERIAL PURULENT MENINGOENCEPHALITIS IN ADULTS

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Bacterial purulent meningoencephalitis (BPM) is an acute infection of subarachnoid space with meningitis and brain parenchyma involvement. It is one of 10 most common causes of death due to infectious diseases. Annually, approximately 1.2 mln infections are noted worldwide. In Western European countries and North America, incidence is 5/100 000. In developing countries, these rates are 10-fold higher (2). A total of 192 (incidence 0.5/100 000), 120 (0.31/100 000) and only 11 (incidence 0.03/100 000) infections caused by *Streptococcus pneumoniae, Neisseria meningitidis* and *Heamophilus influenzae* were reported in Poland in 2014, respectively. Other and unspecified infections predominated - 746 (3). In recent 25 years, there were considerable changes in the epidemiology of these infections resulting from making vaccinations more accessible. At present, adults are mainly affected by infections caused by *S. pneumoniae* (50%), *N. meningitidis* (25%), group B *Streptococcus* (15%), *Listeria monocytogens* (10%) and *H. influenzae* (<10%). Gram-negative enteric cocobacilli are a more common cause of infections, especially in the elderly and persons with chronic diseases resulting in an impaired immune system. In Poland, according to the data of the National Reference Centre for Bacterial Meningitis (NRCBM), the most prevalent were infections of *N. meningitidis* aetiology of the following serogroups: B (48.8%), C (36.6%), sporadically Y (1.2%) and W-135 (1.2%). The highest mortality rate was reported for infections caused by *N. meningitidis* serogroups B (10.3%) and C (8.8%). Analysis of the susceptibility to antibiotics of 1373 isolates revealed that all strains were susceptible to the third generation cephalosporins, chloramphenicol and ciprofloxacin. A total of 84.2% and 14.3% of meningococcal isolates showed high and medium susceptibility to penicillin (PNC), respectively. Only 1.5% of strains were resistant to penicillin and 1% to rifampicin. Diagnosis of BPM is based on the analysis of cerebrospinal fluid (CSF). Most frequently, CSF leaks under increased opening pressure (200-500 mm H_20) and is of turbid appearance. Sometimes, it is a dense pus of elevated consistency, which is hardly released from puncture needles. Pleocytosis, in >80% mostly neutrophilic, exceeds 1000 cells per 1 μL with the exceptions of infections caused by Gram-negative bacteria in newborns and listeriosis in which lymphocytes predominated. Protein is raised, beginning from 1-5 g/L and over. Glucose level is low, or sometimes undetectable. Culture is a gold standard in the diagnosis of BPM. Its diagnostic effectiveness is 70-85% on average, i.e. 96%, 87% and 80% in infections caused by *H. influenzae*, *S. pneumoniae* and *N. meningitides,* respectively. Bacterioscopic examination is a simple, inexpensive and rapid diagnostic method with sensitivity ranging from 75 to 90% (5, 17, 25). Staining of preparation of the CSF deposit, using Gram's method or methylene blue allows for differentiating bacterial types - Gram-positive or Gram-negative and determining their morphology: cocci, coccobacilli (12, 13). Sensitivity of this method is dependent on the bacterial species. For *S. pneumoniae* and *S. aureus,* it amounts to 90%, while for *H. influenzae* – 86%, *N. meningitidis* – 75%, Gram-negative coccobacilli – 50%, *L. monocytogenes* and anaerobic bacteria - <50%. If testing is performed prior to the initiation of antibiotic therapy, when there is a high concentration of bacteria, then sensitivity and specificity are 60-90% and >97%, respectively. Latex tests are used for rapid qualitative detection of antigens of alive and dead bacteria in CSF or urine, which allows for initial determination of aetiology, even following the initiation of antibiotic therapy. Tests for the detection of antigens of *H. influenzae* type B, *S. pneumoniae, N. meningitidis* serogroups A, B, C, Y I W135, group B *Streptococcus* and *Escherichia coli* K1 are available on the market. Specificity of tests for the antigens of *S. pneumoniae* and *N. meningitidis* ranges from 95 to 100%, which enables to determine the aetiology, while the sensitivity for pneumococcal and meningococcal antigens amounts to 70-100% and 33-70%, respectively. Therefore, negative result of latex agglutination test does not permit to exclude

infections with these bacteria. It ensures 100% sensitivity and 97% specificity of test result. A benefit is that it is possible to obtain positive results following the initiation of antibiotic therapy. Blood cultures should be performed if lumbar puncture is contraindicated, prior to the initiation of antibiotic therapy. Neuroimaging does not have any effect on determination of BPM aetiology. However, it is useful for diagnosing cerebral oedema and/or inflammatory lesions in brain nervous tissue, including abscesses. Neuroimaging allows for assessing the intensity of oedema and recognizing complications such as hydrocephalus, haemorrhagic lesions or ischemia. CT/MRI should be performed also in the presence of symptoms indicative of intracranial pressure. If such symptoms are not reported, imaging testing leads to an unnecessary delay and consequently therapy is retarded. Thus it should not be a routine procedure (13, 20, 24). Initial diagnosis is made on a basis of cardinal symptoms, including headaches, fever, meningismus and characteristic inflammatory lesions in CSF. Irrespective of the intensity of clinical symptoms, such disease should be always suspected if there are high neutrophilic pleocytosis, low glucose level and high protein concentration in CSF. As a delay in therapy always results in exacerbation of prognosis, empiric antibiotic therapy should be initiated as soon as possible, without awaiting for laboratory and neuroimaging test results.

Empiric antibiotic therapy

For BPM, prognosis is poor. It is dependent on etiological agent, patient's age, comorbidities and time of initiation of proper therapy (4). Its effectiveness is determined by quick initiation of antibiotic and supplementary therapy (1). Due to a severe course of disease, high mortality and possibility of early complications, especially in the initial phase of disease, patient should be hospitalized on an intensive care unit (ICU) (5, 6). Empiric antibiotic therapy should be initiated quickly, optimally, within the first hour of hospitalization. Elements of therapy should be determined not only based on the mode of drug action and permeability through blood–brain barrier, but also other non-age-dependent factors indicative of the aetiology, including comorbidities, past surgeries, injuries and local epidemiological situation. It is required to differentiate between community and hospital-acquired infection. Selection of antibiotics is affected by higher prevalence of multidrug-resistant bacteria, not only in hospital strains, but also community strains. Irrespective of the aetiology, clinical presentation is similar. However, in-depth

Table I. Regimens of empiric antibiotic therapy of BPM by estimated risk factors and other variables affecting the choice of therapy

Risk factors	**Etiological agent**	**Empiric therapy regimen**
Patient's age < 1st month of life	*S. agalactiae; E. coli;* *L. monocytogenes*; Gram-negative enteric cocobacilli	ampicillin + cefotaxime or ampicillin + aminoglycoside
1-month old – 5 years old	*N. meningitidis; S. pneumoniae; H. influenzae*	ceftriaxone + vancomycin
Children ≥ 5 years old and adults ≤ 50 years old	*N. meningitidis; S. pneumoniae*	ceftriaxone + vancomycin
> 50 years old	*S. pneumoniae; N. meningitidis;* *L. monocytogenes*	ampicillin + ceftriaxone + vancomycin
Immunodeficiencies, cancer, alcoholism	*L. monocytogenes*; Gram-negative enteric cocobacilli	ampicillin + ceftriaxone + vancomycin
Neurosurgery; head injury	*S. pneumoniae; S. aureus*; Gram-negative enteric cocobacilli; *P. aeruginosa*	cefepime + vancomycin or meropenem + vancomycin
Ventricular – abdominal valve infection (atrial)	*S. aureus*; coagulase-negative staphylococci; Gram-negative enteric cocobacilli	cefepime + vancomycin or meropenem + vancomycin
Hospital-acquired infection	multidrug-resistant Gram-negative cocobacilli; methicillin-resistant staphylococci	meropenem + vancomycin
Allergy to penicillin	*S. pneumoniae; N. meningitidis; H. influenzae* *L. monocytogenes*	meropenem + vancomycin or moxifloxacin co-trimoxazole or meropenem
Gram-method staining results		
Gram-negative cocci (diplococci)	*N. meningitidis*	ceftriaxone or cefotaxime
Gram-positive cocci (diplococci)	*S. pneumoniae*	ceftriaxone + vancomycin
Gram-positive coccobacilli	*L. monocytogenes*	ampicillin + aminoglycoside
Gram-negative coccobacilli	*H. influenzae*; Gram-negative enteric cocobacilli; Gram-negative non-fermenting cocobacilli	cefepime + aminoglycoside

analysis of interview data, infection circumstances and symptoms allows for a cautious prediction of aetiology. Infection with *H. influenzae* is indicated by infection occurring under the age of 5 years old and lack of proper vaccinations. In case of adults, this bacterium is a rare etiological agent, <10% of infections. Abrupt infection, under the age of 5 years old or in adolescence, typically in winter or spring, short incubation period, characteristic rash on skin, mucosae and conjunctivae and sudden course of disease most probably are indicative of infection with *N. meningitidis*. Pneumococcal aetiology should be suspected in infants under the age of 2 years old, adults over 65 years old, and, irrespective of the age, in persons with immunodeficiencies, with difficult to determine time of incubation, sudden onset or gradual increase of symptom intensity when a starting point is purulent lesion in ear or paranasal sinuses. Number of antibiotics should be restricted to a required minimum as their excess favours selective pressure, resistance development and adverse drug effects. The most important empiric antibiotic therapy regimens were presented in Table I. Of importance for prognosis is to administer antibiotic quickly, most optimally within the first hour of hospitalization. In case of justified suspicion of *N. meningitides* infection, it should be considered to apply the first dose of proper antibiotic prior to referring the patient to hospital. Having selected antibiotics, not only mode of drug action, but also its permeability into subarachnoid space, imperative for achieving therapeutic concentration should be taken into account. Antibiotics should be administered intravenously in the same dose for the whole therapy as with the resolution of inflammation, the activity of blood-brain barrier improves. Consequently, its permeability decreases and concentration of drugs may be suboptimal. Drugs of small molecular mass, low degree of protein binding, good lipid solubility and low degree of ionization in physiological pH show higher permeability. High protein concentration and density of bacteria in CSF restrict the bactericidal action. The greatest capacity for obtaining high concentration in CSF, over minimal inhibitory concentrations (MIC), is displayed by β-lactam antibiotics. Administration of drugs through intrathecal or intraventricular routes is restricted to specific clinical situations. It may be considered in patients who underwent neurological surgeries or those with decompression valves as well as in case of infections with multidrug-resistant strains of *Staphylococcus aureus* or non-fermenting Gram-negative cocobacilli. Most frequently, vancomycin, aminoglycosides and colistin are then applied. Posology of antibiotics was presented in Table II. In therapy, β-lactam antibiotics are applied such as penicillins, cephalosporins, monobactams, carbapenems and β-lactamase inhibitors. Irrespective of the fact that these drugs do not entirely permeate through blood-brain barrier, they achieve higher than MIC concentrations in CSF for the majority of pathogens causing BPM. Permeability of these antibiotics into CSF increases considerably during inflammatory process. Thus, antibiotics of such group are basic drugs adopted in the therapy of such infections (15, 17). Natural penicillins – benzylpenicillin (penicillin G) – achieve therapeutic concentrations in CSF with a daily dose of 24 mln IU and higher if administered 4-6 times a day. Nowadays, however, due to increasing resistance, especially in

Table II. Recommended posology of antibiotics (chemotherapeutics) in the therapy of BPM.

Drug	Route of administration	Posology (in adults) /24 hours	Posology (in children) /24 hours
Penicillin G	Intravenous	4 x 6 mln IU	4 x 75,000 IU/kg bw
Ampicillin	Intravenous	6 x 2 g	6 x 50 mg/kg bw
Ceftriaxone	Intravenous	2 x 2 g	1 x 100 mg/kg bw
Cefotaxime	Intravenous	4 x 3 g	4 x 50 mg/kg bw
Ceftazidime	Intravenous	3 x 2 g	3 x 50 mg/kg bw
Cefepime	Intravenous	3 x 2 g	3 x 50 mg/kg bw
Meropenem	Intravenous	3 x 2 g	3 x 40 mg/kg bw
Aztreonam	Intravenous	3 x 2 g	3 x 50 mg/kg bw
Amikacin	Intravenous	3 x 5 mg/kg bw	3 x 5 mg/kg bw
Amikacin	Intrathecal	1 x 0.02 g	
Gentamicin	Intravenous	3 x 2.5 mg/kg bw	3 x 2.5 mg/kg bw
Vancomycin	Intravenous	2 x 1 g	4 x 15 mg/kg bw
Vancomycin	Intrathecal	1 x 0.01 – 0.02 g	
Ciprofloxacin	Intravenous	2 x 0.4 g	-
Moxifloxacin	Intravenous	1 x 0.4 g	-
Linezolid	Intravenous	2 x 0.6 g	2 x 5 mg/kg bw
Metronidazole	Intravenous	3 x 0.5 g	3 x 10 mg/kg bw
Rifampicin	Oral	1 x 0.6 g	1 x 10-20 mg/kg bw
Colistin	Intrathecal	3 x 2-3 mln IU	-
Co-trimoxazole	Intravenous	4 x 5 mg/kg bw (with respect to trimethoprim)	4 x 5mg/kg mc (with respect to trimethoprim)

Table III. Recommended therapy regimens in BPM by the resistance of isolated etiological agents.

Etiological agent	Recommended therapy	Alternative therapy
S. pneumoniae susceptible to penicillin	penicillin G	ceftriaxone; cefotaxime
decreased susceptibility to penicillin	ceftriaxone or cefotaxime	meropenem; cefepime
penicillin-resistant *S. pneumoniae* (PRSP)	ceftriaxone or cefotaxime + vancomycin	moxifloxacin; moxifloxacin + rifampicin
N. meningitidis susceptible to penicillin	penicillin G	ceftriaxone or cefotaxime
decreased susceptibility to penicillin	ceftriaxone or cefotaxime	meropenem; moxifloxacin
H. influenzae β-lactamase negative	ampicillin	ceftriaxone; cefotaxime; cefepime; aztreonam
β-lactamase positive	ceftriaxone or cefotaxime	cefepime; aztreonam; fluoroquinolones
S. aureus; coagulase-negative staphylococci methicillin-resistant (MRSA/ MRCNS)	vancomycin	linezolid; co-trimoxazole or rifampicin in combined therapy
decreased susceptibility or vancomycin-resistant (VISA/ VRSA)	linezolid	co-trimoxazole or rifampicin in combined therapy
Enterococcus spp. vancomycin-resistant (VRE)	linezolid	
Gram-negative cocobacilli ESβL	meropenem	ciprofloxacin; moxifloxacin; aminoglycosides
Gram-negative cocobacilli AMPC	meropenem	cefepime; aminoglycosides; fluoroquinolones;
Gram-negative cocobacilli MBL	colistin	aztreonam; fluoroquinolones; aminoglycosides
Gram-negative cocobacilli KPC	colistin	

pneumococci, penicillin is not recommended as a drug of choice in empiric therapy (16). Administration of penicillin G is indicated in case of infections caused by meningococci, pneumococci, group B *Streptococcus* and *L. monocytogenes,* of confirmed susceptibility to this drug. A basic indication for the use of ampicillin is infection of *L. monocytogenes* aetiology; if it is supplemented with aminoglycoside, then bactericidal action is increased. Ampicillin CSF concentration achieves nearly 15% of its level in serum (15,18). Third generation cephalosporins are characterized by a broad mode of action, covering Gram-positive and negative bacteria, including frequently those which cause BPM. Therefore, they are antibiotics of choice in empiric therapy. Ceftriaxone or cefotaxime are drugs of choice (19). Cefotaxime is an antibiotic favoured in children as it is characterized by lower degree of protein binding, lack of secretion with bile, lower risk of hyperbilirubinaemia and poorer effect on intestinal microflora compared to ceftriaxone (15). If there is no expected improvement following administration of ceftriaxone or cefotaxime, infection with Gram-negative coccobacilli should be suspected which demonstrate the ESβL resistance (extended-spectrum β-lactamase), AMPC (β-lactamase type AmpC), MBL (metallo-β-lactamase) or KPC (carbapenemase type KPC) or infections caused by bacteria which are naturally resistant to these antibiotics, i.e.: *L. monocytogenes*, *Staphyloccocus spp*., *Enterococcus spp.* or pneumococci resistant to penicillin and ceftriaxone (20). Ceftriaxone demonstrates the greatest action against *H. influenzae* and *N. meningitidis*. In case of confirmed meningitis of *Pseudomonas aeruginosa* aetiology*,* ceftazidime is the antibiotic of choice (15). Cefepime, belonging to the fourth generation cephalosporins, is characterized by similar mode of action as the third generation cephalosporins (21). Monobactam antibiotic – aztreonam is mainly indicated in therapy of meningitis caused by *H. influenzae* or *P. aerugionosa*. Its CSF concentration achieves nearly 30-52% compared to that in blood (15). Out of carbapenemases, exclusively meropenem is recommended as the use of imipenem is associated with a risk of convulsions (22). Meropenem is characterized by high permeability into blood-cerebrospinal fluid barrier and broad mode of action, covering the majority of pathogens causing BPM (15). Out of glycopeptide antibiotics, used in therapies, exclusively vancomycin is applied in the treatment of meningitis as teicoplanin does not permeate into blood-cerebrospinal fluid barrier (15). In general, vancomycin should be reserved for targeted therapy. However, its use is allowable in empiric therapy provided conditions are met which suggest infection with staphylococci, high percentage of MRSA strains or pneumococci resistant to penicillin and cephalosporins. Vancomycin is an antibiotic of low permeability to CSF, thus, it should be applied in combination with β-lactam antibiotics (15, 23). Due to increasing resistance, second generation fluoroquinolones should not be used in empiric therapy and monotherapy. Moxifloxacin should be a drug of choice, which permeates to CSF very well. Its concentration in blood is ca 50%. This antibiotic is characterized by high mode of action to Gram-positive cocci,

including *S. pneumoniae* strains resistant to penicillin (1, 24). In Poland, moxifloxacin is not registered for an intravenous administration. Aminoglycosides poorly permeate to CSF under physiological conditions, while much better in inflammatory process. Thus, they are conditionally authorized for use in the treatment of BPM. A disadvantage consists in poor permeability through lipid barriers, low activity in the environment of purulent fluid and under low pH and relatively anaerobic conditions. To achieve required concentration in CSF, high doses of aminoglycosides are to be used which increases the risk of adverse effects. Such antibiotics should be used exclusively in targeted therapy and in combination with β-lactam antibiotics or glycopeptides (15). Rifampicin is characterized by good lipophilic features. Thus, it may be used as an antibiotic of second choice in combination with vancomycin in BPM caused by MRSA strains. In case of pneumococcal meningitis, rifampicin may be applied in combination with vancomycin as an effect of synergy is observed (25). Out of sulfonamides in the treatment of BPM, co-trimoxazole is applied. Co-trimoxazole concentration in CSF achieves ca 40-50% of its concentration in serum. It is listed in second choice regimens of targeted therapy of infections caused by MRSA strains (15). Metronidazole CSF concentration is comparable to that in serum. This chemotherapeutic is used in the treatment of cerebral abscesses, which are frequently caused by anaerobic bacteria (15). Linezolid, oxazolidinone antibiotic, has action against multidrug-resistant strains of *S. pneumoniae*, enterococci resistant to vancomycin and staphylococci resistant to methicillin and vancomycin. In CSF it achieves 60% concentration of that in blood. It is indicated in infections caused by *Staphylococcus* strains of reduced susceptibility or those resistant to vancomycin (VISA/ VRSA) or enterococci resistant to vancomycin (VRE) (1, 26). Due to its unfavourable pharmacokinetic and pharmacodynamic properties, macrolides, lincosamides, tetracyclines, tigecycline, ketolides and colistin are not applied in the treatment of BPM (15). Colistin may be administered intraventricularly in infections caused by multidrug-resistant non-fermenting coccobacilli strains (27). Empiric antibiotic therapy should be verified following the identification of etiological agent and matched to the results of antibiogram. Recommended therapy regimens by the resistance of etiological agents causing BPM were presented in Table III. Therapy duration is dependent on the clinical course and etiological agent identified. Antibiotic therapy should last for at least 7-10 days, and successive 5 days following the resolution of fever. In case of infections with *N. meningitidis* or *H. influenzae,* this time should not be shorter than 7 days, while for *S. pneumoniae* infection – 14 days, *Streptococcus agalactiae* - 14-21 days, *L. monocytogenes* - at least 21 days, *Pseudomonas aeruginosa* – 21 days; similarly, in case of infections with Gram-negative enteric coccobacill – 21 days; *S. aureus* – 14 days and removal of infected valve (2, 11). To reduce inflammation, which is intensifying following the administration of bactericidal antibiotics, it is recommended to apply dexamethasone in the dose of 10 mg every 6 hours, ca 15-20 minutes prior or together with the first dose of antibiotic. It should be continued for 2-4 days. Application of dexamethasone at a later time does not improve the therapy outcomes. Furthermore, it does not reduce increasing inflammation. Cerebral oedema and elevated intracranial pressure may be decreased by head elevation at an angle of 30-45^0, pharmacological therapy with mannitol and furosemide, reducing body temperature, hyperventilation (use of already applied respiratorotherapy) or placing a patient in pentobarbital-induced coma. Severe, recurrent convulsions should be dynamically eliminated as they may lead to ischemic CNS injury, especially vulnerable regions of temples, cerebellum and thalamus, while in epilepsy – to permanent brain injury. Firstly, anticonvulsants are applied: lorazepam/diazepam, if such therapy fails, then long-acting drugs are administered – phenytoin or phenytoin with phenobarbital. It is also required to initiate antithrombotic therapy, apply proton-pump inhibitors, and in case of respiratory failure – adopt oxygen therapy or respiratorotherapy. In some instances (more frequently in children than adults), syndrome of inappropriate secretion of antidiuretic hormone accompanied by hyponatremia and normovolemia is developed. Duration of hyponatremia is correlated with the frequency of neurological complications. There is a necessity to sustain normal blood pressure as to prevent the consequences of brain hypoperfusion (1, 12, 28). Indications concerning care include lying in bed in the acute stage of disease, physiotherapy and proper nourishment. Following resolution of fever and other symptoms, patient is allowed to rise, if assisted, exclusively for the purpose of hygiene and physiological needs. Patient should mainly lie in bed for the successive 14 days.

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