

Effective Empiric Antimicrobial Therapy of Bacterial Meningitis and Encephalitis

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ABSTRACT

Bacterial meningitis-encephalitis (ME) management therapy is critical to appropriately manage clinical outcomes. This study aims to provide recommendations on appropriate empiric antimicrobial to support the healing period and reduce the risk of disease severity. A cross-sectional study, including inpatients without comorbid diagnosed with bacterial ME, was conducted, and records of antimicrobial prescriptions were obtained. Sociodemographic, clinical (diagnostic), and pharmacological (antimicrobial) variables were assessed. Through multivariate analysis, variables associated with the use of antimicrobials for bacterial infections were identified. A total of 45 patients with ME. The patients, who were from surrounding Center Java and Yogyakarta, had a mean age of 11.27 ± 16.93 years and a male predominance of 56.9% ($n = 23$). The most frequent bacterial infections were caused by: *S. haemolyticus* and *S. epidermidis* (25.93%). A total of 100% the patients ($n = 45$) received a prescription for empiric antibiotics, predominantly 3rd generation cephalosporin e.c ceftriaxone (35.56%) and cefotaxime (13.33%). Empiric antimicrobials are frequently prescribed for the first management of bacterial ME, are considered an inappropriate practice due to a lack of clinical benefits, increased generation of antimicrobial resistance, and risk of adverse reactions due to the use of medications that patients do not require. Drug utilization studies are a great tool for monitoring how antimicrobial is being used and planning interventions to improve their use.

Keywords: empiric antimicrobial, meningitis-encephalitis bacterial.

Introduction

Infectious disease is a serious health problem that causes high morbidity and mortality rates. There are various kinds of infectious diseases, one of the most dangerous are central nervous system (CNS) infections. One of the CNS infections that require special treatment is meningitis or arachnoiditis. Meningitis is an inflammatory reaction in the brain and spinal cord lining. Sensitivity reactions to meningitis occur in the arachnoid, parameter, and cerebrospinal fluid. The inflammatory process in cases of bacterial meningitis is not limited to meninges, but also the brain parenchyma-meningoencephalitis (Brouwer *et al*, 2010). In 2016 neurological disorders led to 276 million disability-adjusted life years (DALYs) and 9.0 million deaths, constituting the first and second-ranked causes from the global disease burden, respectively. Meningitis contributed 7.9% to neurological DALYs after stroke, migraines, Alzheimer and other dementias (Khater and Elabd, 2016).

Data from the Ministry of Health Republic Indonesia reported that by the end of 2010 the number of meningitis cases had died at 1,025 patients. Deaths that occurred on the publication of Stockdale *et al* can be caused by delays in the introduction of signs and symptoms or diagnosis, late administration of antibiotics, and inappropriate antibiotic administration. ME bacterial therapy is still done by administering broad-spectrum antibiotics intravenously. This method is

expected to work effectively to kill and inhibit by penetrating the blood-brain barrier (BBB) and being able to enter the cerebrospinal fluid (CSS). Empirical antibiotics often used for the treatment of meningitis are third-generation cephalosporins, such as cefotaxime, ceftriaxone, and carbapenem groups (Van de Beek *et al*, 2012).

Based on the development of ME bacterial growth, some antibiotics used in therapy experience resistance. Some resistant antibacterials include methicillin-resistant *Staphylococcus aureus* and a class of β -lactam antibiotics such as vancomycin, in addition to acinetobacter of carbapenem-resistant meningitis. The administration of vancomycin and carbapenems with corticosteroids has an obstacle to penetrating the blood-brain barrier. These resistance problems in therapeutic effects that are expected to overcome ME bacterial (Nau *et al*, 2013).

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Published research related antibiotic use in cases of ME bacterial is still slightly. Administration of antibiotics to patients during hospitalization is perceived to accelerate patients recovering from the disease and as a consequence can shorten the length of stay in the hospital. Research in Indonesia has not been found that compares the length of treatment between patients who received empirical antibiotics and definitive antibiotics during hospital treatment.

Research Method

This research is a descriptive observational study with a retrospective cohort design to evaluate the suitability of using empirical antibiotics to support the clinical outcomes of ME bacterial patients. Patient data were collected by the medical Record Unit at the two top referral hospitals in Central Java. Period January 2016 – January 2020.

Data research is carried out by observing medical data related to diagnosis, laboratory results, development of the patient's clinical condition, drugs received by patients, and funding as long as the patient is treated in the hospital. The sampling technique was carried out using the total sampling method, namely by taking data on all hospitalized patients diagnosed with bacterial meningitis and meningoencephalitis with or without comorbidities in all age groups. Patients which died went home on their own accord, and patients with other ME not

caused by bacteria (e.g serosa, TB, HIV) were not included in this study.

The suitability of empirical antibiotics is to look at the suitability of the selection of empirical antibiotics, dose, frequency, and duration of antibiotic administration based on the Guidelines for the Use of Antibiotics (PPAB) at the hospital and international guidelines therapy.

Clinical outcome is the result of empirical antibiotic therapy achieved in the treatment of ME bacterial patients who are hospitalized, which was determined based on the clinician's decision, stating that he was cured (improved) or not improving.

At this stage, the variables to be evaluated such as age, weight, type, dose, frequency, and duration of antibiotics given and clinical outcomes achieved, were collected and tabulated. Data analysis was carried out to see the suitability of empirical antibiotics to clinical outcomes.

Results and Discussion

This research was 41 patients with a diagnosis of bacterial meningitis, encephalitis, and meningoencephalitis with or without comorbidities (Table 1). For all pediatric, adult, and geriatric patients with bacterial meningitis and meningoencephalitis, as much as 41 (100%) get empirical antibiotics.

Table 1 presents characteristic data patients, based on age groups, there were 41.46% of patients in 1 month - <2 years (babyhood) old age group who was suffering from meningitis

and meningoenephalitis bacterial. This number is greater than patients in the age group 20 years - <40 years (17.07%), and another age group. The incidence of meningitis and meningoenephalitis bacterial in patients aged 1 - 12 months was significantly greater compared to patients > 26 years of age with an odds ratio of 2.54 (95% CI 1.730 - 3.730; p <0.05) and 1.83 (95% CI 1.31-2.56; p <0.05) respectively (Karanika et al, 2009). One of the factors underlying the association between a decrease in the incidence of meningitis and meningoenephalitis bacterial and an increase in age is immunity factor and

bleeding, as conveyed in a publication (Japardi, 2012).

Blood laboratory tests were found in 9 patients, while liquor cerebrospinal (LCS) laboratory test examination was only found in 27 patients including causative bacterial. The research presented predominant causative bacteria: *Staphylococcus hominis* ssp *hominis* in blood, another find in *S. Epidermidis* and *S. haemolyticus* (25.93%) in LCS. On average, certain types of bacteria are distributed in equal numbers in the blood (Table 2). *Staphylococci* cause more of the suppurative-inflammatory cases and nosocomial infections.

Table 1. Characteristics of meningitis, encephalitis, and meningoenephalitis bacterial patients

No	Patients Characteristics	1 st Hospital		2 nd Hospital	
		Summary (n)	Percentage (%)	Summary (n)	Percentage (%)
1	Age				
	< 1 month	0	0	0	0
	1 month - <2 year	17	41.46	18	56.25
	2 year - <12 year	6	14.63	6	18.75
	12 year - <18 year	3	7.32	2	6.25
	18 year - <20 year	2	4.88	0	0
	20 year - <40 year	7	17.07	6	18.75
	40 year - 60 year	5	12.20	0	0
	> 60 year	1	2.44	0	0
2	Sex				
	Male	23	56.09	18	56.25
	Female	18	43.90	14	43.75
3	Financing status				
	General	2	4.87	4	12.52
	JKN Non-PBI	22	53.66	15	46.87
	JKN PBI	8	19.51	7	21.87
	James	5	12.20	5	15.62
	Jamkesda (INA CBG) Mandiri	4	9.76	1	3.12
4	Diagnose				
	Meningitis bacterial	20	24.69	24	28.92
	Encephalitis bacterial	1	1.24	0	0
	Meningoenephalitis bacterial	20	24.69	8	9.64

Table 2. Causative bacterial types and samples identified meningitis-encephalitis bacterial

Bacterial types	Blood (n = 9)		LCS (n = 27)	
	n	%	n	%
Gram-negative bacteria				
<i>Actinobacillus ureae</i>	0	0	1	3.70
<i>Acinetobacter baumannii</i>	0	0	1	3.70
<i>Escherichia Coli</i>	0	0	0	0
<i>Haemophilus influenza</i>	0	0	1	3.70
<i>Klebsiella pneumonia ssp pneumonia</i>	0	0	1	3.70
<i>Pseudomonas aeruginosa</i>	1	11.11	2	7.41
<i>Salmonella typhosa</i>	1	11.11	0	0
Gram-positive bacteria				
<i>Staphylococcus aureus</i>	1	11.11	3	11.11
<i>Staphylococcus coagulase-negative</i>	0	0	0	0
<i>Staphylococcus epidermidis*</i>	1	11.11	7	25.93
<i>Staphylococcus haemolyticus</i>	1	11.11	7	25.93
<i>Staphylococcus hominis ssp hominins</i>	3	33.33	2	7.41
<i>Staphylococcus sciuri</i>	0	0	1	3.70
<i>Staphylococcus viridans</i>	0	0	0	0
<i>Kochuria roseae*</i>	1	11.11	1	3.70
	9	100	27	100

There are several classes of antibiotics used for empiric therapy of bacterial ME. Empirical antibiotic therapy is given for 2 – 3 days (48 – 72 hours) or until culture results are obtained from the Clinical Pathology Laboratory Installation. Observations were made for 48-72 hours, if there was no improvement in the patient's clinical condition, antibiotics would be replaced by using one class of antibiotics with a newer generation or replaced by another class of antibiotics.

In this study, more patients were given antibiotic monotherapy than combination of antibiotics. As long as the patient is treated, the patient can be given more than one antibiotic.

The most frequently used combination of antibiotics is the

penicillin class of antibiotics (ampicillin) with the cephalosporin group (cefotaxime) as many as 8.89%. Other antibiotic combinations listed in the guidelines are rarely used. Ampicillin is a penicillin class of antibiotics that has activity against gram-positive and gram-negative bacteria. While cefotaxime is a cephalosporin antibiotic that has broad activity against gram-negative bacteria and enterobacteria.

Ceftriaxone (35.56%) and cefotaxime (13.33%) are third-generation cephalosporin antibiotics used as monotherapy. Both are active against Enterobacteriaceae, including beta-lactamase strains. While gentamicin is an aminoglycoside antibiotic that has gram-negative aerobic bacteria activity.

Table 3. Overview of the use of empirical antibiotics

Antibiotic	Summary (n)	Percentage (%)	Clinical Outcome	
			On care (improve)	Not improve
Single-antibiotic				
Inj. Ampicillin	1	2.22	1	0
Inj. Gentamicin	6	13.33	5	1
Inj. Ceftazidime	1	2.22	0	1
Inf. Ciprofloxacin	2	4.44	0	2
Inj. Cefotaxime	6	13.33	6	0
Inj. Ceftriaxone	16	35.56	14	2
Inj. Cefixime	1	2.22	1	0
Inj. Streptomycin	1	2.22	0	1
Inj. Chloramphenicol	1	2.22	1	0
Inj. Levofloxacin	1	2.22	1	0
Inj. Vancomycin	5	11.11	5	0
Combination antibiotic				
Inj. Ampicillin + Inf. Cefotaxime	4	8.89	4	0
	45	100	38	7

Based on ME's guidelines for using bacterial antibiotics, ceftriaxone is the primary desire of therapy for suspected meningitis for ages three months and older. This management became suitable and noticed the patient's situation at some stage in treatment improved without any aspect outcomes while the antibiotic was selected as an empiric antibiotic

Conclusion

Empiric antimicrobials are frequently prescribed for the first management of bacterial ME, considered an inappropriate practice due to a lack of clinical benefits, increased generation of antimicrobial resistance, and a risk of adverse reactions due to the use of medications that patients do not require.

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