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Prevalence and Antibiotic Resistance of Bacteria Isolated from Cerebrospinal Fluid of Neurosurgical Patients in Malang, Indonesia

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Abstract

Background: Central nervous system infections are a critical concern in neurosurgical practice, often leading to severe complications and prolonged hospital stays. Understanding the prevalence and antibiotic resistance patterns of the bacteria causing these infections is essential for effective patient management. This study aims to investigate the prevalence and antibiotic resistance profiles of bacteria isolated from cerebrospinal fluid in neurosurgical patients in Malang, Indonesia.

Materials and Methods: A retrospective analysis was conducted to investigate the positive cerebrospinal fluid (CSF) cultures in patients who underwent craniotomy within the period of January 2019 to December 2021. The gathered data encompassed the identification of etiological agents and the determination of their respective antimicrobial susceptibilities. Data analysis was performed on a total of 33 individuals, with 67 isolates out of 239 patients and 515 CSF culture samples.

Results: The preponderant microorganism identified in the sample was coagulase-negative Staphylococci, with a majority exhibiting methicillin resistance, commonly referred to as methicillin-resistant coagulase-negative Staphylococci (MRCoNS). All specimens exhibited susceptibility to both vancomycin and tigecycline. Klebsiella pneumoniae, a Gram-negative bacterium, was identified as the predominant etiological agent and exhibited resistance to a substantial proportion of the antimicrobial agents tested, specifically 13 out of the 16 antimicrobials evaluated.

Conclusions: The sensitivity rates of ceftriaxone and meropenem were found to be 0% and 100%, respectively. The predominant bacteria is MRCoNS, which is completely susceptible to tigecycline, vancomycin, linezolid, and nitrofurantoin. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae is difficult to treat, especially in central nervous system infections when antimicrobials are scarce.

Keywords: Antibiotic resistance, Neurosurgery, PCNSI, Prevalence

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INTRODUCTION

Postoperative central nervous system infections (PCNSI) are rare but can have severe consequences following specific brain surgeries, such as craniotomies. They may result in negative patient outcomes, including extended hospitalization, increased medical expenses, and the necessity for additional surgeries.[1] Craniotomy is a common surgical procedure used to treat head injuries, intracranial bleeding, brain tumors, and the placement of external ventricular devices.[2] Several studies have found the incidence of PCNSI varies from 0.9 to 8.9%.[3,4] PCNSI diagnosis is a complex procedure that requires careful clinical assessment and cerebrospinal fluid (CSF) investigation via lumbar puncture. As a result, without knowledge of the specific pathogen responsible and the most effective treatment choices, selecting appropriate preventative measures and antibiotics becomes complicated.[5,6]

The epidemiological features of bacterial infections can vary based on factors such as time, age, location, medical or neurosurgical conditions, race, vaccination status, how the infection spreads, and the use of antibiotics in the community.[3] The majority of data suggest that Gram-positive bacteria, particularly *Staphylococcus aureus*, are the primary cause of central nervous system pyogenic infections.[1] However, in recent years, there has been an increase in the number of negative bacteria, particularly *Acinetobacter,* as PCNSI pathogens.[7,8] Furthermore, the prevalence of multi-antibiotic-resistant bacteria has increased, such as methicillin-resistant Staphylococcus aureus (MRSA) and strains producing extended-spectrum lactamases (ESBL).[9] The extensive use of empirical vancomycin and antipseudomonal-lactam antibiotics is one suspected cause of these diseases.[10]

In the selection of antibiotics, it is critical to consider not only the bacterial species and their antibiotic resistance profile when selecting antibiotics but also the complicated nature of the blood-brain barrier.[11] Bacterial resistance to antibiotics in the lab has been proven since the 1940s.[12] Since then, resistance against antimicrobial agents has increased worldwide, and bacteria that are resistant to many antibiotics have become increasingly common.[13] In the Indonesian healthcare system, there is a lack of data on the prevalence and antibiotic resistance patterns of bacterial infections causing PCNSIs. Saiful Anwar Hospital Malang is a referral hospital that performs a wide range of surgeries, including craniotomies, particularly in the neurosurgery department. This study aims to investigate the prevalence and antibiotic resistance profiles of bacteria isolated from the CSF of neurosurgical patients in Malang, Indonesia. Our ultimate goal is to offer guidance to medical professionals in choosing the most appropriate empirical antibiotic treatments.

MATERIALS AND METHODS

A retrospective analysis was conducted to investigate the positive cerebrospinal fluid (CSF) cultures in patients who underwent craniotomies. The CSF culture results isolated from hospitalized patients were examined using a computerized log that had records from January 2019 to December 2021. The WHO Net was used to collect data on patients with positive culture isolates, which included the present inquiry concerning the identification of causative microorganisms and the concomitant antimicrobial susceptibility testing. Culture contamination was determined by clinical laboratories and neurosurgical specialists based on microorganism identity and clinical features. The statistical analysis was conducted using Microsoft Excel software. The data collected from this study were analyzed descriptively to calculate percentages. This study was approved by the Ethics Committee of the Health Research Ethics Commission (Number: 400/103/K.3/102.7/2023)

The main inclusion criterion for this study was a positive CSF culture result. The finding of identical strains taken from a single patient within a week was considered a single isolate and was not recounted. A history of prior cranial interventions, including elective and urgent surgical operations, was also required for inclusion in the study. Exclusion criteria for this study included patients who had spinal surgery or simple wound revision without drill holes and those who had concomitant persistent meningitis or encephalitis that was not caused by a microbial infection.

All patients received a 1 g dosage of second-generation cephalosporin one hour before the surgical incision as prophylactic medication, followed by a 24-hour period of postoperative treatment. Strict procedures were implemented throughout surgery, including applying an antibacterial film to ensure perioperative sterility. The Clinical and Laboratory Standards Institute (CLSI) technique assessed antibiotic susceptibility. The antibiotic susceptibility results were evaluated

using CLSI method. Pathogenic organisms were considered resistant if they demonstrated intermediate or high resistance to any of the investigated agents, which encompassed cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, extended-spectrum penicillins, macrolides, and β-lactams/ β-lactamase inhibitors.

RESULTS

From 2019 to 2021, we obtained 515 cerebrospinal fluid (CSF) culture samples from 239 patients. The present study reports a postoperative central nervous system infections (PCNSI) incidence of approximately 13.9% (33/239) with an estimated culture-positive rate of infection of approximately 100% (33/33). A cohort of thirteen individuals has been diagnosed with polymicrobial infections. The findings of the study indicate that the prevalence of Gram-positive and Gram-negative distributions was 53.7% and 46.3%, respectively **(Table 1)**. The predominant isolate of Gram-positive bacteria was identified as coagulase-negative *Staphylococci,* accounting for 97.2% of the total isolates. The present study reports that Klebsiella pneumoniae was the predominant gram-negative pathogen identified, representing 32.3% of the total isolates, while Escherichia coli accounted for 16.1% of the isolates.

Table 1 Bacteria isolated from cerebrospinal fluid

Organism	% (n)
Gram-positive bacteria	
Sthaphylococcuscoagulasenegative	52.2 (35)
Enterococcus faecalis	1.5 (1)
Gram-negative bacteria	
Klebsiella pneumonia	14.9 (10)
Escherichia coli	7.5 (5)
Acinetobacterbaumannii	4.5 (3)
Enterobacter cloacae	4.5 (3)
Bacillus cereus	4.5 (3)
Others Gram-negative	10.4 (7)
Total	100% (67)

Notes: *Sthaphylococcuscoagulasenegative: Staphylococcus haemolyticus* (n=11), *Staphylococcus hominis* (n=11), *Staphylococcus epidermidis* (n=6), *Staphylococcus cohnii* (n=5), *Staphylococcusgallinarum* (n=2)

Of the Gram-positive isolates, coagulase-negative Staphylococci isolates were sensitive to tigecycline (100%), vancomycin (100%), linezolid (94%), and nitrofurantoin (94%). Enterococcus faecalis isolates were 100% sensitive to ampicillin, gentamicin, penicillin, linezolid, nitrofurantoin, tigecycline, and vancomycin. Meanwhile, of the Gram-negative isolates, Klebsiella pneumoniae is sensitive to ertapenem (100%), meropenem (100%), and fosfomycin (89%). Echeria coli was 100% sensitive to amoxicillin, ceftazidime, ertapenem, cefepime, nitrofurantoin, meropenem, tigecycline, and piperacillin. Acinetobacter baumannii was 100% sensitive to amikacin and tigecycline. Enterobacter cloacae were 100% sensitive to amikacin, ciprofloxacin, levofloxacin, and tigecycline. Bacillus cereus was 100% sensitive to ciprofloxacin, erythromycin, trimethoprim-sulfamethoxazole, tetracycline, and vancomycin. The others were 100% sensitive to ceftriaxone, ertapenem, nitrofurantoin, and ampicillin/sulbactam. The present study elucidates the in vitro antibiotic sensitivities of both Gram-negative and Gram-positive isolates in a comprehensive manner **(Table 2)**

DISCUSSION

PCNSI is a rare but serious neurosurgical complication that occurs after cranial surgery. PCNSI often leads to adverse patient outcomes, including extended hospital stays, increased total healthcare costs, and the necessity for multiple surgical interventions.[12] The incidence of PCNSI varies globally. In our study, we identified PCNSI cases using CSF culture, and we found an incidence rate of approximately 13.9% (33 out of 239 patients). This finding is notably higher than the previously reported range of 0.9% to 4.7%.[3,13] However, other studies have reported higher rates of PCNSI, ranging from 6.5% to 7.4%. [14,15,16] One possible explanation could be attributed to differences in patient population size. In our research, only culture-positive postoperative patients were included, implying a lower false-positive rate.

Numerous studies have shown the mortality rate associated with PCNSI. In a study conducted in 2017 by Shi et al.,[14] the reported mortality rate of PCNSI was 1.8%. However, a more recent study by Chang et al.[3] documented a considerably higher mortality rate of 8%. Chang et al.[3] suggested that these differences in mortality rates may be attributed to the diagnostic criteria used. In cases with higher mortality rates, the diagno-

Table 2 Gram negative and Gram positive antibiotic sensitivity rates

Antibiotic	Organism Gram-Positive		Organism Gram-Negative					
	Sthaphylococcus coagulase negative	*Enterococcus faecalis*	*Klebsiella pneumoniae*	*Escherichia coli*	*Acinetobacter baumannii*	*Enterobacter cloacae*	*Bacillus cereus*	*Others*
AMP	-	100	0	0	-	0	-	0
AMC	-	-	40	100	-	0	-	0
AMK	-	-	100	80	100	100	-	86
ATM	-	-	0	25	-	0	-	67
CAZ	-	-	0	100	67	0	-	71
CFR	0	-	-	-	-	-	-	-
CIP	33	-	80	0	67	100	100	71
CLI	19	-	-	-	-	-	-	-
CRO	-	-	0	0	67	0	-	100
CTX	-	-	-	-	-	-	0	-
CZO	11	-	0	0	0	0	-	29
ERY	18	-	-	-	-	-	100	-
ETP	-	-	100	100	-	0	-	100
FEP	-	-	20	100	67	0	-	86
NIT	94	100	40	100	-	9	-	100
GEN	55	100	0	20	67	0	-	71
LVX	36	-	80	0	-	100	-	0
LNZ	94	100	-	-	-	-	-	-
MEM	-	-	100	100	67	0	-	83
MFX	42	-	-	-	-	-	-	-
OXA	9	-	-	-	-	-	-	-
PEN	0	100	-	-	-	-	0	-
SAM	-	-	0	60	67	0	-	100
SXT	61	-	0	25	67	0	100	83
TCY	85	-	-	-	-	-	100	-
TGC	100	100	20	100	100	100	-	86
TZP	-	-	20	100	67	0	-	86
VAN	100	100	-	-	-	-	100	-
FOS	-	-	89	-	-	-	-	100

Notes: ln%. AMP: ampicillin, AMC: amoxicillin-clavulanate, AMK: amikacin, CAZ: ceftazidime, CFR: cefadroxil, CIP: ciprofloxacin, CLI: clindamycin, CRO: ceftriaxone, CTX: cefotaxime, CZO: cefazolin, ERY: erythromicin, ETP: ertapenem, FEP: cefepime, NIT: nitrofurantoin, GEN: gentamicin, LVX: levofloxacin, LNZ: linezolid, MEM: meropenem, OXA: oxacillin, PEN: penicillin, SAM: ampicillin/sulbactam, SXT: trimethoprim-sulfamethoxazole, TCY: tetracycline, TGC: tigecycline, TZP: piperacillin, VAN: vancomycin, FOS: fosfomycin

sis of PCNSI often relies on pathogen isolation rather than clinical manifestations, potentially leading to the exclusion of infected patients with negative cultures. Consequently, this could result in an overestimation of mortality while underestimating the overall incidence of PCNSI. It is important to acknowledge that variations in both incidence and mortality rates of PCNSI across studies may arise from differences in inclusion criteria, making direct comparisons challenging.

Gram-positive bacteria were the most common organisms found in this study, accounting for approximately 53.7% of all isolates. The major organisms were *coagulase-negative staphylococci*, which include *Staphylococcus hominis, Staphylococcus haemolyticus, Staphylococcus epidermidis,* and *Staphylococcus cohnii. Klebsiella pneumonia* and *Escherichia coli* were the most common Gram-negative pathogens, accounting for 46.3% of all isolates. In this study, the microbiological findings were consistent with most previous findings, with Gram-positive organisms being the most common in culture.[17] However, in most studies, *Staphylococcus aureus* was the predominant Gram-positive organism.[17,20] Furthermore, in our study, *Klebsiella pneumoniae* was the most frequently isolated Gram-negative bacterium. However, in other studies, it's been found that *Enterobacteriaceae* are the most commonly identified Gram-negative bacteria.[13]

According to this study, 29 of the 35 coagulase-negative staphylococci (82.9%) were methicillin-resistant coagulase-negative staphylococci (MRCoNS). Our research findings emphasized that vancomycin and tigecycline were the most effective treatments against MRCoNS. Vancomycin is widely regarded as the ultimate choice for treating central nervous system infections caused by Gram-positive bacteria.[19] In our study, methicillin-resistant Staphylococcus aureus (MRSA) was not detected in the Staphylococcus aureus isolates we analyzed, resulting in an MRSA prevalence of 0% percent in our samples. While our findings indicate the absence of MRSA in our samples, several previous studies have raised concerns about MRSA. For comparison, a study by Chang et al.[3] reported that they found MRSA in approximately 25% of the *Staphylococcus aureus* isolates they examined. However, it is important to note that MRSA prevalence can vary significantly between studies, and in the context of our sample, MRSA was not a significant concern.

The susceptibility of *Klebsiella pneumoniae* was analyzed in Gram-negative isolates. There were ten patients with ten *Klebsiella pneumoniae* isolates, all of which were Extended Spectrum Beta Lactamase (ESBL) bacteria. The data presented here may add to the evidence of the wide distribution of *Klebsiella pneumoniae* ESBLs. Thus, the emergence of ESBL *Klebsiella pneumoniae* as one of the ESKAPE pathogens needs to be a major medical concern, given the scarcity of treatment options for ESBL *Klebsiella pneumoniae* infections. In this study, meropenem and ertapenem were the most effective antibiotics for ESBL *Klebsiella pneumoniae*, with a sensitivity rate of 100%, respectively. Further research on treatment strategies is needed in the future.

The Centers for Disease Control and Prevention (CDC's) recent observation of an increase in medication resistance reflects a global challenge in the management of diseases,[22] particularly central nervous system infections. The decision over which empirical antibiotic medication to use is becoming increasingly important for healthcare providers all around the world.[20] The identification and administration of effective antimicrobial drugs are critical components of PCNSI management.[21,22] It should be highlighted, however, that this study has significant limitations, including data limits that do not give thorough clinical information, notably regarding specific symptoms of central nervous system infections and surgical locations within the brain. Furthermore, there is a possibility of selection bias affecting the study's findings, and the data used is from a single healthcare institution, thus limiting the generalizability of these findings.

CONCLUSIONS

Postoperative central nervous system infection (PCNSI) is a serious complication that can significantly increase mortality. The prevalence of PCNSI was approximately 13.9% among neurosurgical patients in Malang, Indonesia. Gram-positive bacteria, mainly coagulase-negative Staphylococci, accounted for 53.7% of isolates, while Gram-negative bacteria, including Klebsiella pneumoniae, constituted 46.3%. Methicillin-resistant coagulase-negative Staphylococci (MRCoNS) were prevalent but susceptible to tigecycline and vancomycin, while *Klebsiella pneumoniae* exhibited resistance to several antibiotics, emphasizing treatment challenges.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by TAL, DR, FB, DWW, and BRS. The first draft of the manuscript was written by BRS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicting Interest

All of the authors stated that they have no conflicts of interest.

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