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BACTERIAL MENINGITIS – PRINCIPLES OF ANTIMICROBIAL TREATMENT

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ABSTRACT

Bacterial meningitis is associated with significant morbidity and mortality despite the availability of effective antimicrobial therapy. The management approach to patients with suspected or proven bacterial meningitis includes emergent cerebrospinal fluid analysis and initiation of appropriate antimicrobial and adjunctive therapies. The choice of empirical antimicrobial therapy is based on the patient's age and underlying disease status; once the infecting pathogen is isolated, antimicrobial therapy can be modified for optimal treatment.
Successful treatment of bacterial meningitis requires the knowledge on epidemiology including prevalence of antimicrobial resistant pathogens, pathogenesis of meningitis, pharmacokinetics and pharmacodynamics of antimicrobial agents. The emergence of antibiotic-resistant bacterial strains in recent years has necessitated the development of new strategies for empiric antimicrobial therapy for bacterial meningitis.

Key words*: bacterial meningitis, antimicrobial therapy, antibiotic-resistant*

INTRODUCTION

Bacterial meningitis and encephalitis are the acute infectious diseases accompanied by inflammation of meninges protecting the brain, spinal cord, subarachnoid cavity and brain parenchyma. The characteristic element of cerebrospinal fluid (CSF) analysis is pleocytosis with significant predominance of neutrophiles, increase of protein concentration and decrease of glucose level (1). The incidence of bacterial meningitis worldwide is approximately 5.0 cases per 100,000 on an annual basis in the West Europe and the United States. However, in the developed countries the morbidity and mortality may be 10 times higher (2). In Poland, a total of 1,018 cases of bacterial meningitis were notified in 2011 (incidence: 2.67 per 100,000). Given the three major etiological agents, the incidence per 100,000 population in 2011 amounted to 0.5, 0.45 and 0.03 for *N. menigitidis, S. pneumoniae* and *H. influenzae,* respectively (3). The prognosis is also serious and is dependent on etiological agent, patient's age, coexisting diseases and the quickness of introducing appropriate treatment (4). The treatment effectiveness depends not only on early diagnosis of disease but also on suspicion or identification of etiological agent and possibly the quickest application of antibiotic and supplementary treatment (1). Taking into account the serious course of the disease, high mortality and possibility of early complications occurrence, the treatment should be provided in the first phase of the disease and on the intensive care unit of infectious diseases (5, 6).

ANTIBIOTIC TREATMENT OF MENINGITIS

The antibiotic treatment is of significance in the therapy of bacterial meningitis. Due to the fact that the disease is life-threatening, the decision of applying antibiotics after diagnosing or suspecting the meningitis should be as quick as possible. The empiric antibiotic therapy should be introduced after collecting the sample of cerebrospinal fluid and/or blood for laboratory test (2). In the case where the imaging examination of CNS is required before lumbar puncture, the first dose of antibiotic should be administered prior to radiological examination. However, prior to administration of

antibiotic, the collection of blood sample for culture is recommended, especially if invasive meningococcal or pneumococcal disease is suspected (7). According to the recommendations, the antibiotic therapy should be started within 60 minutes after patient's admission to hospital and it should not exceed 90-120 minutes (4). Each delay in antibiotic treatment commencement deteriorates the prognosis. According to the Danish researchers, the delay in antibiotic treatment of one hour increases the risk of complications of 30% (8). The appropriate selection of antibiotic determines the success of therapy. The basic rule of antibiotic treatment, i.e. selection of antibiotic on a basis of antibiogram of isolated pathogen, is not always practicable in the case of bacterial meningitis. The major reason which precludes from introducing the targeted antibiotic treatment is negative test result of CSF culture (9). The cerebrospinal fluid is a very specific material for microbiological diagnostics because the mistakes made during its collecting have negative effects on test result. Thus, the quick transport of material to the laboratory, storage of collected CSF samples in the temperature of circa 37^0C and collecting the material to proper, heated growth medium at patient's bed are of significance in the CSF diagnostics. The successive factor delaying the implementation of targeted therapy is the waiting time for test result which includes isolation time, identification of etiological agent and determination of drug-sensitivity. The average time of bacteriological diagnostics ranges from 24 to 72 hours. This long period of time results in the fact that the physician is forced to introduce empiric antibiotic therapy in the treatment of bacterial meningitis (10).

EMPIRIC ANTIBIOTIC THERAPY

The empiric antibiotic therapy consists in estimating the probable etiological factors depending on particular clinical situation and selection of antibiotic/ chemioterapeutic agent of possibly the best antimicrobial spectrum. In the empiric therapy of bacterial meningitis, three significant elements may be distinguished. If these elements are met, the treatment should be effective.

I. During the selection of antibiotic therapy, after diagnosis establishing, the following should be taking into account: :
- patient's age
- environmental epidemiological data
- coexisting diseases - alcoholism, cancers, immunodeficiency, diabetes etc.
- community and health-care acquired infection – the increase of multiresistant strains of bacteria is observed, both hospital and community strains. The example could be the infection caused by pneumococci resistant to penicillin and III cephalosporin, increase of prevalence of *N. meningitidis* resistant to penicillin and multiresistance of Gram-negative coccobacilli
- neurosurgical procedures, the presence of ventricular drain, brain injuries are the reason of *Staphylococcus* increase, including methicillin-resistant

The analysis of the aforesaid data enables to determine the suspected etiological agent and the selection of optimal treatment scheme. In the treatment of bacterial meningitis the possibly lowest number of antibiotics should be employed. The ideal solution would be to administer one drug covering with its spectrum all suspected etiological agents. Multidrug schemes contribute to the selection of resistant strains of bacteria and raise the risk of drug side-effects occurrence (11).

II. Direct bacterioscopy of CSF is indispensable and valuable element in the diagnostics of bacterial meningitis. The staining of specimen of CSF by using Grahm's metod, enables to determine the type of bacteria - Gram-positive or Gram-negative and their morphology: cocci, coccobacilli. This data enables to potential modification of empiric therapy (12, 13).

III. Serologic and molecular examination of CSF enable to identify the type (serotype) of etiological agent which serves as the basis of antibiotic therapy directed to a given pathogen (2, 14). The examples of empiric therapy schemes are presented in Table I.

ANTIMICROBIAL DRUGS IN CNS INFECTIONS

The most important aspect in the treatment of bacterial meningitis is quick introducing of empiric antibiotic therapy, immediately after collecting the material to microbiological examinations. The valid element in the selection of antibiotic/ chemioterapeutic agent is the knowledge on drug properties regarding the transmission via the blood-cerebrospinal fluid barrier. The antimicrobial effectiveness of a drug depends largely on achieved concentration of antibiotic in CSF (15). The factors which have an effect on transmission of a drug via blood-CSF barrier and maximum antimicrobial effectiveness are as follows:

- farmacokinetics properties of antibiotic/ chemioterapeutic agent – more effective transmission ensure: low molecular mass, peptide bond, good solubility in lipids, low ionization in physiological pH
- inflammation intensification – the higher inflammatory process, the better transmission to the subarachnoid cavity
- characteristics of bacterial meningitis – the negative effects have: high protein concentration, high bacteria density

Table I. Empiric antibiotic regimens purulent meningitis, depending on the estimated risk factors and other variables that affect the choice of treatment.

Risk factor	Etiological agent	Empiric therapy scheme
Patient's age to 1 month old	*S.agalactiae; E.coli; L.monocytogenes*; Gram-negative intestinal coccobacilli	ampicilin + cefotaxime or ampicilin + aminoglicosyde
1 month - 5 y.o.	*N.meningitidis; S.pneumoniae;* *H.influenzae*	ceftriaxone + vankomycin
Children from 5 y.o. and adults to 50 y.o.	*N.meningitidis; S.pneumoniae*	ceftriaxone + vankomycin
> 50 rż	*S.pneumoniae; N.meningitidis;* *L. monocytogenes*	ampicilin + ceftriaxone + vankomycin
Immunodeficiency, cancer, alkoholism	*L.monocytogenes;* Gram-negative intestinal coccobacilli;	ampicilin + ceftriaxone + vankomycin
Neurosurgical procedure; brain injury	*S.pneumoniae; S.aureus*; pałeczki Gram-negative intestinal coccobacilli; *P.aeruginosa*	cefepime + vankomycin or meropenem + vankomycin
Infection of ventriculo-peritoneal valve	*S.aureus*; *Staphylococcus* coagulase-negative; Gram-negative intestinal coccobacilli	cefepime + vankomycin or meropenem + vankomycin
Nosocomial infection	Multiresistant Gram-negative coccobacilli; methicillin resistant staphylococci	meropenem + vankomycin
Allergy to penicilin	*S.pneumoniae; N.meningitidis;* *H.influenzae* *L.monocytogenes*	meropenem + vankomycin or moxifloxacin co-trimoxazole or meropenem
Results of Gram staining		
Cocci (diplococcii) Gram-negative	*N.meningitidis*	ceftriaxone or cefotaxime
Cocci (diplococcii) Gram-positive	*S.pneumoniae*	ceftriaxone + vankomycin
Coccobacilli Gram-positive	*L.monocytogenes*	ampicilin + aminoglicosyde
Coccobacilli Gram-negative	*H.influenzae*; Gram-negative intestinal coccobacilli; Gram-negative non-fermenting coccobacilli	cefepime + aminoglicosyde

- the antibiotics ability to achieve concentration in CSF significantly exceeding minimal inhibitory concentration (MIC) - beta-lactams
- administration of antibiotics of bactericidal properties
- administration of drug in maximum permissible doses and continuing of such dosage scheme in the course of treatment
- intravenous route of administration (15)

In special clinical situations, the intraspinal and intraventicular routes of drug administration may be applied, e.g. after neurosurgical procedures or in patients with transurethral ablation of valves in infections caused by multiresistant strains of *Staphylococcus aureus* or Gram-negative non-fermenting coccobacilli. In the intraspinal or intraventicular treatment, the most frequently used are vancomycin, aminoglycosides or colistin. The daily dose for the adult in intraventicular treatment is 30 mg, 4-8 mg, 10-20 mg and 10 mg for amikacin, gentamicin, vancomycin and colistin (11, 15,16). The recommended dosage of antimicrobial drugs used in bacterial meningitis was presented in Table II. Among the groups of antibiotics, chemioterapeutic agents which are well-known since many years and new antimicrobial drugs which have been introduced recently administered in the course of bacterial meningitis are used beta-lactams, including penicillin, cephalosporins, monobactams, carbapenems and inhibitors of beta-lactams. Despite the fact that they do not are fully transmitted via blood-CSF barrier, they achieve significantly higher concentration compared to MIC for the majority of pathogens causing meningitis. The ability to penetrate increases significantly in the inflammation process. Thus, the antibiotics of this group are the basic drugs applied in the treatment of such infections (15, 17).

- Natural penicilins – benzylpenicillin (penicilin G) – the therapeutic concentration in CSF is achieved with the daily dose of 24 million units and higher and the dosage of 4 - 6 times a day. Nowadays, penicillin is not recommended as the antibiotic of the first-line empiric therapy, which results from the increasing

Table II. The recommended dosage of antibiotics (chemotherapy) in the treatment of purulent meningitis.

Drug	Route of administration	Dosage (in adults) / 24h	Dosage (in children) / 24h
Penicilin G	intravenous	4 x 6 mln units	4 x 75 thosuand units/kg
Ampicilin	intravenous	6 x 2 g	6 x 50 mg/kg
Ceftriaxone	intravenous	2 x 2 g	1 x 100 mg/kg
Cefotaksime	intravenous	4 x 3 g	4 x 50 mg/kg
Ceftazidime	intravenous	3 x 2 g	3 x 50 mg/kg
Cefepime	intravenous	3 x 2 g	3 x 50 mg/kg
Meropenem	intravenous	3 x 2 g	3 x 40 mg/kg
Aztreonam	intravenous	3 x 2 g	3 x 50 mg/kg
Amikacin	intravenous	3 x 5 mg/kg	3 x 5 mg/kg
Amikacin	intraspinal	1 x 0,02 g	
Gentamicin	intravenous	3 x 2,5 mg/kg	3 x 2,5 mg/kg
Vankomycin	intravenous	2 x 1 g	4 x 15 mg/kg
Vankomycin	intraspinal	1 x 0,01 – 0,02 g	
Ciprofloksacin	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
Metronidazole	intravenous	3 x 0,5 g	3 x 10 mg/kg
Rifampicin	intravenous	1 x 0,6 g	1 x 10-20 mg/kg
Colistin	intraspinal	3 x 2-3 million units	-
Co-trimoxazole	intravenous	4 x 5 mg/kg (calculation for trimethoprim)	4 x 5mg/kg (calculation for trimethoprim)

resistance to this drug, especially in pneumococci (16). The indications too use penicilin G are as follows infections caused by meningococci, pneumococci, group B streptococci and *Listeria monocytogenes,* of confirmed sensitiveness to this drug.

- Ampicilin – in CSF achieves approximately 15% concentration in serum; the major indications are the infections of *Listeria monocytogenes* etiology; the greater bactericidal effect is obtained while using combined therapy with aminoglycosides (15, 18)
- Cephalosporins of 3rd generation – due to the extended spectrum of activity in relation to Gram-positive and Gram-negative bacteria causing the bacterial meningitis, they are the first-line antibiotics in the empiric therapy. Among the numerous cephalosporins of 3rd generation, the usage of ceftriaxone or cefotaxime is recommended (19). Cefotaxime is especially recommended in bacterial meningitis in children as it is characterized by lower level of protein bond and lower risk of hiperbilirubinemia than in the case of ceftriaxone (15). The lack of improvement after introducing of ceftriaxone or cefotaxime may indicate the infections caused by Gram-negative coccobacilli which demonstrate the ESβL resistance (β-lactams of widened spectrum of activity), AMPC (β-lactams of AmpC type), MBL (metalo-β-lactams) or KPC (carbapenem of KPC type), infection caused by bacteria naturally resistant to these antibiotics: *L.monocytogenes*, *Staphylococcus spp*. or *Enterococcus spp.* and pneumococci resistant to penicillin and ceftriaxone (20). Ceftriaxone is the most active antibiotic among cephalosporins of 3rd generation in relation to the following bacteria: *Haemophilus influenzae* and *Neisseria meningitidis*. In the case of confirmed meningitis of *Pseudomonas aeruginosa* etiology, the antibiotic of choice is ceftazidime (15).
- Cephalosporins of 4th generation – cefepime is characterized by the similar spectrum of activity as the cephalosporins of 3rd generation and may be employed in the treatment of bacterial meningititis (21).
- Monobactams – aztreonam is mainly used in the targeted therapy of meningitis of *H.influenzae* or *P.aerugionosa* etiology. Is is transmitted well via blood-CSF barrier and achieves in CSF from 3 to 52% of concentration in blood (15).
- Carbapenems – in this group of antibiotics, only meropenem is recommended as the usage of imipenem raises the risk of tremor occurrence (22). Meropenem is well transmitted via blond-CSF barrier and has wide spectrum of activity – generally it has an effect on the majority of pathogens caused bacterial meningitis (15).

- Glycopeptides – from the available antibiotics of this group, the only used medicine in the treatment of bacterial meningitis is vancomycin. Teicoplanin does not penetrate the blood-CSF barrier (15). Vancomycin should be used in targeted therapy. However, the usage of vancomycin in empiric therapy should be justified with the strong epidemiological rationale, i.e. known risk factors indicating the infection of *Staphylococcus*, observed high percentage of MRSA

strains or pneumococci resistant to penicillin and cephalosporins. Due to the fact that vancomycin poorly penetrates to CSF should be administered together with beta-lactams (15, 23).

- Fluoroquinolones – given the observed phenomenon of increasing resistance to quinolones of 2nd generation, they are not recommended in empiric therapy as well as in monotherapy. Moxifloxacin should be the drug of choice. It penetrates well to the CSF and achieves approximately 50% of concentration in blood. It is also of high activity in relation to Gram-positive cocci, including *S. pneumoniae* resistant to penicilin (1, 24). In Poland, moxifloxacin is not registered in the form to be administered intravenously.
- Aminoglycosides – antibiotics penetrating to CSF only in the inflammatory process; thus, they are used conditionally in the treatment of bacterial meningitis. It results from the fact that they poorly penetrate via lipid barriers, demonstrate poor activity in the environment of fluid - low pH and because of the relatively anaerobic conditions. To achieve the appropriate concentration in CSF, it is necessary to apply large doses, which raises the risk of side-effects occurrence. Antibiotics of this group should be only employed in the targeted therapy and together with the beta-lactams or glycopeptides (15).
- Rifampicin – because of the good lipophilicity it may be used as the second-line antibiotic in combined therapy with vancomycin in the treatment of bacterial meningitis caused by MRSA strains. In the case of *S. pneumoniae* infection, rifampicin may be added to vancomycin as the synergistic activity is observed (25).
- Sulfonamides – co-trimoxazole achieves in CSF approximately 40-50% concentration in serum and is used as a second-line drug in the targeted therapy of infections caused by MRSA strains (15).
- Derivatives of nitroimidazole – metronidazole in CSF achieves the concentration similar to the one observed in serum. This chemioterapeutic agent is used in the meningitis or cerebral abscess caused by anaerobic bacteria (15).
- Oxazolidinones – antibiotics of this group demonstrate activity in relation to multiresistant strains of *S. pneumoniae*, enterococci resistant to vancomycin and *Staphylococcus* resistant to methicillin and vancomycin. Linezolid in CSF achieves approximately 60% concentration in blood. It is recommended in the treatment of meningitis caused by *Staphylococcus* strains of decreased sensitiveness or resistant to vancomycin (VISA / VRSA) or enterococci resistant to vancomycin (VRE) (1, 26).

Table III. Proposed treatment regimens purulent meningitis, depending on the resistance pattern isolated etiological factors

Etiological agent	Proposed treatment	Alternative therapy
S. pneumoniae resistant to penicylin	penicilin G	ceftriaxone; cefotaksime
decreased sensitivity to penicilin	ceftriaxone or cefotaksime	meropenem; cefepime
resistant to penicilin (PRSP)	ceftriaxone or cefotaksime + vancomicin	moxifloxacin; moxifloxacin + rifampicin
N. meningitidis sensitive to penicilin	penicylina G	ceftriaxone or cefotaksime
decreased sensitivity to penicilin	ceftriaxone or cefotaksime	meropenem; moxifloxacin
H. influenzae β-lactames - negative	ampicilin	ceftriaxone; cefotaksime cefepime; aztreonam
β-lactames - positive	ceftriaxone or cefotaksime	cefepime; aztreonam; fluoroquinolones
S. aureus; staphylococii koagulaso-negative methicillin resistant (MRSA / MRCNS)	vancomicin	linezolid; co-trimoxazole or rifampicin in combined therapy
obniżona wrażliwość or resistant to vancomicin (VISA / VRSA)	linezolid	co-trimoxazole or rifampicin in combined therapy
Enterococcus spp resistant to vancomicin (VRE)	linezolid	
Gram-negative coccobacilli ESβL	meropenem	ciprofloxacin; moxifloxacin; aminoglicosydes
Gram-negative coccobacilli AMPC	meropenem	cefepime; aminoglicosydes; fluoroquinolones; aminoglicosydes
Gram-negative coccobacilli MBL	colistin	aztreoname; fluoroquinolones; aminoglicosydes
Gram-negative coccobacilli KPC	colistin	

The antibiotics which are not used in the treatment of bacterial meningitis due to their unfavourable pharmacokinetic and pharmadynamic properties are: macrolides, lincosamides, tetracyclines, tigecycline, ketolides and colistin (15). Colistin may be used conditionally in the intraventicular therapy in the case of infections caused by multiresistant strains of non-fermenting coccobacilli (27). The empiric antibiotic therapy should be always verified after identification of etiological agent from CSF or blood and selected on the basis of antibiogram results. The phenomenon of increasing resistance to antibiotic, which is observed recently, compels to frequent modification of standard schemes of bacterial meningitis treatment. The therapeutic options for possible mechanism of resistance for pathogens causing the bacterial meningitis were presented in Table III.

THE PERIOD OF ANTIBIOTIC THERAPY APPLICATION

The appropriate time of antibiotic treatment application constitutes a very important element affecting the bacterial meningitis therapy effectiveness. The duration of antimicrobial treatment depends on clinical course of the disease and etiological agent. The antibiotic therapy should last minimally from 7 to 10 days. After the temperature disappears, the therapy should be continued for the next 5 days. Taking into account the isolated pathogen, the minimal therapy duration amounts to 7 days for *Neisseria meningitidis and Heamophilus influenzae* infection, 14 days for *Streptococcus pneumoniae, Streptococcus agalactiae* and *Staphylococcus aureus* (removal of infected valve) infection and 21 days for *Listeria monocytogenes*, *Pseudomonas aeruginosa* infection as well as the infection caused by Gram-negative intestinal cocci (2, 11).

The treatment of bacterial meningitis is multidimensional and despite administration of antibiotics includes also the anti-inflammatory drugs, drugs for reducing the water-electrolytes imbalance, intracranial pressure and supportive care depending on the emerging complications.

In the supportive treatment, which is to reduce the inflammatory process, the administration of first dose of dexamethasone in approximately 15 - 20 minutes prior to or together with the first dose of antibiotic is recommended. It should be continued for 2-4 days (10 mg per every 6 hours). The aim of dexamethasone administration is the reduction of inflammation, associated with the bactericidal antibiotics application and release of proinflammatory elements of bacteria. Cerebral edema and increase of intracranial pressure may be immediately reduced by head elevation at 30-45^0, usage of mannitol and furosemide, lowering of body temperature, hyperventilation (in the case of respiratory equipment usage). The anticonvulsants treatment is necessary to prevent from damages caused by the ischemia of CNS, especially the sensitive temporal area, cerebellum and the hill. The anticoagulant prophylaxis is also indispensable, usage of proton-pump inhibitors and in the case of respiratory failure the oxygen therapy, replacement or supplementary breathing is necessary.

The treatment of water-electrolytes accompanied by hyponatremia and normovolemia is an important element of therapy as the duration of hyponatremia correlates with neurological complications. It is indispensable to sustain the blood pressure within normal limits to prevent from the consequences of brain hypoperfusion (1, 12, 28). The patient should stay at bed in the acute phase of the disease and should be also provided with physical therapy and proper nourishment.

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