# Correlation between clinical outcomes and empirical antibiotic therapy in patients with bacterial meningitis and meningoencephalitis

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ABSTRACT

Bacterial meningitis and meningoencephalitis are increasing in incidence. The aim of this study was to evaluate the clinical outcomes of the empirical use of antibiotics in bacterial meningitis and meningoencephalitis patients.Antibiotic therapy was considered appropiate if the right type (guideline), dose, interval and duration of administered.Estimated the association between concordance empirical antibiotic therapy with clinical outome patients. There are67 patients with bacterial meningitis and meningoencephalitis in the hospital. The suitability of empirical antibiotics was evaluated using the Gyssens algorithm. Relationship between empirical antibiotics and clinical outcome patients are analyzed with Chi Square (P<0,005). The results from this study showed there were 29 women (43.3%) and 38 men (56.7%). Culture tests were found in only 31 (46.3%) patients. The most commonly used antibiotic is Ceftriaxone. Based on clinical outcomes, 51 (76.2%) patients improved, 15 (22.4%) did not improve. Based on statisticsanalyze there was showed P value <0.05 it was 0,028 for meningitis and 0,039 for meningoencephalitis therapy. The data mean of the appropriateness of empirical antibiotic administered affects to clinical outcomes of patients. The research results obtained can be concluded that the antibiotics used are effective in achieving patient clinical outcomes.

Keywords : Meningitis, Meningoencephalitis, Antibiotic, Clinical Outcomes

## INTRODUCTION

Infectious disease is a serious health problem that causes which high morbidity and mortality rates. There are various kinds of infectious diseases, due to the sentences one of the most concerning infections is central nervous system (CNS) infections. CNS infections that require special treatment are meningitis or arachnoiditis. Meningitis is an inflammatory reaction in the lining of the brain and spinal cord. Meningitis issues are indicated through disturbances in the arachnoid, phyrameter, and cerebrospinal fluid. The inflammatory process in cases of bacterial meningitis is not limited to the meninges, but also to the brain parenchyma or meningoencephalitis(Natarajan et al., 2017). Incidence of meningitis and encephalitis has been reported in as many as 100,000 populations per year. Most of the diagnoses of meningitis and encephalitis are known late or not recognized before, this is because in some cases the pain experienced by the patient is not specific when tell to medical personnel(Shin & Kim, 2012). Cases of bacterial meningitis in developing countries become a frightening infectious disease. This case causes high mortality and morbidity, around 1.2 million cases of bacterial meningitis occur every year in the world with a death rate reaching 135,000 patients. The mortality rate of bacterial meningitis patients is 2-30% depending on the causative bacteria(Polage & Cohen, 2016).Facts from the Ministry of the Health Republic of Indonesia mentioned SKDR data for the last 3 years, the number of Meningitis suspected cases in 2015 was 339 cases, in 2016 as many as 279 cases, and in 2017 as many as 353 cases(Kementrian Kesehatan Republik Indonesia, 2019).

Infectious disease will be critical inflammation's proximity to the brain and spinal cord; so, the condition is classed as a medical emergency. Most cases of infectious disease are treated with antibiotics that reach the blood vessels as quickly as possible. As a result of the treatment typically begins before the precise microorganism accountable is known, the antibiotics used might modification(Priya et al., 2019). The deaths of patients can be caused by delays to recognizing signs and symptoms or diagnosis, delays in antibiotic administration, and inappropriate antibiotic administration. Broad-spectrum intravenous antibiotics are the preferred therapy for meningitis. High doses and intravenous administration are effectively to achieved concentration of cerebrospinal fluid quickly, thereby can reduce the risk complications. This method is expected work effectively to kill and inhibit by penetrating the blood-brain barrier or Blood-Brain Barrier (BBB), as well as being able to enter the cerebrospinal fluid(Stockdale et al., 2011).
Empirical antibiotics often used for the treatment of meningitis are third-generation cephalosporins, such as cefotaxime, ceftriaxone, and carbapenem groups . Along with the development of meningitis, some antibiotics used in therapy some of them have been resistant(Sudhakar & Dhakshinamoorthy, 2021). Antimicrobial resistance is not a new problem, but it's still threatens health worldwide and still necessary to monitor the impact of resistance. Therapy of bacterial meningitis patients is expected to be appropriate to use of antibiotics, this as an effort to prevent resistance and reduce fault of antibotic usage(Marnoor, 2017). Strategy globally stewardship antimicrobial are carried out to address the threat of various species of gram-positive and gram-negative bacteria. Administration of antibiotics to patients during hospitalization is perceived to accelerate patients' recovery from the disease and as a consequence can shorten the length of stay in the hospital(Andarsari et al., 2019).Appropriate of empirical antibiotics selected when providing patient care will improve patient recovery and reduce the potential drug resistance.

## AIM AND OBJECTIVE

This study aims to evaluate the clinical outcomes of the empirical use of antibiotics in bacterial meningitis and meningoencephalitis patients.

## MATERIAL AND METHODS

Data source :

This study was used neurological inpatient ward medical record data at Top Referral Hospital. Data covered on bacterial meningitisand meningoencephalitis patients (ICD-10 code: G00.3, G00.8, G00.9, G03.9, G01, G04.2) were collected as samples. Patient’s medical records used in research must include demographics, diagnoses, vital signs, laboratory data, medications, and treatments.

Methods :

This research is a cohort study with observational design and analytical approach. A complete data encompassing 67 inpatients with specific criteria. The study population included pediatric to elderly patients, according to WHO criteria. Samples are patients who receive therapy procedure starting from visit at an emergency department or during ≥72 hours of until treated at hospital. The patients’sclinical data used to see the types of empirical antibiotics used, types of pathogen bacteria, and observed of clinical outcome of patients. Data collection was continued to evaluated and described. Data on this research were summarized using frequencies and percentages. The characteristics of the patients are expected to fulfill the inclusion criteria in this study. Inclusion criteria were as followed: (1) patients with diagnosed meningitis and meningoencephalitis bacteria (2) patients without comorbid, (3) patients with empiric antibiotic therapy, and (4) pathogenic bacteria. The protocol has been granted ethical approval by the Ethical Committee MHREC Faculty of Medicine, Gadjah Mada University KE/FK/0066/EC were before the data collection.

Statistics :

The appropiate of empirical antibiotic used to patients was analyzed with Gyssensalgorithm method. The correlation between empiric antibiotics and clinical outcomes was analyzed by Chi Square analysis.

RESULTS

There are 67 patients with bacterial meningitis and meningoencephalitis were enrolled in this study. Characteristics of the patients are described by age, sex, length of stay.

Table. 1 Characteristics Patients with Bacterial Meningitis and Meningoencephalitis

| Characteristics | Meningitis 53 | | Meningoencephalitis 14 | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | N | % |
| Age, N (%) | | | | | | |
| 0 - 1 years | 24 | 45,3 | 2 | 14,3 | 26 | 39 |
| < 2-10 years | 13 | 24,5 | 4 | 28,6 | 17 | 25 |
| < 11-19 years | 7 | 13,2 | 2 | 14,3 | 9 | 13 |
| < 20 - 60 years | 8 | 15,1 | 6 | 42,9 | 14 | 21 |
| > 60 years | 1 | 1,9 | 0 | 0 | 1 | 1,5 |
| Sex, N (%) | | | | | | |
| Male | 31 | 58,5 | 7 | 50 | 38 | 57 |
| Female | 22 | 41,5 | 7 | 50 | 29 | 43 |
| Length Of Stay, N (%) | | | | | | |
| ≤ 14 days | 31 | 58,5 | 8 | 57,1 | 39 | 58 |
| > 14 days | 22 | 41,5 | 6 | 42,9 | 28 | 42 |

Based on data, the majority of patients meningitis and meningoencephalitis are pediatrics0-1 years (39%) and males are more dominate (57%) than females. During hospitalized therapy the longest length of stay of 67 patients was ≤ 14 days (58%)

Table 2. Causative Bacteria in Meningitis and Meningoencephalitis Patients

| Strains | Types of Causative Bacteria | Sample | | Case | |
|---|---|---|---|---|---|
| | | LCS | Blood | N | % |
| Meningitis Bacteria | | | | | |
| Gram (+) | *Staphylococcus aureus* | 1 | 2 | 3 | 17,6 |
| | *Kochuriaroseae* | 1 | | 1 | 5,9 |
| | *Staphylococcus epidermidis* | 5 | | 5 | 29,4 |
| | *Staphylococcus sciuri* | 1 | | 1 | 5,9 |
| | *Staphylococcus haemolythicus* | 1 | | 1 | 5,9 |
| | *Staphylococcus hominis ssp hominis* | | 1 | 1 | 5,9 |
| Gram (-) | *Actinobacillusureae* | 1 | | 1 | 5,9 |
| | *Pseudomonas aeruginosa* | 1 | 2 | 3 | 17,6 |
| | *Haemophilus influenza* | 1 | | 1 | 5,9 |
| Meningoencephalitis Bacteria | | | | | |
| Gram (+) | *Staphylococcus epidermidis* | 4 | 1 | 5 | 41,7 |
| | *Staphylococcus haemolythicus* | 3 | 1 | 4 | 33,3 |
| | *Staphylococcus hominis ssp hominis* | | 1 | 1 | 8,3 |
| Gram (-) | *Acinetobacter baumannii* | 1 | | 2 | 16,7 |

Table 2. showed causative bacterial meningitis and meningoencephalitis can be caused by gram-positive and gram-negative strains (table 2). The most common causative bacteria from totally types of bacteria were found are *Staphylococcus epidermidis* (29,4%) is caused meningitis and (41,7%) caused meningoencephalitis.

Table 3. Types of Empirical Antibiotic for Bacterial Meningitis and Meningoencephalitis

| Types of Antibiotics | Group Of Antibiotics | Total (N) | Percentage (%) | Clinical Outcomes | |
|---|---|---|---|---|---|
| | | | | Recover | Still bad/ Worsens |
| Single Antibiotics Meningitis (N=53) | | | | | |
| Inj. Ampicillin | Penicillin | 3 | 3,7 | 3 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Inj. Cefepime | Cephalosporin IV | 2 | 2,5 | 1 | 1 |
| Inj. Cefotaxime | Cephalosporin III | 19 | 23,5 | 14 | 5 |
| Inj. Ceftazidime | Cephalosporin III | 9 | 11,1 | 6 | 3 |
| Inj. Ceftriaxone | Cephalosporin III | 27 | 33,3 | 22 | 5 |
| Inj. Chloramphenicol | Chloramphenicol | 1 | 1,2 | 1 | 0 |
| Inf. Ciprofloxacin | Quinolone | 1 | 1,2 | 1 | 0 |
| Inj. Gentamycin | Aminoglycosid | 7 | 8,6 | 6 | 1 |
| Inj. Levofloxacin | Fluoroquinolone | 1 | 1,2 | 0 | 1 |
| Inj. Meropenem | Beta-lactam | 4 | 4,9 | 4 | 0 |
| Inj. Vancomycin | Glycopeptide | 1 | 1,2 | 1 | 0 |
| Combine Antibiotics | | | | | |
| Inj. Ampicillin + Inj. Gentamicine | Penicillin + Aminoglycosid | 1 | 1,2 | 1 | 0 |
| Inj. Ampicillin + Inj. Cefotaxime | Penicillin + Cephalosporin III | 5 | 6,2 | 4 | 1 |
| | | 81 | 100 | 64 | 17 |
| Meningoencephalitis (N=14) | | | | | |
| Single Antibiotics | | | | | |
| Inj. Ampicillin | Penicillin | 1 | 4,2 | 0 | 1 |
| Inj. Ceftazidime | Cephalosporin III | 1 | 4,2 | 1 | 0 |
| Inj. Cefotaxime | Cephalosporin III | 1 | 4,2 | 0 | 1 |
| Inj. Ceftriaxone | Cephalosporin III | 11 | 45,8 | 10 | 1 |
| Inj. Gentamicin | Aminoglycosid | 2 | 8,3 | 2 | 0 |
| Inj. Levofloxacin | Fluoroquinolone | 1 | 4,2 | 1 | 0 |
| Inj. Vancomycin | Glycopeptide | 2 | 8,3 | 2 | 0 |
| Inf. Ciprofloxacin | Quinolone | 3 | 12,5 | 2 | 1 |
| Inj. Cefoperazone sulbactam | Cephalosporin III | 2 | 8,3 | 2 | 0 |
| | | 24 | 100 | 20 | 4 |

Cephalosporins were the most dominated to prescribed from all of types antibiotics used for therapy. Ceftriaxone is the dominant used, there was 36% empirically for meningitis and 45,8% for meningoencephalitis. From empirical antibiotics administered showed that 64 patients with meningitis and 20 patients with meningoencephalitis are support to recovered the clinical condition of patients.

Table 4. Correlations of Appropiate Empirical Antibiotics with Clinical Outcomes

| | | | Clinical Outcomes | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Recovered | | Still bad/ Worsens | | P |
| | | | n | % | n | % | |
| Meningitis Bacteria | Types Antibiotic (V) | | | | | | 0,028 (P <0,05) |
| | Rational | 52 | 39 | 75 | 13 | 25 | |
| | Irrational | 1 | 0 | 0 | 1 | 100 | |
| | Dose (IIA) | | | | | | |
| | Rational | 50 | 38 | 76 | 12 | 24 | |
| | Irrational | 2 | 1 | 50 | 1 | 50 | |
| | Interval (IIB) | | | | | | |
| | Rational | 44 | 35 | 79,5 | 9 | 20,5 | |
| | Irrational | 6 | 3 | 50 | 3 | 50 | |
| | Duration (IIIA/IIIB) | | | | | | |
| | Rational | 37 | 32 | 86,5 | 5 | 13,5 | |
| | Irrational | 7 | 3 | 42,9 | 4 | 57,1 | |
| Meningoencephalitis Bacteria | Types Antibiotic (V) | | | | | | 0,039 (P<0,05) |
| | Rational | 14 | 12 | 85,7 | 2 | 14,3 | |
| | Irrational | 0 | 0 | 0 | 0 | 0 | |
| | Dose (IIA) | | | | | | |
| | Rational | 13 | 11 | 84,6 | 2 | 15,4 | |
| | Irrational | 1 | 0 | 0 | 1 | 100 | |
| | Interval (IIB) | | | | | | |
| | Rational | 13 | 11 | 84,6 | 2 | 15,4 | |
| | Irrational | 0 | 0 | 0 | 0 | 0 | |
| | Duration (IIIA/IIIB) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Rational | 12 | 10 | 83,3 | 2 | 16,7 |
| | Irrational | 1 | 1 | 100 | 0 | 0 |

Based on table 4 it evaluated the suitability of empirical antibiotics to 53 bacterial meningitis patients who were hospitalized, there were 52 patients who received the appropriate antibiotics. The clinical outcome showed that the condition improved by 75% with the other 25% still not improving. From the evaluation of dose suitability , there were 50 patients who received the appropriate dose, and 76% of them recovered. The interval suitability showed an recovered patients are 79.5% from 44 patients, while about duration suitability showed 37 patients 86.5% of them are recovered. There are a relationship between appropriate of empirical antibiotics with clinical outcomes meningitis patients P<0,05 (0,028).

Meningoencephalitis patients who received empirical antibiotics are 14 patients. Inappropiate in drug administration appeared in the duration of empirical antibiotic administration, even though there are 83.3% showed an improved condition.There are a relationship between appropriate of empirical antibiotics with clinical outcomes meningitis patients P<0,05 (0,039).

## DISCUSSION

The majority of the patient's with bacterial meningitisand meningoencephalitis are pediatrics (39%), it was similar some study in …. which 6.5% are meningitis bacteria almostpediatric patients with age <16 years. Age is associated with the incidence of bacterial meningitis and meningoencephalitis, including immune factors and bleeding risk, as described in the publication(Long et al., 2019).

Male are dominate (57%) moreover females to diagnosed bacterial meningitisand meningoencephalitis. Meningitis in male adults differs significantly from female adults, the male was higher than females. For genetic reasons, male-only has one X chromosome involved directly or indirectly in immunoglobulin synthesis, it is instead of two as in females. Lack of the X duration of antibiotic administration. The duration of antibiotics administered should be based on chromosomes to be more susceptible to infections(Schurz et al., 2019).

Length of stay patients ≤14 days or more are related to the causative bacteria which obtained from cerebrospinal fluid (CSF) or blood culture. The standard of duration therapy with antibiotics to patients is almost of 7 days. When patients is admitted with a diagnosis that cannot be certainty established, the patient will be given empirical antibiotic therapy. If the causative bacteria are known, then therapy is continued with definitive antibiotics for a period of 10-14 days (Van De Beek et al., 2016).

Clinical outcomes of patients can be influenced by empirical antibiotic. The data results as in table 2 indicated ceftriaxone which belongs to the Cephalosporins antibiotics group is the dominant choice therapy to (35.56%) empirical. Broad-spectrum antibiotics such as cephalosporins are recommended for empiric therapy, they have consistent liquor cerebrospinal (LCS) penetration and potential against pathogens of bacterial meningitis and encephalitis. Appropriateness antibiotics can also affect the duration and condition of treatment patient at hospital(Van De Beek et al., 2016).

This study showed *Staphylococcus epidermidis* (29.4%) are bacterial causes meningitis and (41,7%) meningoencephalitis. Other bacteria as *S. Haemolyticus* (33,3%) is causes meningoencephalitis. This data has similarities with some published research evidence, that shows that the most common cause of bacterial meningitis and meningoencephalitis in Guang Xi, China at 12 hospitals. There are shows 34 types of pathogenic bacteria which found in many skin and mucosal tissues, bacterial as *S. aureus*, *S. epidermidis*, and *S. haemolyticus* cause the most frequent occurrence of bacteremia, especially in neonates and immunocompromised patients. Infection occurs through contact between patients' medical personnel and medical equipment, especially in immunocompromised patients. Currently, it is also some of the bacteria that causes nosocomial in hospitals(Xie et al., 2015). Assumed contaminants of *Kochuriaroseae* and *Actinobacillusureae* bacteria are found in this study. They actually rare found as bacterial cause meningitis. Cases of infection due to this bacteria are found in patients with immunocompromised conditions, like as patients with cancer, peritonitis, endocarditis, and patients with the installation of medical devices such as catheters(Muñoz Montoya et al., 2017).

The evaluation of appropriateness prescribing empirical antibiotics was based on Gyssens method, with the appropiate category if category 0-I and inappropriate if it was included in one of the categories I-VI. Table 4 shows that the accuracy of prescribing empirical antibiotics at types, dose, interval, and duration.The appropiatness empirical types of antibiotics from 53 bacterial meningitis patientsand 14 bacterial meningoencephalitis patients are reach more than 50%. The choice of antibiotics affectsof duration in 7 meningitis patients and 1 meningoencephalitis patient, can caused

there are too long or too short administration of time.Assessment of the clinical condition of patients, usingfollowing criteria, namely: temperature ≤37.8°C, heart rate ≤100/minute, respiratory rate ≤24/minute, blood pressuresystolic ≥90 mmHg, oxygen saturation ≥90%, able to communicate, not having seizures, crouching, and brudzinski, can receive food, and normal mental status.

The appropriate of prescribing antibiotics are expected to improve the clinical outcomes of patients. It was P value 0,028 (<0,05) which shows the relationship between appropriateness of empirical antibiotic administration and clinical outcomes meningitis patients. It also shown the chi square analysis of meningoencephalitis patients, where there was a relationship between appropriate ofempirical antibiotic administration and clinical outcome patients 0,039 (P<0,05).This study related as the observational studies about impact of time to antibiotic therapy on clinical outcome in patients with bacterial infections, which all data showed an association between delayed antibiotic therapy and worse clinical outcome(Nauclér et al., 2021).

## CONCLUSION

Clinical outcome of patients with meningitis and meningoencephalitis caused causative bacteria, showed the condition improvement rate is quite high more than 50%.There is a significant correlation between qualityadministration of antibiotics with clinical outcomes in patients with bacterial meningitis andmeningocephalitis.

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