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Microorganism and Antibiotik Sensitivity Pattern of Children Bacterial Meningitis in Denpasar Tertiary Hospital 2019-2020

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Abstract: *Introduction*: Bacterial meningitis is a severe acute infection of the central nervous system that caused by bacteria. The antibiotic should be given immediately. An appropriate antibiotic may reduce the morbidity and mortality caused by bacterial meningitis. This study aims to evaluate the bacterial pattern and antibiotic sensitivity in children bacterial meningitis at tertiary hospital in Denpasar. *Material and methods*: This retrospective descriptive study was using a cross-sectional design that involved pediatric patients aged 1 month-18 years old with suspected bacterial meningitis who underwent a lumbar puncture at Sanglah Hospital from January 2019 to December 2020. The diagnosis of bacterial meningitis was made based on cerebrospinal fluid culture and antibiotic sensitivity test. Samples were taken by consecutive sampling method and would be excluded if the medical record was incomplete. *Results*: There were ninety five pediatric patients treated with suspected meningitis. Thirty-three subjects had positive cerebrospinal fluid culture results with eight of them were contaminants. The proportion of bacterial meningitis was 26.3%. Bacterial meningitis was more common in children younger less than two years old (72%) compare with older children. The most gram-positive bacteria were *Staphylococcus sp.* while for gram-negative was *Acinetobacter sp. and Sphingomonas paucimobilis*. Vancomycin had a high sensitivity (92.8%) for gram-positive therapy, while for gram-negative it was cephalosporin drug which is ceftriaxone and cefepime (63.6%). *Conclusion*: Ceftriaxone as the main choice of empiric therapy still has high sensitivity to gram-negative bacteria but low sensitivity to gram-positive bacteria.

Keywords: Bacterial Meningitis, Children, Pathogens, Antibiotics

1. Introduction

Meningitis is a severe acute infection of the central nervous system (CNS), which is inflammation of the meninges, the membranes that cover the brain and spinal cord [1]. Meningitis can be caused by several micro-organisms such as bacteria, viruses or fungi or non-infectious conditions. Bacterial meningitis can be established through the results of CSF culture containing bacteria. Bacterial meningitis is less common than viral but can lead to more serious conditions and even death [2].

Bacterial meningitis can become an epidemic and cause death within 24 hours and leave one in five people with lifelong morbidity after infection [3]. Research conducted by the Global Burden of Disease (GBD) in 2016 estimated the incidence of meningitis cases globally from 2 to 2.5 million in 1990 to 2.82 million in 2016. While global deaths from meningitis decreased by 21% from 1990 to 2016, the overall burden of sequelae after infection remains high [4].

In Indonesia, cases of bacterial meningitis range from 158/100,000 cases per year [5]. The incidence of bacterial meningitis at the Sanglah Central General Hospital, Bali reaches 35-40 cases per year. The mortality rate in patients treated with antibiotic therapy is about 10% of the number of reported cases, while the mortality rate in untreated cases is 50-90% [6, 7].

The cause of specific bacterial meningitis depends on several factors based on age, immune function, immunization status, genetics and geographic location [2]. *Haemophilus influenzae* type b (Hib), *Streptococcus pneumonia* (invasive pneumococcal disease / IPD), *Neisseria meningitides*, *group B streptococcus*, and *Listeria monocytogenes* to date are the most common pathogens causing meningitis in children worldwide [8].

Vaccination in recent decades has helped reduce the rate of bacterial meningitis infection and changed the epidemiology of the disease. The success of Hib and IPD immunization can reduce the incidence of bacterial meningitis in developed countries. However, there has been no research on the success of this vaccine in Indonesia and the coverage of Hib and IPD immunizations is still low. Identification of the causative bacteria in each treatment center is important to be able to assist in patient management [9]. Nevertheless, bacterial meningitis remains a condition that requires rapid diagnosis and early management in its management in order to avoid sequelae and reduce morbidity [8, 9].

Given a quick and accurate antibiotics for bacterial meningitis can reduce the high rate of morbidity and mortality in patients [8, 10]. WHO has now developed a global map to beat meningitis in 2030, one of which is by recording the burden of disease and identifying pathogens [4]. This study was conducted with the aim of knowing the microorganism and antibiotic sensitivity pattern of bacterial meningitis in children at Sanglah Hospital Denpasar in 2019-2020 which is expected to provide benefits in the treatment of patients with bacterial meningitis.

2. Materials and Method

This study was a retrospective descriptive study with a cross-sectional design, to determine the microorganism and antibiotic sensitivity pattern of bacterial meningitis in children treated at Sanglah Hospital in 2019-2020. This research was conducted at Sanglah Hospital, Denpasar, Bali in November 2021. The study used registers of patients with bacterial meningitis at Sanglah Hospital. The sample population in this study were children aged 1-18 years with bacterial meningitis who were treated at Sanglah Hospital from January 2019 to December 2020.

The inclusion criteria in this study were children aged 1 month to 18 years with suspected bacterial meningitis who on a lumbar puncture examination, the results of CSF analysis showed pleocytosis with cells >10/mm^3 and/or increased CSF protein pleocytosis >50 mg/dL and/or decreased CSF glucose <60% serum glucose). CSF culture was performed as the gold standard for the diagnosis of bacterial meningitis and the results of antibiotic sensitivity tests were performed. The exclusion criteria in this study was if there were samples with CSF culture results that had the same results as the previous CSF culture in the same meningitis episode. If the subject meets the inclusion and exclusion criteria, the subject will be included in the study sample.

Sampling was done by consecutive sampling. Based on the calculation of the sample size using a single proportion formula using a prevalence from previous studies of 38% [11] and an acceptable prediction error of 15%, the minimum sample size in this study was 21 subjects. This study used all bacterial meningitis from January 2019 until December 2020.

The collected data was then analyzed statistically using SPSS for Windows version 23.0. Analysis of the data in this study in the form of descriptive analysis aims to describe the characteristics of the subject. Categorical data is presented in percentage form. This research has received ethical approval from the Research Ethics Commission of the Faculty of Medicine, Udayana University/Sanglah Hospital with number 1658/UN14.2.2.VII.14/LT/2021.

3. Result

This study found that 95 pediatric patients were treated with suspected meningitis during the period January 2019 to December 2020. A total of 33 subjects had positive CSF culture results. Eight of them are contaminant bacteria with six sampel are *Bacillus Sp*. while the other two microorganism are *Staphylococcus haemolyticus* and *Staphylococcus warneri*. The proportion of bacterial meningitis was found to be 26.3%. Bacterial meningitis was more common in children younger than 2 years (72%) than in older children. The characteristics of the research subjects are listed in Table 1.

Table 1. *Subject Characteristic.*

Characteristic	n(%) =25
Gender	
Male	13 (52%)
Female	12 (48%)
Age	
1month-2 years	18 (72%)
>2 years	7 (28%)
VP Shunt device	
Yes	6 (24%)
No	19 (76%)

Research has found more gram-negative bacteria as the cause of bacterial meningitis than gram-positive bacteria. A total of 14 (56%) samples with gram-negative bacteria were compared with 11 (44%) samples with gram-positive bacteria. Most gram-positive bacteria were obtained from the family *Staphylococcus sp.* with *Staphylococcus epidermidis* as the most common causative agent. In the gram negative group, *Sphingomonas paucimobilis* and *Acinetobacter sp.* is the dominant agent. In the sample using the VP shunt, the most common causative agents were *Sphingomonas paucimobilis* from the gram-negative group and *Staphylococcus sp.* on gram positive. The data are listed in Table 2.

Antibiotic susceptibility test was performed on twenty-five isolated bacteria. There were two bacterial isolates as multidrug-resistant organism (MDRO) which were classified as gram-negative bacteria and two bacterial isolates as Methicilliin-Resistant Staphylococcus

Epidermidis (MRSE). Ceftriaxone and cefepime had the highest sensitivity of 63.6% against gram-negative bacteria followed by cefoperazone sulbactam and gentamicin at 54.5%. In gram-positive bacteria, the antibiotics with the greatest sensitivity were vancomycin (92.8%) and linezolid (85.7%). Data in Figure 1 and Figure 2.

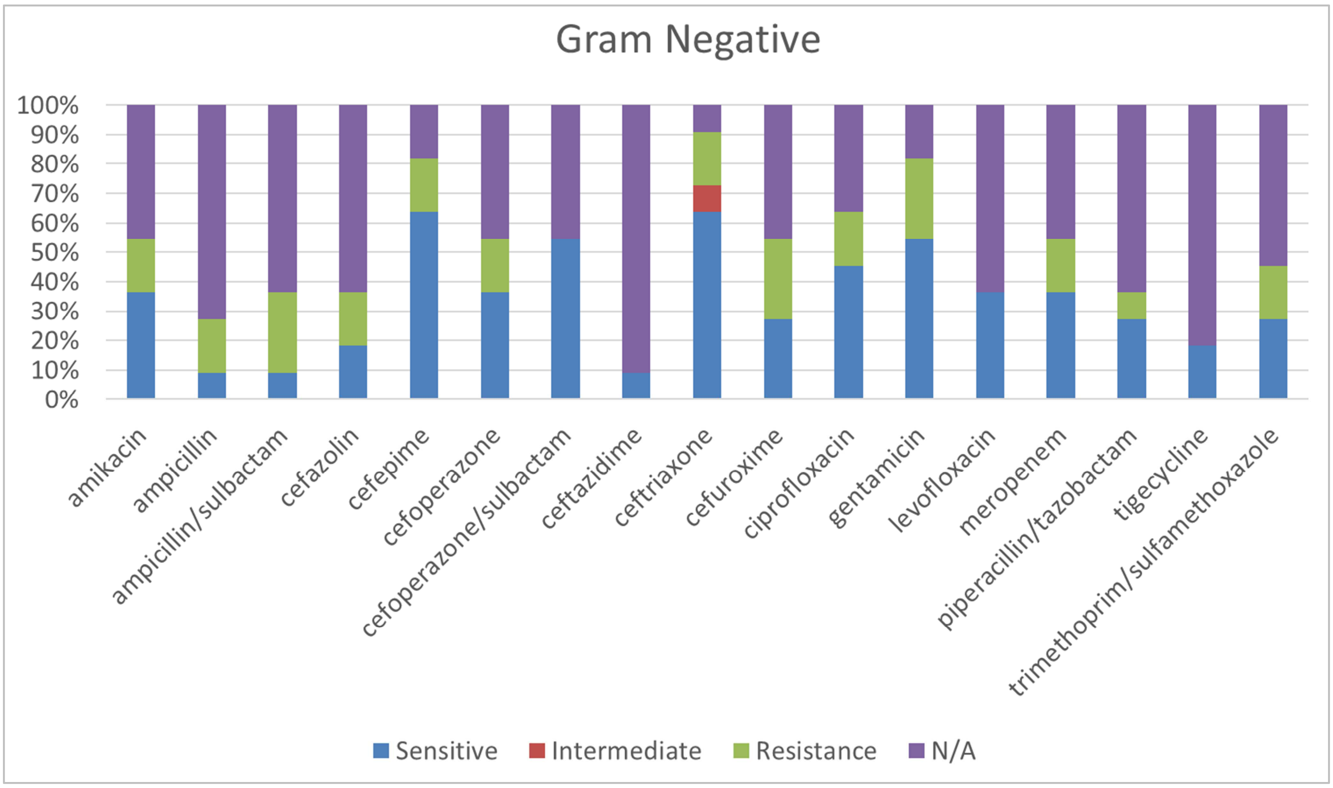

Figure 1. *Antibiotic sensitivity patterns of gram-negative bacteria that cause bacterial meningitis.*

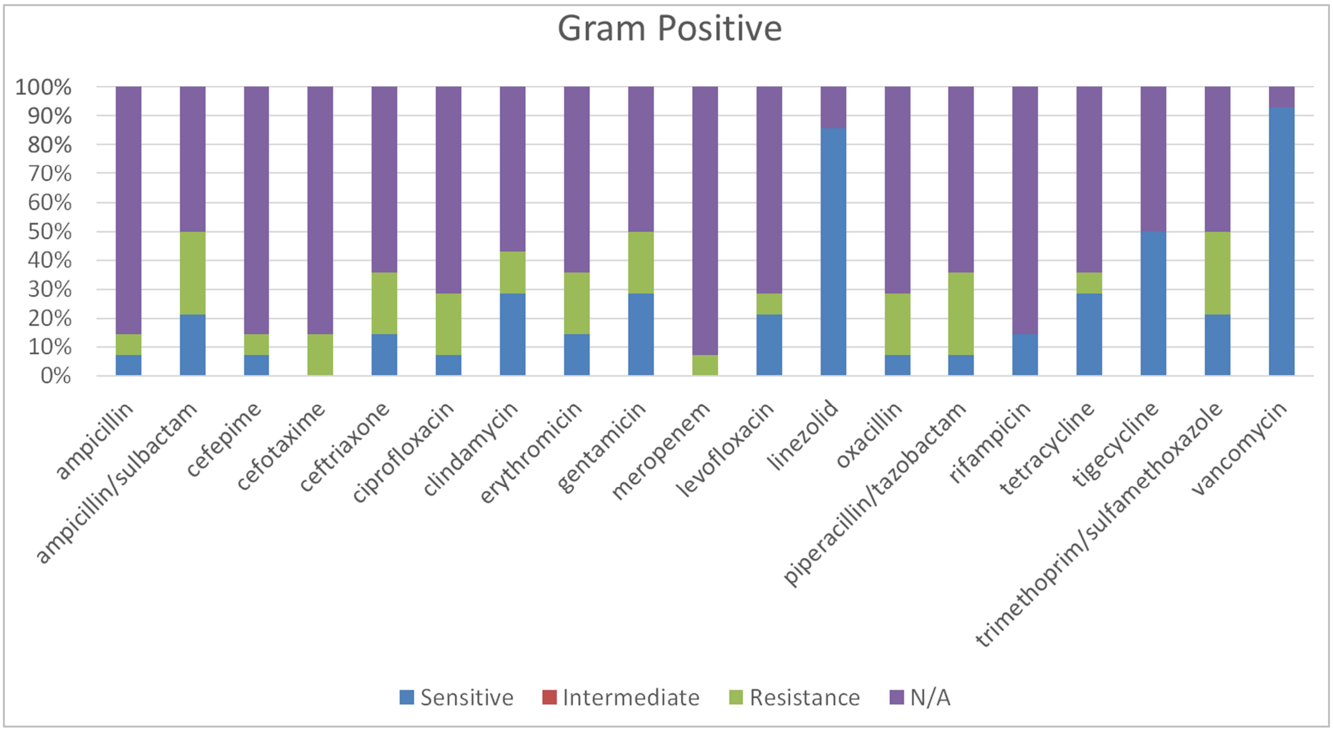

Figure 2. *Antibiotic sensitivity patterns of gram-postive bacteria that cause bacterial meningitis.*

Table 2. *Distribution of microbacterial from positive CSF culture according to age and use of VP Shunt.*

Microorganism	N	(%)	Patient Classification			
			Age		VP Shunt	
			1mo. – 2y.o	> 2y.o	Yes	No
Gram Positive Bacteria	14	56	10	4	4	10
Staphylococcus sp.	7	28	5	2	3	4
Enterococcus sp.	2	8	2	0	1	1
Rothia dentocariosa	1	4	0	1	0	1
Streptococcus pneumoniae	3	12	3	0	0	3
Globicatella sanguinis	1	4	0	1	0	1
Gram Negative Bacteria	11	44	8	3	2	9
Sphingomonas paucimobilis	3	12	3	0	2	1
Acinetobacter sp.	3	12	2	1	0	3
Klebsiella pneumoniae ssp Pneumoniae	1	4	1	0	0	1
Providencia stuartii	1	4	0	1	0	1
Salmonella sp.	1	4	1	0	0	1
Pseudomonas stutzeri	1	4	0	1	0	1
Serratia fonticola	1	4	1	0	0	1
Total	25	100	18	7	6	19

4. Discussion

Bacterial meningitis is an emergency condition. The target of therapy in this condition is the administration of antibiotics within 60 minutes after the patient comes to the emergency department [12]. Establishing a diagnosis and giving prompt and appropriate therapy is very important. To achieve this, it is important to know the most common microorganisms that cause bacterial meningitis and antibiotic sensitivity as a reference in determining empirical antibiotics.

Every patient who presents with suspicion of bacterial meningitis needs to do a lumbal punction to have a CSF culture and also an antibiotic sensitivity test. CSF culture is the standard in establishing a diagnosis and is estimated to show positive results in 70-80% of cases of bacterial meningitis who have not received previous antibiotic therapy [12, 13]. However, it should be noted that the consumption of antibiotics prior to CSF sampling can decrease the sensitivity of the culture results. In addition, it takes a relatively long time of at least 72 hours to obtain culture results. Positive CSF culture results can also be caused by bacterial contamination. In this study we found eight samples (24.2%) containing contaminant bacteria. Garg et al also showed similar results, namely that there was an overall contamination rate of 18.2% in the study carried out [14]. Kristianti et al in a previous study reported that there were 92 samples with positive culture results but only 52 (56.5%) were bacterial meningitis, the rest were contaminants. Delayed in diagnosing the causative bacteria can be avoided by using molecular methods based on polymerase chain reaction or PCR. This method has high sensitivity and specificity, but its use is limited due to high cost [15].

Bacterial meningitis based on the source of infection can be divided into community-acquired and nosocomial. Adil et al reported that community-acquired cases were more common (84.6%) than nosocomial cases. Bacterial meningitis that occurs as a result of nosocomial infection is most often surgical procedures involving the blood-brain barrier, one of which is the use of a ventriculoperitoneal (VP) shunt. This procedure is quite common, especially for cases of hydrocephalus. Previous studies have stated that the most common bacteria causing meningitis in the use of a VP shunt is Staphylococcus bacteria [16]. Despite advances in surgical techniques and infection control, infections associated with VP shunt placement still range from 5 to 18% and are mostly caused by gram-positive bacteria (59%) [17]. This is in accordance with the results of a study which found that 24% of samples with the use of a VP shunt and the most common cause were gram-positive bacteria, namely *Staphylococcus sp.*

In general, patients with bacterial meningitis were dominated by men (55.7%), both in community-acquired and nosocomial cases [16]. Children aged less than 2 years are more susceptible to bacterial meningitis than older children. This is related to the immaturity of the immune system, especially with regard to the phagocytic ability of neutrophils and monocytes [8]. In line with these findings, the majority of the sample in this study came from the age group of less than two years (72%).

The microorganisms that cause meningitis are quite varied, depending on geographic location, socioeconomic status, age, availability of vaccinations and a person's health status [18]. Epidemiological studies in the United States found that the most common cause of bacterial meningitis cases in children was Streptococcus (30.7%) [16]. On the other hand, a study in Namibia, South Africa reported *Streptococcus pneumoniae, Neisseria meningitidis, group B Streptococci, Listeria monocytogenes, Haemophilus influenzae type b (Hib),* and pneumococcal infections [12]. Fenta et al explained that more than 80% of cases of bacterial meningitis were caused by *N. meningitidis, S. pneumoniae, and H. influenza*. Two-thirds of cases are found in children under five years of age (toddlers) and adolescents, but *H. influenza* is mostly found in infants. On the other hand, Group B hemolytic streptococcus (*S. agalactae*) is a common pathogen in neonates [13]. Most cases from the previous study at the same tertiary hospital found most cases were caused by *Staphylococcus hemolyticus* as gram-positive bacteria and *Pseudomonas stutzeri* as gram-negative bacteria. Gram-negative bacteria are more dominant [6]. Not different from previous findings, in this study it was found that the most common gram-positive bacteria was dominated by the family *Staphylococcus sp.* namely *Staphylococcus epidermidis* followed by *Streptococcus pneumonia*. Meanwhile, in this study *Sphingomonas paucimobilis* was the most common gram-negative bacteria causing bacterial meningitis.

Staphylococcus epidermidis is the most common gram-positive coagulase-negative bacteria living on human skin. In their natural environment, these bacteria are harmless. These bacteria are opportunistic. It can cause infection under certain conditions in the human body. Its ability to adhere and form biofilms on foreign body surfaces is thought to be the most significant mechanism in initiating infection. The use of medical and prosthetic devices makes it easier for bacteria to enter the bloodstream [13]. The bacteria are generally associated with neurosurgical devices such as the VP shunt. Meningitis caused by *S. epidermidis* in the absence of these devices are rarely found [19]. In this study, 6 samples were obtained with the use of VP. In the shunt, there were 2 samples with *Staphylococcus epidermidis* as the causative bacteria.

Staphylococcus epidermidis are like *Sphingomonas paucimobilis* is also opportunistic bacteria. These bacteria infect the host with chronic disease or decreased immunity. These bacteria are found multiplying in distilled water, hemodialysis fluids, and sterile drug solutions. Infection by this bacterium can be nosocomial or community-acquired and about 31-52.7% of cases are community-acquired [20, 21]. *Sphingomonas paucimobilis* has a relatively low virulence because it has only a few components of the cell membrane lipopolysaccharide and endotoxin activity [21]. These pathogens are capable of causing bacteremia and septicemia. In hospitalized patients, *S. paucimobilis* has been reported as a cause of catheter-associated bacteremia, sepsis, meningitis, peritonitis, genitourinary infections, and skin infections [22].

Complications that occur in bacterial meningitis can be short-term or long-term. Short-term complications that can occur include seizures, focal neurological deficits, and subdural effusion, while long-term complications include hearing loss, cognitive impairment, hydrocephalus, and epilepsy. Delay in giving antibiotics by 24–72 hours can lead to a poor prognosis and increase the risk of severe neurologic complications. To prevent this, primary and secondary prevention can be carried out. Primary prevention is done through vaccination, while secondary prevention is one of them with antibiotic therapy [23]. Vaccination especially Hib and pneumococcal vaccines as primary prevention is expected to reduce the incidence of bacterial meningitis. Hib vaccination started in the early 1980s led to a significant reduction in the incidence of bacterial meningitis caused by *Haemophilus influenzae* [24]. In this study, no *Haemophilus influenzae* was found, but 3 samples with *Streptococcus pneumoniae* were found as the causative bacteria. We failed to found the immunization history from this research sampel as this study used secondary data. Indonesia has a immunization policy where HiB immunization is included as a basic immunization covered by the government while the PCV vaccine are still not covered.

Empirical therapy should be initiated rapidly if bacterial meningitis is suspected [12]. However, increasing reports of bacterial resistance in vitro to commonly used drugs have led to the idea that current treatment options may not be appropriate. Therefore, it is important to review the latest epidemiological data and carry out susceptibility testing, especially for cases of bacterial meningitis [13].

Fenta et al in their study with predominantly male subjects (53.3%) and age of less than 14 years found that gram-negative and gram-positive bacteria were 100% resistant to penicillin and S. aureus was resistant to amoxicillin (100%), penicillin G. (100%), ciprofloxacin (100%), and erythromycin (100%). There were no isolated bacteria that were resistant to Vancomycin in that study, so it is considered a therapeutic option especially in cases of multidrug-resistant bacteria, together with the cephalosporins [13]. Third-generation cephalosporins such as cefotaxime and ceftriaxone can be given to children. This antibiotic is generally an empiric therapy that can cover almost all common pathogens such as *S. pneumoniae* and *N. meningitides* [23]. In this study, vancomycin had the highest sensitivity (92.8%) for gram-positive therapy followed by linezolid (85, 7%) and tigecycline (50%), while for gram-negative, ceftriaxone and cefepime have a sensitivity of 63.6%. Ceftriaxone is currently the mainstay of empiric therapy in our medical center. Based on the sensitivity test that has been carried out, ceftriaxone has a good sensitivity to gram-negative bacteria but has a low sensitivity (14.2%) to gram-positive bacteria. Vancomycin, linezolid and tigecycline have high sensitivity to gram-positive bacteria. The third and fourth generation cephalosporins still have a high sensitivity to gram-negative bacteria.

Our data was based on single-center experience, thus the results are legitimately associated to the local epidemiological condition. Epidemiological variations, the prevalence of resistant strains in the region, and the type of antibiotic treatments can all be attributed for variances in the bacterial spectrum and antibiotic resistance pattern of isolates identified between contemporary research and older studies. The execution of local epidemiological surveys has a crucial role in the management of children with bacterial meningitis, according to our findings.

5. Conclusion

The most common cause of bacterial meningitis in the study was gram-positive bacteria, namely *Staphylococcus sp.* with vancomycin, linezolid and tigecycline as antibiotics that can be used. Ceftriaxone as the main choice of empiric therapy still has high sensitivity to gram-negative bacteria but low sensitivity to gram-positive bacteria. This can be calculated at a later date before the administration of therapy in cases of bacterial meningitis.

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