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CLİNİCAL DİAGNOSİS AND TREATMENT OF ACUTE BACTERİAL MENİNGİTİS: A COMPREHENSİVE LİTERATURE REVİEW

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SUMMARY

Acute bacterial meningitis (ABM) is still a substantial cause of high mortality and severe neurological morbidity during recent decades, despite the advances in diagnosis and antimicrobial therapy.*Streptococcus pneumonia* (pneumococci), *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis* (meningococci) are the most commonly isolated organisms in the etiology. The entity is often difficult to recognize, for the "classic" constellation of fever, neck stiffness, headache, and obtundation are noted in less than half of the cases diagnosed with ABM. Diagnostic procedures include lumbar puncture, blood cultures, White blood cell count, lactate, glucose and procalcitonin, and CSF analyses (urine reagent strips, glucose, protein, lactate and microscopic examination).Expedient commencement of appropriate antibiotic therapy, airway support, maintenance of proper oxygenation, dexamethasone, seizure control and fluid resuscitation titrated and individualized for each clinical scenario comprise the ideal treatment conditions for the patient. This article reviews the epidemiology, clinical presentation, diagnosis, and treatment of ABM following recent advances and new literature findings to update the primary care and emergency physician in the acute setting.

KEYWORDS: Acute bacterial meningitis, meningitis, central nervous system infection, diagnosis, treatment, lumbar puncture.

I. Definitions, characteristics and outcome predictions: Acute bacterial meningitis (ABM) is described as an acute inflammation of leptomeningeal membranes inflicted by bacteria.[1]

The entity is divided into septic and aseptic groups. Adult ABM resultfrom a potentially wide range of bacterial and viral pathogens. Inflammation of the pia, arachnoid, and sometimes dura has diverse causes and presentations.[2] Central nervous system infections also comprise intracranial abscess, neurocysticercosis, or lead to cerebrovascular sequelae such as the diffuse microvascular occlusion of 'cerebral malaria' or a vasculitis complicating ABM or encephalitis.[3,4] Morbidity and mortality in bacterial meningitides are higher than viral meningitis, despite easier spread is the rule in the latter.

In the meningococcal disease, pathogen transmission happens for respiratory route (droplets) and clinically can lead to meningitis and sepsis (meningococcemia).[5] In Brazil, meningococcemia has been cited as the infectious condition most rapidly fatal to a human being, with 92% of deaths reported within the first two days of hospitalization.[6]

Okike et al. investigated trends in incidence and causes of bacterial, mycobacterial, and fungal ABM (n = 6286) in England within nine years.[7] Most cases with ABM (89%) were caused by Gram-positive or Gram-negative bacteria. Seasonal variation was noted for ABM, with a peak in the winter and nadir in the summer. Fungi (6%) and mycobacteria (5%) were less common causes of ABM whose incidence was stable in the year.

Despite the availability of effective antibiotics, vaccination programmes and skilled acute-care facilities, there is still a significant mortality and morbidity from ABM.[3] The mortality of ABM is given around 11% to 17% in the developed countries[8,9], while the tollexceeds 50% in resource-poor countries.[10,11] Neurological sequelae in survivors are found in up to 50% of the patients, with impaired hearing and neuropsychological deficits being the most common.[12]

A. Signs and symptoms: ABM is mostly difficult to diagnose, because only half of the patients are

admitted with the "classical" presentation with a stiffneck, altered mental status and high core temperature. Fever is seen in 71% of the adult patients, followed by irritability in 60%. Nuchal rigidity was reportedly present in 88% on initial examination and persisted for more than seven days in some patients despite overall improvement.[13] In an Iranian study, the most common signs and symptoms were headache (40%), fever (37%), nausea and vomiting (33%) and stiff neck (20%).[14] Headache with fever and stiff neck were observed inonlyone-sixth of cases. Other signs included reduced loss of consciousness, photophobia and positive Kernig and Brudzinski signs. The "classic triad" was noted to occur more commonly in the elderly with pneumococcal compared with meningococcal meningitis (58 versus 27%).[15]

In a study of 696 patients with community-acquired ABM, cerebral infarction occurred in one-fourth of episodes and in one-third of patients with pneumococcal infections.[16]

Wall et al. derived from a logistic regression model of a discovery database of adult Malawian patients with ABM.[10] Five variables were found to be strongly associated with poor outcome (CSF culture positivity, CSF white blood cell count, hemoglobin, Glasgow Coma Scale, and pulse rate), and were used in the derivation of the Malawi Adult Meningitis Score (MAMS) nomogram. The area under the curve was 0.76 in the diagnoss of ABM. In an eight-year cohort study from Netherland, predictors of unfavourable outcome in adult ABM were found as follows: advanced age, absence of otitis or sinusitis, alcoholism, tachycardia, lower score on the Glasgow Coma Scale, cranial nerve palsy, a CSF white-cell count lower than 1000 cells per μL, a positive blood culture, and a high serum CRP concentration.[9]

The recommended approach to the patient with suspected ABM encompasses the clinical, laboratory and radiodiagnostic examinations in order to verify the diagnosis, concurrent with expedient administration of oxygen, fluids, antibiotics, and corticosteroids in certain conditions.

I. B. Risk factors for ABM: Bagheri-Nesami et al. researched on types and risk factors of ABM in Iran within six years.[14] The majority of risk factors in patients were head trauma, upper respiratory infection, and drug addiction, craniotomy, impaired renal function, and diabetes.

This article reviews the epidemiology, clinical presentation, diagnosis, and treatment of ABM following recent advances and new literature findings to update the primary care and emergency physician in the acute setting.

II. Microorganisms in ABM

The pathogen microorganisms mostly detected in patients with ABM are: *Streptococcus pneumonia* (pneumococci), *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis* (meningococci). Vaccines and their implementation are known to have an impact on theepidemiology of bacterial pathogens. Also, the prevalence and etiologies of ABM vary in different geographical areas.[17] The introduction of conjugate polysaccharide vaccines against S. pneumoniae, Hib, and N. meningitidis during the 1980s and 1990s has substantially changed the epidemiology of ABM.

In Netherlands, the numbers changed with a decreased incidence of meningitis caused by Hib and a boost of meningitis caused by penicillin- and cephalosporin-resistant strains of Streptococcus pneumoniae after vaccination programs.[18] Likewise, immunization program with 13-valent pneumococcal conjugate vaccines (PCV) launched in Nicaragua in 2010 was proven to have an impact on the mortality attributed to Pneumonia and ABM.[19] There was a significant reduction in ABM in the vaccine period in the population as a whole (Adjusted incidence rate = 0.24) and among those aged 5 to 49 years.

Brouwer and van de Beek postulated that community-acquired ABM is most commonly caused by the Streptococcus pneumoniae and Neisseria meningitidis, and is often complicated by hearing loss, cerebrovascular complications, and seizures.[20]

In a recent study, Houri et al. reported that *Streptococcus pneumoniae* (30% [I2 = 56% p < 0.01]), *Hib* (15% [I2 = 82.75% p<0.001]), coagulase negative staphylococci (CoNS) (14% [I2 = 60.5% p < 0.06]), and meningococci (13% [I2 = 74.16% p < 0.001]) were the most common cause of ABM among meningitis cases in Iran.[21]

Many cases of ABM in developing countries have been caused by E. coli (mostly K1 strains) and other enterobacteria.[22] Staphylococcus aureus is also a leading cause, which mostlyinflicts children and adults undergoing shunt operations.[23] Frequency of post-operative ABM associated with shunts isaround 10%.[24] The Centers for Disease Control and Prevention (CDC) pointed out that data from 2005 showed that central nervous system involvement was found in one out of every 16 extrapulmonary tuberculosis cases.[25] Also, non-typable H. influenzae (NTHi), is a prominent cause of acute otitis media[26], which may be complicated with meningitis.[27]

III. Diagnostic advances, biomarkers for identification

Routine blood examinations, such as the WBC counts, neutrophil proportions and platelet counts, are most commonly used to diagnose ABM. To recognize or rule outABMone must perform low-threshold cerebrospinal fluid (CSF) examination with a suspicion ofABM.[18] The

entity can be recognized with the findings in the analysis of the CSF following a lumbar puncture (LP) which is mandatory in any patient in whom ABM is in the list of differential diagnoses, although the procedure can be hazardous in some situations. These are a positive Gram stain/culture of the pathogen with CSF pleocytosis and an elevated CSF lactate level.[28,29]

There is usually a predominance of neutrophils (80 to 95%) in the CSF, but a predominance of lymphocytescan occur.[30,31] Normal or mildly increased CSF WBC counts occur in one-tenth of patients with ABM and are associated with a worse outcome.[30] Gram's staining of CSF renders expedient recognition of the culprit microorganism (sensitivity, 60 to 90%; specificity, ≥97%).

New molecular techniques for detecting bacteria in the CSF by polymerase chain reaction (PCR) can be beneficial in detection of those with negative CSF cultures; such tools have high sensitivity and specificity.[32]

A recent systematic review from Iran disclosed that laboratory features in CSF-culture positive samples were characterized by increased CSF leukocytes counts (753.000 cells/mm3), increased CSF protein (415.5 mg/dl), decreased CSF glucose (30.4 mg/dl).[21] Diagnostic procedures other than routine chemistry and microbiological analyses include LP and blood culture to allow PCR-based detection of the pathogens and even multi-locus sequence typing (MLST) of CSF isolates, yielding genetic signatures of bacterial isolates, coupled with the more traditional analysis of isolates via bacterial culture techniques.[33] It was found that routine use of a multiplex real time-PCR assay testing for S. pneumoniae, N. meningitidis and Hib increased thediagnostic yield for bacterial meningitis by 52%, 85% and 20%, respectively.[34]

Arda et al. reviewed the Turkish literature of acute adult purulent meningitis.[35] Data for 2,408 patients with a diagnosis of acute purulent meningitis were obtained from 30 reports. Overall mortality was 17.6%. In total, nearly 80% had fever (>38 degrees C), 88.2% headache, 89.8% stiffness of the neck, and 82.7% leukocytosis (>10,000/mm3). CSF culture yielded a pathogen in 38.6% patients. The most common pathogen was Streptococcus pneumoniae, followed by Neisseria meningitidis and Staphylococcus aureus.

A recent report pointed out that a point-of-care glucose measurement in the blood and CSF could facilitate rapid detection of ABM.[36] (Table 1). The optimal cut-off of the CSF/blood glucose ratio calculated from a bedside glucometer was 0.46, with a sensitivity of 94.1%, a specificity of 91%, and a positive likelihood ratio of 10. This cheap point-of-care method has the potential to speed up the diagnostic process of patients with ABM.

Lactic acid levels in CSF have been implicated as a valuable diagnostic tool in many reports and in different scenarios in this context. Zhang et al. indicated that this marker has achieved rather high diagnostic accuracy (AUC_{-ROC}=0.891) in patients with post-neurosurgical bacterial meningitis.[37] Likewise, Muñoz-Gómez et al. postulated that if fewer than four of our diagnostic criteria were present, i.e. lactic acid levels above 6 nmol/L, marked CSF pleocytosis (>50 WBC/mm3), a positive CSF Gram stain or a positive CSF culture, extraventricular drain (EVD)- associated nosocomial meningitis was reliably ruledout.[38]

Serum procalcitonin (PCT) and CSF lactate were cited to be among the best discriminative parameters for the differential diagnosis of ABM and viral meningitis.[39] This study demonstrated that the most highly discriminative parameters for the differential diagnosis of ABM proved to be CSF lactate, with a sensitivity of 94%, a specificity of 92%, a negative predictive value of 99%, a positive predictive value of 82% at a diagnostic cut-off level of 3.8 mmol/L (AUC, 0.96), and serum PCT, with a sensitivity of 95%, a specificity of 100%, a negative predictive value of 100%, and a positive predictive value of 97% at a diagnostic cut-offlevel of 0.28 ng/ml (AUC, 0.99).

PCT-guided therapy was claimed to reduce antimicrobial consumption during a viral outbreak in meningitis fifteen years ago.[40] Two recent meta-analyses confirmed PCT's accuracy in differentiating viral from bacterial meningitis.[41,43] A recent meta-analysis recruited 2058 subjects and showed the test's sensitivity of 0.95, a specificity of 0.97, a positive likelihood ratio of 31.7, and a negative likelihood ratio of 0.06.[42] The diagnostic performance was even better when combined with CSF lactate. Serum PCT was found to be more sensitive and specific than CSF PCT. Again in a recent study, Kim et al. demonstrated that PCT was also helpful for prediction of poor outcome, monitoring, and for differentiating from tuberculous meningitis.[44]

A very recent meta-analysis has pointed out that urine reagent strips could provide a rapid and accurate tool to detect CSF pleocytosis, which, if negative, can be used to exclude diagnosis of ABM in settings without laboratory infrastructure.[45]

IV. Advances in Treatment

A focused and well-organized procedure in the emergency setting is necessary to achieve expedient treatment. In this context, antibiotics should be administered within 30 minutes after admission.[46] (Table 2).

Recently, "Goal Directed Therapy" (rapid antibiotics, airway support, oxygenation, seizure control and fluid resuscitation) for adult ABM was launched by Wall et al. in Malawi and was tested using a before/after design.[11] They concluded that Goal Directed Therapy in a

resource-constrained setting was associated with improved delivery of protocolised care, but outcome was unaffected. Successful outcome from ABM warrants management of the neurological complications of raised intracranial pressure, stroke, and seizure activity, while dealing with the pathogen microorganisms.

IV. A. Antibiotic therapy

The early use of appropriate antibiotic therapy is one of the important and explicit steps in the management of severe clinical presentations of ABM. In their multicentric study, Auburtin et al. reported that a door-to-antibiotic time of more than three hours independently confers a higher risk of death from meningitis.[47] They noted that isolation of penicillin-nonsusceptible strains and a delay in antibiotic treatment following admission were predictors of mortality among patients with pneumococcal meningitis, regardless of severity at the time of ICU admission.

Initial empiric treatment in a patient suspected to have meningococcal meningitis may consist of a third generation cephalosporin (ceftriaxone or cefotaxime).[5,48,49] Intravenous route is the preferred route because of vomiting and also rapid commencement of the effect in the circulation. The recommended dose of ceftriaxone in ABM is 50 mg/kg every 12 h (maximum dose of 4 g/d). Cefotaxime should be administered intravenously, at the dose of 50 mg/kg every 4 or 6 h (maximum dose of 12 mg/d).[5,50]

The recommended dose of crystalline penicillin G is 300 000 U.I./kg to 500 000 U.I./kg, in 4 h intervals in patients with high index of suspicionfor community-acquired ABM (maximum dose of 24 million units/d).[5,50] Although debatable, antimicrobial treatment is usually maintained for seven days[51], and individualized according to the clinical response.

Paul et al. conducted a non-inferiority trial in severe infections with meticillin-resistant *Staphylococcus aureus* (MRSA) and reported that trimethoprim-sulfamethoxazole did not achieve non-inferiority to vancomycin in the treatment of severe MRSA infections.[52] The difference was particularly marked for patients with bacteremia. Thus vancomycin is the current treatment of choice in this specific population.

IV. B. Dexamethasone: The outcome of ABM has been linked to the severity of inflammation in the subarachnoid spacein experimental studies, and corticosteroids are thought toalleviatethis inflammatory response. Some authors recommend the use of low dose steroids (hydrocortisone 200 mg/d by intravenous route) in adults with septic shock who do not respond adequately to intravenous fluid replacement and the use of vasoactive amines.[53] Dexamethasone is usually administered to adults and children with ABM while awaiting culture (blood and/or CSF) results.[51]

In the Dutch Municipal Population Register, 301 patients with ABM were randomly assigned to receive adjunctive dexamethasone or placebo.[8] The survival benefit from adjunctive dexamethasone therapy (mortality rates 22% vs. 33%) is obtained in the acute phase of the disease and remains for years. In another broad-based Dutch study, Bijlsma et al reported that adjunctive dexamethasone treatment was associated with substantially improved outcome.[9] The multivariable adjusted odds ratio of dexamethasone treatment for unfavourable outcome was 0·54. On the other hand, Van de Beek et al conducted a meta-analysis and reported that adjunctive dexamethasone in the treatment of ABM does not seem to significantly reduce death or neurological disability.[54] This is in contrast with the findings of the meta-analysis by Assiri et al. who reported that the adjunctive administration of corticosteroids is beneficial in the treatment of adolescents and adults with ABM in patient populations similar to those seen in high-income countries and in areas with a low prevalence of HIV infection.[55]

In their Cochrane review, Brouwer et al. reported that in high-income countries, corticosteroids reduced severe hearing loss (RR 0.51), any hearing loss (RR 0.58) and short-term neurological sequelae (RR 0.64).[56] There was no beneficial effect of corticosteroid therapy in low-income countries. Corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce overall mortality.

Prasad et al. published a systematic review on the efficacy of adjuvant corticosteroids and reported that the beneficial effect varied between high- and low-income countries suggesting greater mortality reduction in high-income countries (RR 0.74) than in lowincome countries (RR 0.87) and a beneficial effect on severe hearing loss in high-income countries (RR 0.32), whereas, sparse data in low-income countries (RR 1.04).[57]

IV. C. Osmotic therapies /Glycerol: Osmotic therapies have been proposed as an adjunct to improve mortality and morbidity from ABM. In this context, glycerol decreases the increased intracranial pressure during meningitis. In 2014, Wall et al. reported that although glycerol may have little or no effect on death in people with ABM (RR 1.09, 1091 participants, four trials, lowquality evidence); or on death and neurological disability combined (RR 1.04), it may reduce the risk of subsequent deafness (RR 0.60, 741 participants, four trials, low-quality evidence).[58]

Vaziri et al. conducted a meta-analysis on the effects of glycerol in ABM and concluded that oral glycerol compared to intravenous dexamethasone can be as successful as dexamethasone in reducing neurological complications of ABM such as deafness.[59] Blaser et al. examined the effects of glycerol in pneumococcal meningitis of infant rats and adult mice. They found no benefit of adjunctive glycerol in these models.[60] The

only osmotic diuretic to have undergone randomised evaluation is glycerol. Data from trials to date have not demonstrated benefit on death, but it may reduce deafness. Osmotic diuretics, including glycerol, should not be given to adults and children with ABM unless as part of carefully conducted randomised controlled trial.

Table 1: Diagnostic features of ABM in the emergency setting.

Test/examinations	Cut-off	Sensitivity (%)	Specificity (%)	Interpretation; pluses /minuses
Clinical findings				
-Fever (14)		51-71		*Low diagnostic yield, valuable if found in a constellation (*stiffneck, headache, altered mental status and fever)
-Neckstiffness		5	95	High specificity, means high power to diagnose ABM if positive
-Altered mental status/obtundation		50		*Low diagnostic yield, valuable if found in a constellation (*stiffneck, headache, altered mental status and fever)
-Headache		55		*Low diagnostic yield, valuable if found in a constellation (*stiff neck, headache, altered mental status and fever)
-Rash (for meningococcal meningitis) (61).		63	92	Highly specific for meningococcal disease, the rash was petechial in 89% of these.
Lab				
- White blood cell count (blood, 10^9/L) (37)	13.85	67	50	Cheap, easy, low accuracy
-Neutrophil % (blood) (37)	81.1	83	26	Cheap, easy, low accuracy although sensitivity is high.
Blood cultures		50-75		Invasive, should be drawn before any antibiotics are given.
Urine reagent strips (CSF) (45)		92	98	Invasive, cheap, point-of-care, does not need advanced laboratory infrastructure,
-lactate level (CSF, mmol/L) (37,61)	3.6 mmol/L or 35 mg/dL	76-93	87-96	Invasive, high specificity, means high power to diagnose ABM if positive
CSF/blood glucose ratio (36)	0.46	94	91	Invasive, high accuracy, means high power to rule out and diagnose ABM
-Procalcitonin (39,43,61)	0.5 mcg/L	95	97-100	High accuracy, means extreme power to rule out and diagnose ABM, diagnostic performance was even beter when combined with CSF lactate.
-Microscopic exam (CSF Gram stain) (3,28,30)		60 to 90	>97	High accuracy, invasive

Table 2: Treatment approach to ABM in the emergency setting.

Treatment	Indication	Dosage
Empiric antibiotic therapy,	All patients with high index of suspicion for ABM	
Ceftriaxone **Cefotaxim**	Pneumococci, meningococci	50-100 mg/kg, IM/IV 2 gr daily
Vancomycin	Resistant to beta lactam, MRSA	15 mg/kg, 1 gr q12h
Ampicillin	Pneumococci, Listeria	50 mg/kg (max. 2 g) IV q4h
Benzylpenicillin	Pneumococci; Undifferentiated community-acquired ABM	1200 mg IV/IM
Fluid therapy	Diagnosis of infection, fluid replacement, dehydration	10-20 mL/kg or 500 mL, titrated to effect
Adjuvant corticosteroids	All patients with suspected ABM	0.15 mg/kg (maximum dose, 10 mg) IV q6h
Osmotic therapies (glycerol)	No clearly established benefit in adult ABM	50-100 ml/kg, q6h

V. CONCLUSİON

ABM is a life-threatening emergency that is still associated with high mortality and poor outcome. Despite improved health care, the disease is still associated with high mortality and poor neurological outcome, which has remained largely unaltered. Findings in blood and CSF analyses following a clinical index of suspicion lead to a high yield of diagnosis. Finally, early utilization of appropriate antibiotics, oxygenation, dexamethasone, seizure control and fluid resuscitation

titrated and individualized for each clinical scenario comprise the ideal treatment conditions for the patient.

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