Diagnosis and Management of Adult Bacterial Meningitis

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Abstract- The early use of appropriate antibiotic therapy is one of the important and explicit steps in the management of potentially fatal adult acute bacterial meningitis (ABM). Changing epidemiology of ABM, especially with regards to the change of the relative frequency of causative pathogens, has been noted in a serial of studies in Taiwan. This change may influence the choice of initial empiric antibiotic treament. In this review, the authors will discuss the epidemiologic trend, diagnosis and management of ABM in Taiwan. For a better understanding, the clinical and laboratory data of 204 adult ABM cases diagnosed at Chang Gung Memorial Hospital-Kaohsiung, collected over a period of 8 years (1999-2006), were included for analysis. This review may help first-line, primary-care neurologists have a better view on handling this critical central nervous system infection.

Key Words: Adult, Acute bacterial meningitis, Diagnosis, Epidemiologic trend, Management

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INTRODUCTION

Acute bacterial meningitis (ABM) in adults is a serious infectious disease of the central nervous system (CNS)[1,2]. Despite the availability of effective antibiotics and the advent of new antibiotics, adult ABM remains a disease of high mortality and morbidity. A delay in early appropriate antibiotic treatment has been associated with worse outcomes. For this critical issue, neurologists are often called on to "rule out" ABM, therefore, a dilemma exist for neurologists who need to accurately diagnose patients with ABM and then rapidly administer appropriate management (antbiotics, adjunctive steroid and/or neurosurgical procedures) for this potentially fatal disease.

In adult ABM patients, little is known about the exact timeframe between the initial onset of symptoms and first visit with a neurologist. Patients in a postneurosurgical state, in that they have had a preceding event such as a brain condition, may have overlapping signs and symptoms of meningitis and this results in a greater difficulty in making a proper ABM diagnosis. Meanwhile, although acute meningitis is usually caused by bacteria or viruses, some pathogens of chronic meningitis such as fungi may have similar clinical presentations. The following two cases are clinical examples of common and uncommon acute meningitis.

Case 1, a 38-year-old man, presented to the emer-

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gency room (ER) of Chang Gung Memorial Hospital-Kaohsiung with a chief complaint of headache, fever and vomiting for 5 days. His past history was unremarkable. Except for the presence of neck stiffness, all other neurologic examinations revealed normal results. Under the impression of acute meningitis, blood and cerebrospinal fluid (CSF) studies were performed and the results revealed peripheral leukocytosis (WBC 21.6 × 103/mm^3) and purulent CSF profile including WBC 1485/mm^3 (neutrophil 90%), glucose < 5 mg/dL, and total protein (TP) 714.3 mg/dL. Leptomeningeal enhcnacement was detected on brain magnetic resonance imaging (MRI) study and multiple liver abscesses were detected on both abdominal echo and computed tomogram (CT) study. Cultures of CSF, blood and pus aspirated from liver abscess grew *K. pneumoniae*. For these infectious problems, this patient received intravenous ceftriaxone (2 gm Q12 hr) therapy and a drainage for liver abscess.

Case 2, a 56-year-old man with diabetes mellitus (DM) and liver cirrhosis, present to the ER with a chief complaint of headache and fever for one day and altered consciousness for half day. Brain MRI study revealed leptomeningeal enhancement and hydrocephalus. CSF study showed leukocytosis (WBC 550/ mm^3), glucose 94 mg/dL and TP 75 mg/dL. A CSF cryptococcal antigen detection revealed a positive result (1:512). This patient was treated with amphotericin B and fluconazole.

For these clinical problems, this review article will focus on the diagnosis and management of adult ABM. Furthermore, the clinical data of 204 adult ABM cases, diagnosed at Chang Gung Memorial Hospital Kaohsiung, collected over a period of 8 years (1999-2006) were included for analysis. The clinical and laboratory data of these patients are shown in Tables 1-5.

IMPLICATED PATHOGENS

One of the important issues that the neurologists have to face is the changing epidemiologic trend of adult ABM in recent years[1-16]. This change may influence the choice of initial empiric antibiotic treatment[1] which is an important strategy for a successful treatment of adult ABM. The prevalence rate of implicated pathogens of ABM is influenced by several factors including age, preceding medical and/or surgical conditions, mode of contraction, geographic distribution, status of vaccination, and the time period of study. For example, *Hemophilius influenzae* type b has nearly been eliminated in many developed countries since routine childhood vaccination was initiated[17]. The same is true for both *Streptococcus pneumoniae* and *Neisseria meningitidis* infections in some regions of the world[18-21].

Table 1 shows the implicated pathogens of the 204 enrolled ABM cases. The listed relative frequency of implicated pathogens of adult ABM is quite different from those reported in western countries[1-5,22]. 185 of these 204 cases involved monomicrobial infection (Gram-negative infection 110, Gram-positive infection 75) and 19 mixed infections. The leading implicated Gram-negative and Gram-positive pathogens were *K. pneumoniae* and staphylococcal species, respectively. Among the implicated pathogens, *K. pneumoniae* is still the most common, accounting for 24.9% (46/185) of monomicrobial infection. This finding is consistent with previous studies of adult ABM in Taiwan[22-24]. Compared with other adult ABM cases, *K. pneumoniae* meningitis is usually a spontaneous, community-acquired infection and most of these cases involve DM and/or liver disease as the underlying conditions[1,22-25]. Concomitant septic metastatic infection is also common in this specific adult ABM in Taiwan[26] and usually requires a drainage procedure during the therapeutic course.

Acinetobacter (A.) spp., *Escherichia (E.) coli*, *Pseudomonas (P.) spp*. and *Enterobacter spp*. are the other freguent Gram-negative pathogens, accounting for 11.4% (21/185), 7.0% (13/185), 6.5% (12/185) and 3.8% (7/185), respectively for adult ABM of a monomicrobial infection. They are all frequent pathogens of ABM patients with a posneurosurgical state[1,27-33]. Our previous study[34] showed that *Acinetobacter* meningntis accounted for 3.3% of monomicrobial ABM, but its incidence has increased markedly and has replaced *Pseudomonas* ABM as the second most common Gram-negative ABM. The emergence of *Acinetobacter* infection and the frequent multiple antibiotic resistant feature of

Table 1. *Causative pathogens of 204 adult bacterial meningitis cases*

Gram-negative pathogens	Gram-positive pathogens	Mixed infection
Klebsiella pneumoniae (46)	*Coagulase-negative staphylococci* (24)	(19)
Acinetobacter species (21)	*Staphylococcus aureus* (20)	
Escherichia coli (13)	*Viridans streptococci* (8)	
Pseudomonas species (12)	*Streptococcus pneumonia* (7)	
Enterobacter species (7)	*Enterococcus species* (7)	
Proteus mirabilis (3)	*Others streptococci* (3)	
Neisseria meningitidis (2)	*Corybacterium species* (3)	
Salmonella species (2)	*Listeria monocytogenes* (2)	
Fusobacterium necleatum (1)	*Micrococcus* (1)	
Sphingomonas paucimobilis (1)		
Serratia marcescens (1)		
Citrobacter diversus (1)		

Acinetobacter strains such as the emergence of pan-drug resistant *A. baumannii* strain have resulted in increased therapeutic difficulty[28,29]. The emergence of 3rd- and 4th-generation cephalosporin-resistant strains in implicated *E. coli*, *Pseudomonas spp*. and *Enterobacter spp*. is also a therapeutic challenge of adult ABM[30-33]. Mixed infection accounted for 9.3% (19/204) of our study group. This type of infection is usually seen in patients with a postneurosurgical state[35] and its incidence did not change when compared with the incidence of mixed infections in our previous study[34].

With regards to the Gram-positive pathogens, Table 1 shows a marked increase in the incidence of staphylococcal infection and a decrease in the incidence of *Streptococcus pneumoniae* infection when compared with the data of our previous report[34]. *Staphylococcal spp*. accounted for 23.8% (44/185) of the implicated pathogens of the monomicrobial ABM. Adult staphylococcal infection is frequently noted in patients with a postneurosurgcial state, especially in those with an insertion of an intracranial device such as ventriculo-peritoneal shunt and extra-ventricular device[36-38]. The increase of staphylococcal infection can be explained by the increased number of patients with a post-neurosurgical state as their preceding event (Tables 2 and 3, 58.8%, 120/204). Most of the implicated staphylococcal strains of adult ABM are methicillin-resistant[36-38] and may also

Table 2. *Underlying conditions of 204 adult bacterial meningitis cases*

	Spontaneous form n = 84	Post-neurosurgical form n = 120
Diaetes mellitus	36	20
Liver disease	14	2
Alcoholism	14	4
Chronic otitis media	5	1
Intravenous drug abuser	5	0
End state renal disease	6	0
Systemic lupus erythematosis	1	1
Malignancy	6	10

Table 3. *Preceding neurosurgical conditions of 120 acute bacterial meningitis cases*

Postneurosurgical conditions	Case number
s/p V- P shunt	32
s/p EVD	32
s/p craniectomy	19
Spontaneous ICH s/p craniotomy s/p EVD	6
Head trauma s/p craniotomy	6
Head trauma	28
Traumatic ICH s/p EVD, craniectomy, V-P shunt	25

s/p: post-state; V-P: ventriculoperitoneal; EVD: external ventricular device; ICH: intracerebral hemorrhage

cause a therapeutic challenge in the choice of initial empiric antibiotics in adult patients with postneurosurgical meningitis. All of these findings may disclose that despite the in-hospital isolation procedures for patients with methicillin-resistant staphylococcal infection, the increasing incidence in recent years suggests the evidence of rapid dissemination of staphylococcal strains with classic oxacillin resistance, especially in patients with nosocomial infection, in Taiwan[37-41]. *Streptococcus pneumonia* is an important leading pathogen of ABM, especially in those with spontaneous, community-acquired infection[2,22,34,42], but its incidence has decreased recently in our comparative studies of epidemiologic trends of adult ABM[1,34]. The exact cause of this decrease is not clear, but it can be explained partially by the increase in nosocomial, post-neurosurgical adult ABM in our study group. The contribution of pneumococcal vaccination in Taiwan in this decrease needs further clarification.

EVALUATION OF SUSPECTED ADULT BACTERIAL MENINGITIS

A. Patient history and clinical presentations

The approach to a patient suspected of having acute meningitis begins with an evaluation of the clinical history. However, the clinical course and classic presentations including fever, headahce, meningismus, and altered consciousness have a poor sensitivity and specificity for the diagnosis of ABM. As shown in Table 4, fever is the most common finding of adult ABM cases (87.5, 178/204) which is consistent with the findings of other reports[2,22]. However, the lack of a fever response can be seen in patients who are elderly, immunocompromised, or in a partially-treated state. The findings of physical examinations including skin rash, Kerning's sign, Brudzinski's sign, meningismus, and impaired jolt acceleration testing are also non-specific for ABM. Despite this poor correlative state, at least one of the above-mentioned essential elements (fever, headahce, meningismus, altered consciousness) is present in 99% of the adult ABM patients[43] which may tell us that certain aspects of history and physical examination can be used to highten suspicion of meningitis even if they cannot alone rule out the diagnosis. Therefore, neurologists should not rely on any single clinical feature or single physical test for ABM diagnosis, but should combine a number of historical and physical examination findings together to form a clinical impression.

Table 4. *Clinical manifestations of 204 acute bacterial meningitis cases*

	Spontaneous meningitis n = 84 (%)	Post-neurosurgical meningitis n = 120 (%)
Fever	76 (90.4)	102 (85.0)
Altered consciousness	56 (66.7)	68 (57.7)
Bacteremia	33 (39.3)	23 (19.2)
Seizure	27 (32.1)	32 (26.7)
Brain abscess	13 (15.5)	8 (6.7)
Hydrocephalus	12 (14.3)	78 (65.0)
Septic shock	9 (10.7)	11 (9.2)
Liver abscess	7 (8.3)	0 (0.0)
Multiple septic abscess	3 (3.6)	3 (2.5)
HHNK or DKA	5 (6.0)	3 (2.5)
Cerebral infarction	3 (3.6)	15 (12.5)
Infections endocarditis	2 (2.4)	0 (0.0)

HHNK: hyperosmolar hyperglycemic non-ketoacidosis; DKA: diabetic ketoacidosis.

B. Neuroimaging study also plays a crucial role in diagnosis and therapeutic decision-making

Unless the capabilities and accessibility of MRI can be expanded, cranial CT scan is used for the evaluation of patients with suspected ABM in most institutions. Cranial imaging can be considered as a way to evaluate for signs of brain shift as a precaution in selected patients before lumbar puncture (LP). It has become common practice to perform cranial CT before performing LP in patients with suspected bacterial meningitis, owing to a perception that this is a standard of care; however, waiting and performing this procedure may delay the start of appropriate antimicrobial therapy[44]. Actually the diagnostic sensitivity of CSF should not be deminished by delaying the LP by 1 or 2 hours after initiating antibiotic therapy[45]. Therefore, patients identified as high risk of brain herniation should have blood drawn for cultures and appropriate empiric antibiotic therapy initiated before undergoing a cranial CT study. But in patients with the following conditions: new-onset seizures, an immunocompromised state, signs of increased intracranial pressure or focal neurologic deficit, or moderate to severe impairment of consciousness, a cranial imaging study should be performed before LP in order to avoid cerebral herniation[46].

Cranial CT and MRI studies in adult patients with ABM may also reveal the following findings: skull pathology (operation wound, fractures, inner ear infection, mastoiditis, sinusitis), leptomeningeal enhancement, hydrocephalus, cerebral edema, epidural or subdural effusion, abscess, vasculitis and vascular events such as cerebral infarct and venous thrombosis[1,34,47]. For each different neuroimaging finding, a different therapeutic strategy should be considered.

C. CSF analysis is the cornerstone of diagnosis and management of bacterial meningitis

Despite advances in medical science, CSF analysis is the cornerstone of ABM diagnosis and the identification of infectious agents in ABM remains highly dependent on it. Although different sensitivity rates have been reported, both Gram's stain and culture may indicate implicated pathogens in 60% to 90% of ABM cases[1,2,22,43,48,49] and can certainly help to make the diagnosis of ABM with a high specificity if contamination can be excluded. In Taiwan, the problem of staphylococcal contamination of CSF samples should be emphasized as an important local issue due to the high incidence and rise of staphylococcal ABM among postneurosurgical adults[36-38]. Therefore, the diagnosis of such infections should be defined in a very strict manner[1,2,15,36-38]. It is also worth noting that partial antibiotic treatment may alter CSF characteristics and may also decrease the diagnostic yield of Gram's stain and cultures. Although we do not have exact data regarding this important therapeutic issue, the partially treated state of adult ABM should be kept in mind while managing this critical CNS infectious disease. Among CSF profiles, CSF protein level is the most resistant to rapid change, with treatment remaining elevated for 10 days or more[48,50]. Glucose ratio is usually < 0.4 or < 2.5 mmol/l if no simutaneous blood glucose level is determined[1,51]. However, when reading the glucose level data, we must keep in mind that changes in the blood glucose level are reflected in parallel changes in the CSF glucose level. A variable time is required before the CSF glucose level reaches a steady-state equilibrium[52]. Thus, the CSF glucose level at any moment is a complex function of the blood glucose level. Therefore, when the blood glucose level is of great diagnostic importance, CSF and blood glucose should be obtained simutaneously with the patient in a fasting state for at least 4 hours[52]. The study of lactate levels in CSF is generally nonspecific in meningitis[51] because the overlapping CSF lactate concentrations seen in different meningitis have limited the value of the assay as a diagnostic test. However, it has been reported that a CSF lactate concentration determination was found to be superior to the glucose ratio for the diagnosis of bacterial meningitis following surgery[53].

In ABM, purulent CSF feature (leukocytosis with predominant poly- morphonuclear cells) is the most important diagnostic finding[1,2]. Although 90% of patients will have a greater than 100 WBC /mm^3 in CSF study and about 60% have a greater than 1000 WBC/mm^3[1-3,49,54,55], 5%-19% of patients still have a CSF WBC count less than 100 WBC/mm^3- a level many would consider predictive for viral disease. The great variability of CSF WBC count is also shown in the 204

Table 5. *Prognostic factors of 204 adult bacterial meningitis cases*

	Fatal group (N = 64)	Non-fatal group (N = 140)	OR	95 % CI	P-Value
Age at meningitis (year)	58.1±14	51.8±17.3			0.013
Gender					
Female	16	43	0.752	0.385±1.47	0.404
Male	48	97			
Clinical feature					
Fever	55	123	1.184	0.497±2.821	0.703
Disturbed consciousness	45	80	0.563	0.299±1.059	0.073
Seizure	20	39	0.85	0.446±1.619	0.62
Septic shock	17	3	0.061	0.17±0.216	0
Hydrocephalus	26	64	1.231	0.676±2.242	0.497
DKA/HHNK	3	5	0.753	0.174±3.252	0.708
CSF leakage	2	8	1.879	0.388±9.109	0.728
Infectious endocarditis	1	1	0.453	0.028±7.363	0.53
Acquisition of infection					
Community acquired	42	68	0.495	0.268±0.913	0.023
Nosocomial acquired	22	72			
Types of infection					
Spontaneous meningitis	35	49	0.446	0.244±0.815	0.008
Postneurosurgical meningitis	29	91			
GCS at the time of admission	8.4±4.4	9.9±4.3			0.014
Underlying diseases					
Diabetes mellitus	18	38	0.952	0.492±1.842	0.884
Liver cirrhosis	9	8	0.37	0.136±1.01	0.45
Alcoholism	7	11	0.694	0.256±1.883	0.472
Chronic otitis media	3	3	0.445	0.87±2.269	0.38
Intravenous drug abuser	2	3	0.679	0.111±4.165	0.65
End-stage renal disease	5	1	0.085	0.1±0.742	0.012
Systemic lupus erythematosus	1	1	0.453	0.028±7.363	0.53
Malignancy	8	8	0.424	0.152±1.187	0.094
Peripheral blood study					
Thrombocytopenia	4	4			
Bacteremia	25	31			
Leukocytosis	45	89			
Laboratory data at the time of admission					
Glucose (mmol/L)	2.8±2.95	3.06±2.9			0.284
Total Protein (g/L)	5.65±7.16	3.03±3.77			0.002
Lactate (mmol/L)	13.7±8.02	9.97±7.95	0.001		
White cell count ($\times 10^6$/L)	23472±100597	2503±5689			0.063

GCS: Glasgow coma score; HHNK: hyperosmolar hyperglycemic nonketotic coma; DKA: diabetic ketoacidosis, OR: odds ratio; CI: confidence interval.

enrolled cases (Table 5). Therefore, in the setting of an elevated WBC count in CSF, there is no single variable that can reliably rule out ABM. Neurologists should rely on combinations of CSF findings to accurately predict ABM. In ABM diagnosis, bacterial antigen study with latex agglutination test is not routinely recommended because of its wide-range of susceptibilities and the presence of false-positive results[51]. Bacterial DNA detection by polymerase chain reaction for common pathogens in CSF is available[51,56]. Use of broad-range real-time PCR and DNA sequencing has an even higher diagnostic rate of ABM[57,58]. In Taiwan, the value of this genetic study in ABM diagnosis needs further large-scale study for a better delineation.

MANAGEMENT OF BACTERIAL MENINGITIS

The main therapeutic strategies of adult ABM[1,51,59-61] include 1) use of appropriate antibiotic(s); 2) application of neurosurgical procedures for certain conditions such as hydrocephalus and focal suppuration, and 3) use of anti-inflammatory therapy.

Since host immune response is incapable of controlling infection in the CNS, mandating the use of bactericidal antimicrobial in the treatment of ABM is required [62-64]. There is no doubt that reducing mortality and morbidity of ABM is critically dependent on rapid diagnosis and on the timely initiation of appropriate anticiotics. But no bacterial disease has undergone a more dramatic change in epidemiology during the past decade than ABM[65] and this may influence the choice of initial appropriate empiric antibiotics[1]. Empiric therapy of ABM must consider the most likely pathogens involved. Therefore, knowing the epidemiologic trend of ABM is important for antibiotic choice[1]. According to a hospital-based study[1,15,16,24,25,29,30,32-38], the present, important epidemiologic trends of ABM in Taiwan are as follows:

1. There is an increase in incidence of postneurosurgical ABM
2. *K. pneumoniae* is still the most common implicated pathogen of overall adult ABM
3. In Gram-negative adult ABM, there is a marked increase of *Acinetobacter* meningitis and this is noted especially in patients with a postneurosurgical state
4. In Gram-positive adult ABM, there is also a marked increase in staphylococcal infection in patients with a postneurosurgical state and most of them are methicillin-resistant strains

Because of these practical problems, it is essential that one considers the events preceding ABM when making the choice of initial, empiric antibiotics with a broad-spectrum coverage of the implicated pathogens. In Taiwan, it would be inappropriate to use ceftriaxone as the initial empiric antibiotic to cover all types of adult ABM, especially in those with a postneurosurgical state as the preceding event because in this group of adult ABM, most of the patients have methicillin-resistant staphylococcal infection or multiple antibiotic resistant Gram-negative infection. Therfore, at this moment, initial empiric antibiotics including vancomycin or linezolid plus ceftazidime or cefepime or meropenem would be more appropriate for this specific group of patients. With this combination, most of the implicated pathogens of postneurosurgical ABM patients can have better coverage. Other antibiotic therapy such as the use of ampicillin in old-aged and/or immunocompromised patients should be also considered[59]. So far, ceftriaxone can only be choosen as one of the initial empirical antibiotics in community-acquired ABM patients without an immunocompromoised and/or postneurosurgical state. The final antibiotic regimen should be adjusted further by the results of pathogen identification and antibiotic susceptibility test.

Excessive inflammation contributes to the pathogenesis of ABM, therefore, anti-inflammatory drugs have important therapeutic potential, and clinical trials have revealed that early treatment with dexamethasone significantly reduces mortality and morbidity from some groups of adult ABM, especially in those with community-acquired *Streptococcus pneumoniae* infection[66-70]. But because of different epidemiologic trends, it is uncertain whether all adults with ABM benefit from treatment with adjunctive dexamethasone[66,71,72]. At present there is no related data from Taiwan and therefore, the early use of dexamethasone (dexamethasone given before or with the first dose of antibiotic and then very 6 hours for 4

days)[60] in adult ABM should be considered with a degree of caution. This concern is primarily related to the high incidence of postneurosurgical conditions as the preceding event and high incidence of DM as the the underlying condition among the adult ABM patients[1,22]. If early dexamethasone therapy is used, a more close monitoring of metabolic derangment should be arranged. On the other hand, use of dexamethasone may significantly decrease the achievement of therapeutic vancomycin concentrations in the CSF because its penetration into the CNS is largely dependent on meningeal inflammation[73,74]. There have been clincal studies conducted regarding this therapeutic issue, but the observational results were quite controversial[75,76]. According to the study results of Richard et al.[76], appropriate concentrations of vancomycin in CSF may be obained when concomitant steroids are used, providing that vancomycin dosage is "adequate".

The therapeutic result of ABM can be influenced by several factors[1,22,77]. As shown in Table 5, the potential prognostic factors of the 204 ABM adults were many. Different prognostic factors were reported in the literature[1,2,22]. As reported by Lu, et al., serial CSF 14-3-3 protein, especially the gamma isoform, check-ups can be of value in predicting the outcome of community-acquired adult ABM[78]. In their study, most of the ABM patients who survived had nearly cleared their 14-3-3 protein from CSF before discharge. However, thus far, when treating adult ABM patients, the early use of appropriate antibiotics still the most consistent positive prognostic factor.

CONCLUSIONS

For a better theraspeutic result, the epidemiologic trends of adult ABM should be examined frequently becaue any change may influence the choice of initially empiric antibiotic greatly. The therapeutic strategies discussed in this review article may help neurologists, especially first-line primary-care neurologists, to have a better understanding of adult ABM in Taiwan and its management.

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