University of Science and Technology
Faculty of Medicine and Health Sciences
Medical Laboratory Department

جامعـــــــــة العـــلوم والتكنولوجيا
كلية الطب والعلــــــوم الصحيـــة
قســــــم المختبرات الطبيـــــــة

Bacteriological profile of meningitis in Sana'a, Yemen: two years retrospective study

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Graduation research project in partial fulfillment of the requirements for Bachelor degree in Medical Laboratories

1444AH

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Dedication

... For Our Fathers and Mothers whose are beside us

... For Our Doctors Whose support us

... For Our University Which give us A lot of things

... For Our Friends Who help us

... For Our Patients Who help us in the research

... For Our Supervisor

Doctor Ibrahim Al-Sabal

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We would strongly like to present our best regards to

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Abstract

Background: One of the most serious and potentially fatal infectious diseases is acute bacterial meningitis (ABM). Current understanding of the organisms that cause CNS illness and their antibiotic susceptibility pattern in a specific environment or location is crucial to ensuring effective therapy. **Aims:** Determining the bacterial isolates and their sensitivity pattern in the cerebrospinal fluid of acute meningitis patients at a USTH in Sana'a city was the purpose of this investigation. **Methods:** The study was carried out retrospectively at USTH, which serves Yemen's urban and rural populations. Between January 2021 and December 2022, 187 samples of erebrospinal fluid (CSF) from meningitis patients with clinical suspicion underwent bacteriological examination. **Results:** A total of 187 CSF samples were examined during the research period. A culture indicating a 9.01% incidence led to the confirmation of 17 of these cases as bacterial meningitis. Children were more likely than adults to have ABM. Gram-negative (76.5%) bacteria were the most prevalent type of organism. Pseudomonas aeruginosa and Staphylococcus spp. were the most frequently isolated microorganisms, followed by Klebsiella pneumoniae. Gram negative and positive bacterial isolates showed higher resistance to beta-lactam antibiotics and to other commonly prescribed antibiotics. **Conclusion:** The three main etiological agents of bacterial meningitis in our area are *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *S. aureus*. Among the bacterial isolates, the prevalence of both single and multiple antibiotic resistances was quite high. Thus, it is crucial to conduct microbiological monitoring to identify prevalent infections and their patterns of antimicrobial sensitivity in order to choose an appropriate empirical antimicrobial therapy based on local and global data to prevent the establishment of resistant organisms.

Chapter 1: Introduction

Introduction

Meningitis is an inflammatory affects the meninges, which are the three membranes that envelop the brain and spinal cord (1,2). Due to the tight physical link between the cerebrospinal fluid (CSF) and the brain, meningitis can also involve the brain cortex and parenchyma (3). Involvement of the brain cortex and parenchyma due to either direct inflammation or vascular problems may induce behavioral changes, localized neurological abnormalities, and impairment of consciousness, which are commonly thought of as signs of encephalitis (1- 4).

Meningitis can be caused by pathogens including bacteria, viruses, fungi, or parasites, as well as by autoimmune, malignancy, or drug responses (1,4). Malnutrition, home overcrowding, HIV infection, lack of vaccination, indoor air pollution, and sickle cell disease are risk factors that put people at risk for meningitis and epidemics (1,5). The majority of meningitis-related fatalities are caused by infectious agents; however the causative agent has a different effect on the disease's clinical severity (1,3).

The most severe form of meningitis, with a high case fatality rate and potential for neurological impairment, is bacterial meningitis (3,6,7). An estimated one million cases of bacterial meningitis occur worldwide each year, with 200,000 deaths (5). According to the World Health Organization, meningitis claimed the lives of almost 290,000 individuals in 2015 (4). Despite a 21% decrease in the number of meningitis-related deaths from 1990 to 2016, the total burden of meningitis remains high (4). Without treatment, the fatality rate from bacterial meningitis can reach 70% and varies by geography, country, age, pathogenic bacterial species, etc (4,7). In developed nations, case fatalities vary from 3% to 19%, while in developing nations, they range from 37% to 60% (4).

In addition to a high mortality rate, bacterial meningitis may leave survivors with a significantly high degree of disability (8,9). Among the survivors of bacterial meningitis, 20% t0 50% may experience long-lasting neurological sequelae (4,5,10), such as hemiparesis, hydrocephalus, seizures, and cranial nerve palsies. The vast majority of cases of disability (98%) occur in low- and middle-income countries (4).

Prior to the implementation of vaccination programs, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Hemophilus influenzae* type b (Hib) were the main causes of bacterial meningitis (1,4,8,11,12).

Meningitis can be decreased by using preventive immunization against the main etiological agents, such as immunization against *H. influenzae* type B (Hib), *S. pneumoniae*, and *N. meningitides* (1,13). According to published reports, the widespread use of the PCV7 (against S. pneumoniae) and Hib (against H. influenza) vaccines has significantly reduced the incidence of bacterial meningitis globally, in both vaccinated and non-vaccinated populations (2).

(18) While powerful antibiotics and effective vaccinations are readily available, the fatality rate from acute bacterial meningitis is still quite high in undeveloped countries including Yemen (9,11,14). As the microorganisms that cause meningitis change with time, geography, and patient age, periodic evaluations of bacterial meningitis are necessary both locally and globally for the right and prompt treatment of meningitis.

With the exception of a few sporadic old single-hospital-based studies (15,16,17), no local research has been done recently to explore the bacteriological profile of meningitis in Yemen.

In light of this, the purpose of this research was to investigate the bacterial profile and antimicrobial sensitivity pattern of bacteria isolated from the cerebrospinal fluid (CSF) of patients with clinically suspected meningitis who were admitted at the University of Science and Technology Hospital (USTH) and other main clinical labs in Sana’a.

Chapter 2: Literature review

2.1 Meningitis definition

Meningitis is a severe infection of the meninges that surrounds the brain and spinal cord and is typically caused by a bacterial, viral, or fungal infection (1,2). Meningitis poses a great threat to life of people all over the world. It is essential to know if meningitis is caused by a virus or bacterium since it affects the severity of the illness and the course of treatment (18).

2.2 Bacterial meningitis

One of the most prevalent infectious disorders worldwide is bacterial meningitis (19). There are several bacteria that cause bacterial meningitis such as: *Haemophilus influenza*, *streptococcus pneumoniae*, *Neisseria meningitidis* serogroup A, B, C, W135, *Echerechia coli*, *Listeria monocytogenes*, *Staphylococcus aureus* and the most common are *Haemophilus influenza*, *streptococcus pneumoniae*, *Neisseria meningitides* (20). But the prevalence of acute bacterial meningitis varies from place to place and is influenced by the patient's age, the season, and geographic region (20). Children who survive acute bacterial meningitis (ABM) are more likely to experience long-term neurological impairment. ABM is a significant contributor to pediatric mortality (21).

2.3 Epidemiology of bacterial meningitis

The epidemiology of bacterial meningitis has significantly changed during the past 20 years. A spectacular example of a successful immunization effort is the disappearance of Haemophilus influenzae, a once significant cause of meningitis, in developed nations (1). These days, both in the US and in Europe, pneumococci constitute the major cause of bacterial meningitis in both children and adults. The disease affects between 1.1 and 2 people per 100,000 in the US and Western Europe, but 12 people per 100,000 in Africa each year. The risk of disease is greatest in people under the age of five and in those beyond the age of sixty. There are certain established risk factors, including previous splenectomy, malnutrition, and sickle cell disease. In areas where conjugate pneumococcal vaccinations are being used, invasive pneumococcal illness, particularly meningitis, has significantly decreased. Increased beta-lactam antibiotic resistance in pneumococci is a new issue. Neisseria meningitides has replaced Haemophilus as the most common cause of meningitis in poorer nations, but it is still a serious health concern in the US and Europe. The region with the highest prevalence is the sub-Saharan meningitis belt, where cyclic epidemics happen at least once every ten years (16,22,23).

2.4 Common etiology of bacterial meningitis

2.4.1 *Streptococcus pneumonia*

One of the most frequent causes of bacterial meningitis worldwide is *Streptococcus pneumoniae*. Streptococcus' name translates to "twisted chain." This phrase perfectly captures the microscopic appearance of this particular bacterial group. Streptococcus produces lengthy, twining chains of spherical cells. It is a bacterium that is encapsulated and has 93 different serotypes based on the unique polysaccharide characteristics of the capsule. Although other serotypes have the potential to cause disease, serotypes 1 and 5 are primarily responsible for the bulk of infections in developing countries (24). *Streptococcus pneumoniae* is to blame for about 60% of adult pneumonia cases results in swelling and inflammation within the lungs. What connection does this bacterium have to meningitis? The same bacteria have the ability to cause bacteremia and pneumococcal meningitis (25). Since Streptococcus is a gram-positive bacterium, it causes diseases through releasing a range of exotoxins. Exotoxins are secretions that bacteria emit from their cell walls that harm the host cells. The exotoxins known as pyrogens are responsible for the high fever linked to pneumococcal meningitis. The skin and mucous membranes are affected by a rash caused by other exotoxins, such as the pyrogenic and erythrogenic toxins which are exotoxins that cause an allergic reaction. Various enzymes, also, produced by *S. pneumoniae* in its other secretions can kill host cells and tissues. Hemolysins are enzymes that break down red blood cells results in a more serious illness. break down RBCs provides bacterium with a rich source of protein and iron for the quick growth of *S. pneumonia* (26).

2.4.2 *Neisseria meningitides*

Through epidemic or sporadic meningitis and/or septicemia, *Neisseria meningitidis* (the meningococcus) significantly increases morbidity and mortality in children and young adults around the world (27). *Neisseria meningitidis* is a fastidious, encapsulated, aerobic gram-negative diplococcus. Genome sequence typing has recently been added to the phenotypic categorization of meningococci, which was previously based on structural variations in the capsular polysaccharide, lipooligosaccaride (LOS), and outer membrane proteins. (28).

Neisseria meningitidis has 12 distinct serogroups, or kinds, but only the types A, B, C, Y, and W135 of these strains can harm humans. For the majority of meningococcal meningitis cases, serogroups A, B, and C are to blame (27).

Despite effective antibiotics and partially effective vaccines, *Neisseria meningitidis* remains a global problem. The most common cause of meningitis and rapidly developing fetal sepsis in otherwise healthy people worldwide is *Neisseria meningitidis*. Each year, there are more than 500000 meningococcal cases, a number that is frequently made worse by significant epidemic outbreaks. Due to these figures, bacterial meningitis is now among the top ten infectious causes of death globally (29).

A multifaceted process including pili, LOS, opacity associated, and other surface proteins is used by *Neisseria meningitidis* to colonize mucosal surfaces. Some clonal groups have greater ability to enter the bloodstream, avoid innate immune defenses, reproduce, and cause systemic illness (30).

A wide range of human diseases is brought on by the meningococcus, nevertheless, is most frequently linked to meningitis with sudden onset and severe sepsis meningococcemia. Septic, arthritis, pneumonia, purulent pericarditis, conjunctivitis, otitis, sinusitis, and urethritis are other symptoms of meningococcal illness. Fever, rash, joint pain, and headache are symptoms of the unusual illness chronic meningococcemia, which can last for several weeks. Meningococcal disease has a case-fatality rate of 10–20%, and an equal percentage of survivors experience long-term effects like deafness, mental retardation, and other neuronal sequelae (31).

2.4.3 *Haemophilus influenza*

Is a gram-negative, facultative anaerobic, non-motile coccobacillus that needs a specific growth factor, factor X (hemin), and NAD to survive (factor V). Depending on whether a polysaccharide capsule is present or not, *Haemophilus influenzae* strains are split into two groups Six serotypes, labelled as serotypes A through F, have been discovered based on antigenically unique polysaccharide capsules (32,33).

In infants and children, the serotype B strain can produce an invasive infection. Non-typeable strains frequently colonize the upper respiratory system and infect the mucous membranes of kids and adults. Microbiologists who were cultivating the bacterium in culture gave it the name *Haemophilus influenzae* when they noticed with blood. Haemo is Greek for "blood," and philus is Latin for "to love." Many parents are aware of the ear and eye infections in kids brought on by *H. influenzae*. One of the conditions the bacterium most frequently causes is conjunctivitis, usually known as pinkeye. The second part of the organism's name, however, comes from the fact that it is also known to cause respiratory infections that resemble the flu. Coughing, sneezing, and touching are all effective ways to spread it from one person to another. Those youngsters, who don't wash their hands, can spread H. influenzae to their family, friends, and classmates by touching their lips or noses. Children under the age of five are especially susceptible to meningitis caused by *H. influenzae*. Up until the widespread adoption of immunizations, it was a major contributor to meningitis among children in the United States; today, it is only a problem in areas of the world where infants are not vaccinated. Doctors have found that meningitis caused by a specific strain of *H. influenzae* known as Hib. *H. influenzae* type B is known as Hib. The "B" stands for a polysaccharide, which is a sugar-like compound that is present on the bacterium's surface. *H. influenzae* is distinct from many other bacteria because it has a covering on its surface known as a capsule. *H. influenzae* is able to adhere to cell surfaces and is kept from drying out thanks to the capsule. When *H. influenzae* starts to multiply rapidly and travels outside of the mucous membranes of the nose and throat, illnesses start to develop. Mucous membrane inflammation is brought on by high *H. influenzae* populations in the lower respiratory tract. Through irritated regions of the inflammatory mucous membrane, the germs might occasionally reach the bloodstream. The meninges and cerebrospinal fluid are both accessible to *H. influenzae* after it enters the bloodstream. Serotypes are genetic differences that *H. influenzae*, like many bacteria, possesses. There are numerous *H. influenzae* serotypes, according to recent investigations. Different parts of the world are often characterized by different serotypes. This aids public health authorities in determining the cause of a specific meningitis case. There have been some serotypes linked to infections that are more likely to result in severe meningitis. (34).

2.5 Neonatal Meningitis

Neonatal meningitis continues to be a fatal condition despite improvements in newborn critical care. *Escherichia coli* (*E. coli*) and Group B Streptococcus (GBS) are common in some developed nations and were identified as the primary bacterial meningitis pathogens in newborn neonates (35). The microorganisms responsible for neonatal meningitis variy somewhat globally, and regional variations in incidence are significant also (35). Neonatal bacterial meningitis is most frequently caused by *Streptococcus agalactiae* (group B Streptococcus), *Escherichia coli*, and *Staphylococcus aureus* (36,37).

2.5.1 Epidemiology of Neonatal Meningitis

According to WHO estimates, 4 million newborns die each year. The vast majority (99%) take place in underdeveloped nations (38). In addition to other infections, preterm, and birth asphyxia, neonatal meningitis is a major contributor to the burden of newborn morbidity and mortality. It's possible that the true prevalence of neonatal bacterial meningitis is underreported, especially in countries with few resources (39).

These include challenges in detecting newborn meningitis, variations across studies conducted in hospitals and communities, regional variations, and unreported deaths in places with low access to healthcare.

The early infant or neonatal period's definition is up for debate. Numerous studies say the neonatal period lasts up to 30 or 90 days old; the WHO considers 60 days to be the "young infant" age. Within these constraints, the annual estimated number of cases of neonatal meningitis is 126 000, with more than 50 000 fatalities.

In sub-Saharan Africa, mortality rates range from 0.7 to 1.9 per 1,000 live births, whereas they are 0.33 to 1.5 in the Middle East and North Africa and 0.4 to 2.8 in the Americas and Caribbean (40,41).

2.6 Meningitis Pathophysiology

Meningitis can be contracted in a variety of ways, depending on the disease. Some are not contagious at all, while others are more easily transmitted. Bacterial meningitis can be transmitted via eyes, nose, mouth secretions, birth, blood, as well as dirty hands. Living in close quarters for an extended period of time or coughing on, sneezing or kissing someone can also cause *Streptococcus pneumonia*, *Haemophilus influenza* type b and *Neisseria meningitidis* to spread and inhaled by other healthy people (42).

Before entering the central nervous system, pathogenic bacteria must cling to surfaces and invade mucosa before moving into the intravascular space and surviving there. Pathogenic bacteria can bind to epithelium mucosa by many types of adhesions such as pili and capsules.

Bacteria must escape secretory IgA found in mucous membrane. IgA proteases are secreted by almost all clinical isolates of *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*. These enzymes cleave the IgA protein's proline-rich hinge region, rendering it inactive and facilitating bacterial attachment to the epithelium.

A successful meningeal pathogen must specifically colonize the host's mucosal epithelium, infiltrate and persist in the intravascular space, pass the blood-brain barrier, and persist in the cerebrospinal fluid in order to spread throughout the meninges (CSF).

The most frequent bacteria cause meningitis (*S. pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Escherichia coli*) have the ability to avoid a number of host defenses, which is related to their neurotropic potential.

Bacteria can survive in the bloodstream by avoiding the alternate complement pathway, which is a virulence trait related to capsular polysaccharide. Each significant meningeal pathogen has a different molecular mechanism for complement avoidance.

The process of bacterial entry into the CSF and passage of the blood-brain barrier is the stage in the pathogenesis of meningitis that is least understood (43).

Bacteria are likely to survive after they enter the CSF since humoral defenses, in particular immunoglobulin and complement activity, seem to be almost nonexistent. Opsonic activity is undetectable in the CSF of healthy individuals and fluctuates even when the blood-brain barrier breaks down due to bacterial meningitis (44).

Therefore, the production of multiple bacterial virulence factors that override successive human defenses and enable the pathogen to enter and proliferate in the CSF is associated to the pathogenesis of meningitis.

2.7 Neuronal Damage

Multiple processes contribute to the brain damage in bacterial meningitis those results in death and long-term neurologic consequences. Inflammation, leukocyte invasion, and microglia activation are all facilitated by bacterial invasion and the production of bacterial chemicals (45). Free radicals, proteases, cytokines, and excitatory amino acids are released by leukocytes, macrophages, and microglia, which ultimately results in energy failure and cell death. Secondary brain injury is brought on by vasculitis, localized ischemia, and brain edema as a result of elevated cerebrospinal fluid outflow resistance, perforation of the blood-brain barrier, and swelling of necrotic cells (46).

Numerous factors, including bacterial toxins, the inflammatory response to the invader, or the cytotoxic components of the complement system, are thought to have contributed to the CNS damage brought on by the invading bacterium (46).

2.8 Meningitis Clinical Presentation

Clinical presentation varies depending on age, duration of illness, host susceptibility and pathogen. In 25–50% in adults, the traditional combination of fever, stiff neck, and disturbed mental status occurs; however, in children, this combination may be less common. Small children, for instance, may instead exhibit nonspecific symptoms such fever or hypothermia, fatigue, anorexia, vomiting, diarrhoea, dyspnea, convulsions, or enlarging fontanelles. Older kids react more like adults do, and symptoms like fever, headache, photophobia, nausea, vomiting, confusion, exhaustion, or irritability are more common among them. While there is less data on sex-related differences in clinical presentation and laboratory results, boys have a greater case fatality rate for acute bacterial meningitis than girls (47).

2.9 Meningitis complications

If untreated, bacterial meningitis can be fatal or result in a number of problems, including seizures, intellectual impairment, speech abnormalities, hearing loss, and learning disabilities in survivors. These problems can occur at a rate of up to 50%. The probability of obtaining these depending on the organism involved, the patient's age, the severity of the condition, and the effectiveness of the care given. These issues are more frequent in little children and can result in significant brain problems that frequently have a tendency to persist a lifetime (48,49).

2.10 Diagnosis of Bacterial Meningitis

Meningitis is under the category of illnesses that cannot be diagnosed merely through physical examination. Almost all types of meningitis start out as what seems to be a normal cold or respiratory condition (50). The illness eventually advances to a septic state that can become meningitis. The three bacteria that cause meningitis all proceed in a similar manner. In order to narrow down the precise diagnosis, clinical laboratory testing must also be performed in addition to a physical examination. Because it resembles so many other diseases, meningitis can be challenging to diagnose at first (51).

2.10.1 Collection, Transportation, Receipt, and Storage of CSF

CSF is subject to general safety measures, such as barrier protection, hand washing, proper waste disposal, avoiding the production of aerosols, etc. Readers are reminded that two cases of *N. meningitidis* disease acquired in a clinical laboratory have been documented (52). When selecting an effective antibiotic therapy and handling the infection management components of bacterial meningitis, the physician frequently needs to know what bacteria are causing the illness. CSF and blood culture specimens from patients who have clinical signs and symptoms of meningitis should be collected, and they should be delivered right away to the laboratory, in order to begin the conclusive identification of a bacterium that causes meningitis. Because CSF is hypotonic, neutrophils may lyse, and counts in CSF specimens kept at room temperature may drop by 32% after an hour and by 50% after two. Fastidious organisms like *N. meningitidis, S. pneumoniae,* and *H. influenzae* may not withstand lengthy transit times or temperature changes. Therefore, CSF specimens should be maintained at room temperature or in an incubator (37°C) if they can't be processed right away because refrigeration may hinder the recovery of these organisms (51, 53).

One of the few clinical microbiology procedures that must be completed right away is the processing of a CSF specimen. The physician treating the patient should be informed as soon as the findings of quick tests are available (e.g., Gram stain, antigen detection assays, Limulus amebocyte lysate [LAL] assays, etc.), and a permanent record of the communication should be made (51).

2.10.2 CSF concentration

By concentrating the bacteria in a CSF specimen, the chances of finding bacteria by culture and staining methods are improved. Before CSF samples are taken, around 50% of meningitis patients receive antibiotic medication, which can lower the number of organisms in the CSF by 10^2 to 10^6 times (51,54).

Centrifugation should be used to concentrate the samples for at least 15 minutes at 1,500 to 2,500 x g when >0.5 ml of CSF is available for microscopic analysis and culture. Use the sediment to inoculate culture media and get smears ready for staining (51,54).

2.10.3 CSF microscopic examination

All CSF samples should be stained with the Gram stain (or a similar stain) and viewed under a microscope. Since the concentration of bacteria in the CSF of patients with bacterial meningitis (10 to 109 CFU/ml) determines the diagnostic utility of staining methods, all CSF specimens of adequate quantity should be treated to concentrate pathogens before microscopic examination and culture. Sequentially laying tiny amounts of previously concentrated CSF onto the same region of a microscope slide and allowing each amount to dry completely will result in a slight increase in concentration for Gram stain purposes. This layering strategy, which depends primarily on the specimen's uncertain adherence to the slide, obviously seriously jeopardizes quick turnaround time.

A quick, reliable, low-cost approach for identifying bacteria and inflammatory cells in CSF from patients with bacterial meningitis is the Gram stain. Gram stain positivity is present in 75–90% of CSF culture-positive specimens; however, this percentage drops to 40–60% in patients who have already received antimicrobial medication (51,54).

2.10.4 CSF culture

Regularly used media for CSF bacterial culture include chocolate agar, 5% sheep blood agar, and enrichment broth (e.g., thioglycolate, Columbia, brucella, supplemented peptone). The culture plates should be kept in an environment with 5 to 10% CO2 for at least 72 hours at 37°C. In the absence of a CO2 incubator, a candle jar may be utilized. For a minimum of five days, the enrichment broth should be incubated at 37°C with the cap loose. A MacConkey agar plate can also be inoculated if the Gram stain shows the presence of gram-negative rods that resemble members of the Enterobacteriaceae family.

Cultures should be checked every day. A doctor treating the patient should be contacted by phone with the findings of a gram stain for colonial or broth growth (51,54).

2.10.5 Antibiotics susceptibility testing

All therapeutically important bacteria obtained from CSF should generally undergo thorough antibiotic susceptibility testing. The production of beta-lactamase by *H. influenzae* should be assessed using a chromogenic or acidimetric assay. The clinical efficacy of chloramphenicol may also be evaluated using an assay for the detection of chloramphenicol acetyl transferase. When an isolate of *N. meningitidis* comes from a patient who isn't responding well to antibiotic therapy, it's important to check for beta-lactamase production. To check for frank and relative penicillin resistance in *S. pneumoniae*, the oxacillin agar screen method should be used initially. The agar screen method does not distinguish between the two types of resistance; it just finds them both. An isolate is either obviously resistant to penicillin or just moderately susceptible if the screen test results show a 19-mm zone of inhibition.

Meningitis patients who have *S. pneumoniae* isolates from their CSF that are relatively resistant to penicillin as determined by dilution testing should always be reported as resistant because they are likely to not respond clinically to penicillin (51,54).

2.10.6 Detection of Bacterial Antigen

For the quick and accurate identification of soluble bacterial antigens in CSF of patients suspected of having bacterial meningitis, counter-immunoelectrophoresis (CIE), coagglutination (COAG), and latex agglutination (LA) have been developed. These assessments are frequently employed in clinical microbiology laboratories and may be significant add-ons to CSF specimen culture and Gram staining. When culture and Gram stain findings are negative for meningitis patients who have undergone antibiotic therapy, rapid antigen detection assays may nevertheless yield true-positive results. A doctor may also decide to start early and targeted antimicrobial therapy as opposed to the broad-coverage therapy that is typically started until culture and antibiotic susceptibility data are available, which typically takes 18 to 24 hours or more (55,56).

The most frequent pathogens of the central nervous system to which antigen detection tests have been applied are Streptococcus group B, *S. pneumoniae*, *H. influenzae* type b, and the serogroups A, B, C, Y, and W135 of *Neisseria meningitidis*. These bacteria, with the exception of Streptococcus group B, have soluble, type-specific capsular polysaccharide antigens that are released into the CSF and bodily fluids around the bacteria as they multiply (55,56).

2.10.7 Other Methods for Detecting Bacteria and their components in CSF

- Enzyme immunoassays (EIAs).
- Limulus Amebocyte Lysate (LAL) assays.
- Gas-liquid chromatography (GLC).
- The polymerase chain reaction (PCR).

2.11 Treatment of bacterial meningitis

Treatment for meningitis is very difficult. The fact that some medications cannot pass the blood-brain barrier contributes to the issue by reducing the number of antimicrobials available to treat meningitis. Meningitis, however, can cause death or chronic brain damage even with prompt treatment (57).

When infections that lead to meningitis are diagnosed, antimicrobial drugs such antibiotics are administered.

Large doses of intravenous antibiotics are administered to patients with severe meningitis. Unfortunately, a few bacteria have become resistant to every type of common antibiotic. Before the antibiotic started to lose its effectiveness against some bacteria twenty years ago, penicillin was used to treat a variety of bacterial infections.

Anti-inflammatory medications are used to treat inflammation of the meninges and other body organs. As the condition worsens, certain varieties of meningitis may require the use of potent medications known as corticosteroids. They could be administered during the entire course of antibiotic treatment until all symptoms of the illness have vanished. Dexamethasone is most commonly used. Intravenous fluids to reduce dehydration are given to counteract vomiting (58,59).

2.12 Meningitis prevention

The first preventive step is identifying the people at risk for meningitis. There is a population that is susceptible to each form of bacterial meningitis. *H. influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* seldom cause meningitis in newborn infants. While the child is still in the uterus, the mother's immune system temporarily immunizes fetus (60). *Streptococcus pneumoniae*, *H. influenzae*, and *Neisseria meningitidis* are commonly observed by adult females as colonizers. The bacteria that live in the female reproductive tract and on the skin are more likely to cause meningitis in infants. Doctors have discovered that pregnant women with high levels of *S. agalactiae* in the vagina have a significant risk of having children who suffer meningitis. Knowing this, physicians can employ prenatal care to reduce the risk of meningitis. In the latter stages of pregnancy, many doctors culture vaginal mucous samples (61). Women who have *S. agalactiae* bacteria are then treated (62). The occurrence of Influenzas type B meningitis in the United States was decreased by diligent immunization campaigns that were launched in the 1980s. In locations where vaccination rates for children were low, educational activities were pushed. The majority of strains of *Streptococcus pneumoniae* cannot always be prevented by vaccination. However, all serotypes of *Neisseria meningitidis*, with the exception of serotype B, are adequately protected against in young adults by modern vaccines. Programs to improve personal hygiene are one method of lowering the risk of meningitis kinds that are transmitted by human contact. To stop the transmission of infectious agents, many schools advise young people to wash their hands often (60,61,63).

2.13 Study objectives

2.13.1 General objective

This study aimed to evaluate retrospectively the various bacterial meningitis characteristics during the preceding two years in a number of hospital/lab in Sana'a city.

2.13.2 Specific objectives

1- To analyze the changes in bacterial meningitis cases across the research period in terms of the number.

2- To determine the frequency of different etiological agents that cause bacterial meningitis.

3- To identify the antibiotic susceptibility patterns of the bacterial isolates that caused meningitis.

Chapter 3: Methodology

3.1 Study design and setting

This retrospective record-based study was carried out at the USTH and other main clinical labs in Sana'a, Yemen's capital. The USTH is, a tertiary referral and teaching hospital with 282 beds located

3.2 Study period

The recent 2 years' data, from January 2021 to December 2022, were collected and analyzed

3.3 Study population

This study included all clinically suspected meningitis patients during the study specified period who met the study inclusion criteria.

3.4 Sample size

There was no predetermined sample size. Consequently, all consecutive cases of meningitis recorded in the chosen hospitals and laboratories throughout the specified study period were collected.

3.5 Processing of CSF sample

Using sterile plastic containers in the chosen facilities, CSF samples were collected from those who seemed to have meningitis and sent to the microbiology lab. As soon as the samples are received, they are typically processed for analysis, culture and antibiotic sensitivity test. CSF samples' macroscopic appearance was assessed for turbidity and any signs of hemorrhage. The Gram's stain procedure was used on a portion of the CSF sample. All CSF samples were inoculated into Chocolate agar and MacConkey agar. Subsequently, the inoculated culture plates were incubated for 24-48 hours at 37°C with 5% CO_2. Daily checks were made to see whether there was any growth on the culture plates.

As growth appeared, the isolates were identified using conventional techniques, and antibiotic susceptibility tests were performed using the disk diffusion method in line with CLSI, 2016 criteria and interpreted accordingly (64).

3.6 Data collection

From the accessible hospitals and labs records, the clinical and laboratory data were compiled and analyzed. The demographics, clinical presentation, and laboratory test results of patients were extracted from their medical records by the research team.

3.7 Data analysis

The Statistical Package for Social Sciences (SPSS) version 23 software was used for data analysis. For categorical and continuous variables, frequencies, percentages, median and range were used. For statistical analysis, the Chi-square test/Fisher's exact test was applied. Statistical significance was be determined by a p-value of less than 0.05.

3.8 Ethical considerations

Permission from the administration of laboratories and hospital was gained in order to access the required primary records and utilize the retrospective data from the patient's clinical records.

Chapter 4: Results

4.1 Results

This study comprised 187 individuals who were clinically thought to have pyogenic meningitis. Of them, 119 (63.6%) were male and 68 (36.4%) were female. The patients' age range was from 3 days to 75 years, with a mean age of 19.11 years.

Among the 187 suspected cases, only 17 patients with a total isolation rate of (9.1%) had definitive laboratory confirmation of bacterial meningitis.

Out of 17 culture positive cases, 12 (70.6%) were male, and the age group with the highest isolation rate was ≤ 1 year, with an isolation rate of 8 (47%) followed by the age group > 29 years, with an isolation rate of 5 (29.4%), table (1) and figure (2). The results of this study showed a relative increase in the incidence of bacterial meningitis in the fall season, isolation rate of 7 (41.2%), followed by the summer season, isolation rate of 6 (35.3%), table (1) and figure (3).

Table (1) shows that the male to female ratio for all culture-positive cases was 2.4:1. Among the bacterial pathogens that were isolated and confirmed by culture, 13 (76.5%) were gram-negative bacteria, whereas 4 (23.5%) were gram-positive, figure (4). The most prevalent bacterium was determined to be *Pseudomonas aeruginosa* and *Staphylococcus spp.* with a frequency of 4 (23.5%) for each, followed by *Klebsiella pneumoniae* 3 (17.6%), *E. coli* and *Acinetobacter baumannii* 2 (11.8%) for each, Table (2) and figure (5).

The isolated bacteria were subjected to commonly used antibiotics susceptibility testing. According to the results of the antibiotic susceptibility test, the following pattern was observed.

Resistance to beta lactam antibiotics likes amoxicillin + clavulanic acid was higher in Gram negative bacteria. Resistance rates for cephalosporins such as cefotaxime, ceftriaxone, and ceftazidime were likewise on the higher side, table (3).

Staphylococcus spp, a gram-positive bacterium, exhibited complete drug resistance to penicillin and ampicillin (100%), and high resistance rates (75%) to the most tested antibiotics, table (4).

Table 1; shows the distribution of bacterial meningitis cases according to gender, age, and season

Variable		Frequency	
		N	%
Gender	Male	12	70.6
	Female	5	29.4
Age	<= 1	8	47
	> 1 to 9	0	0
	> 9 to 19	2	11.8
	> 19 to 29	2	11.8
	> 29	5	29.4
Season	Fall	7	41.2%
	Winter	3	17.6%
	Spring	1	5.9%
	Summer	6	35.3%

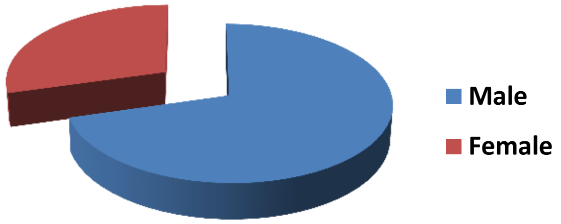

Figure 1; illustrates the distribution of bacterial meningitis cases according to gender.

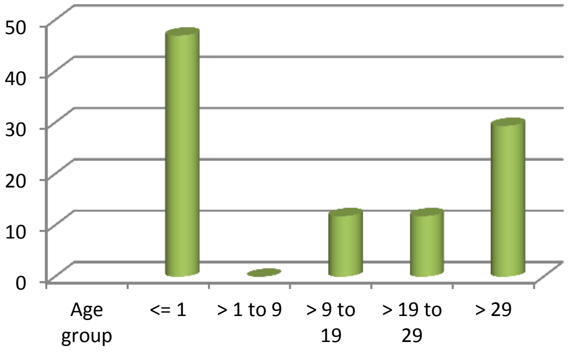

Figure 2; illustrates the distribution of bacterial meningitis cases according to age.

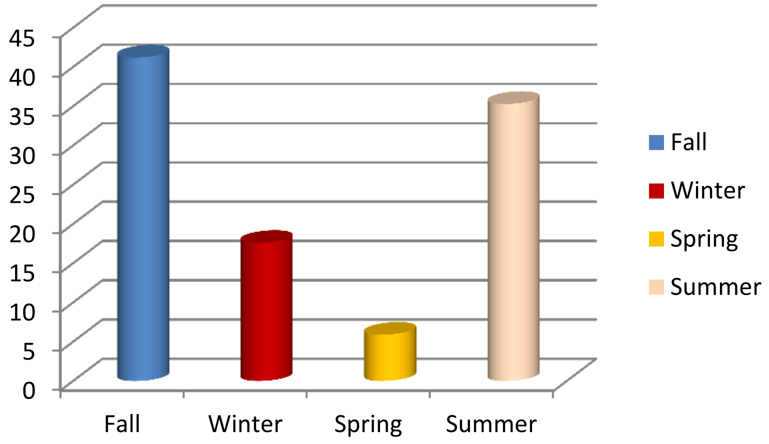

Figure 3; illustrates the distribution of bacterial meningitis cases according to season

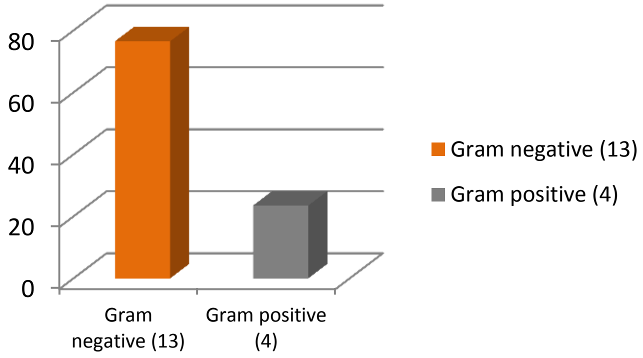

Figure 4 illustrates the distribution of meningitis-responsible bacteria according to Gram staining

Table 2; shows the frequency of bacterial species isolated from meningitis cases

Bacterial species	**Frequency of isolates**	
	N	**%**
Pseudomonas aeruginosa	4	23.5
Klebsiella pneumoniae	3	17.6
Staphylococcus aureus	3	17.6
Acinetobacter baumannii	2	11.8
Escherichia coli	2	11.8
Serratia marcescens	1	5.9
Burkholderia cepacia	1	5.9
Staphylococcus haemolyticus	1	5.9

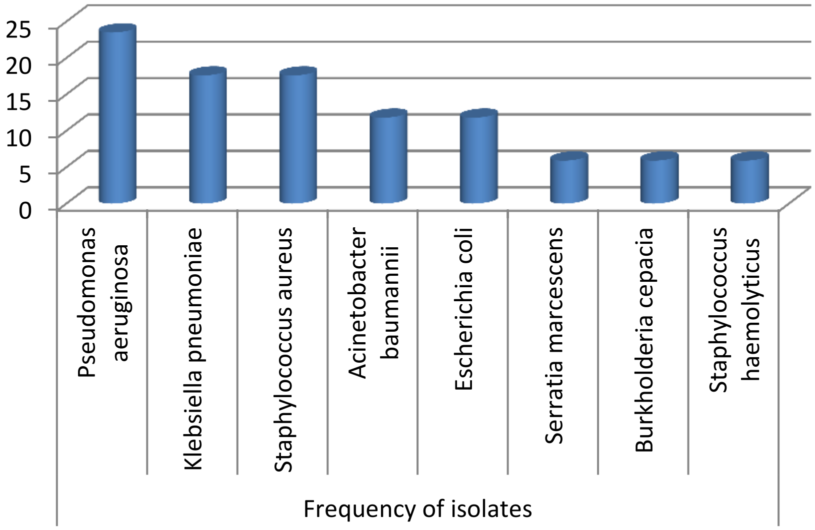

Figure 5; illustrates the frequency of bacterial species isolated from meningitis cases

Table (3); shows antibiotic Susceptibility pattern of Gram positive cocci (*Staphylococcus spp*.) isolated from CSF samples in Sana'a city

Antibiotic	**Antibiotic Susceptibility pattern of *S. aureus* (3) and *S. haemolyticus* (1)**		
	S	**I**	**R**
	N (%)	**N (%)**	**N (%)**
Ampicillin/ Sulbactam	1 (25)	0	3 (75)
Ampicillin	0	0	4 (100)
Amoxicillin + Clavulanic Acid	1 (25)	0	3 (75)
Ceftriaxone	1 (25)	0	3 (75)
Cefotaxime	1 (25)	0	3 (75)
Ciprofloxacin	1 (25)	0	3 (75)
Erythromycine	2 (50)	1 (25)	1 (25)
Gentamicin	1 (25)	0	3 (75)
Moxifloxacin	3 (75)	0	1 (25)
Oxacillin	1 (25)	0	3 (75)
Penicillin	0	0	4 (100)
Rifampicin	2 (50)	0	2 (50)
Trimethoprim + Sulfamethoxazole	1 (25)	0	3 (75)
Tetracycline	2 (50)	0	2 (50)
Vancomycin	3 (75)	1 (25)	0

Table (4); shows antibiotic resistance levels of Gram negative bacilli isolated from CSF samples in Sana’a city

Isolated bacteria	**Antibiotic resistance pattern of Gram negative bacteria; 13 (%)**														
	AK	**AUG**	**CAZ**	**CFX**	**GM**	**IMP**	**LVX**	**MER**	**MIN**	**T/S**	**P/T**	**TGC**	**TO**	**CL**	**CP**
P. aeruginosa (4)	0	100	25	100	0	25	25*	25*	100*	100	0	100*	25	25	50
K. pneumonia (3)	67	100	100	100	67	100	100	100	67	100	100	33	100	100	100
A. baumannii (2)	100	100	100	100	100	100	100	100	0	100	100	100	100	100	100
E. coli (2)	50	100	100	100	100	50	50	50		100	50	50	100	0	100
S. marcescens	S	R	R	R	R	R	S	S		S	R	S	R	R	S
B. cepacia	S	R	R	R	S	S	S	S		R	R		S	I	S

Chapter 5: Discussion

5.1 Discussion

Acute bacterial meningitis is a serious medical emergency that can be fatal and leave survivors with long-term neurological disabilities. Early diagnosis and treatment can save lives and lower morbidity and death rates. In this study, 187 CSF samples from 119 male and 68 female patients hospitalized to various wards were obtained.

According to the results of our study based on culture, only 17 patients out of 187 CSF samples were identified as having bacterial meningitis with isolation rate of 9.01%.

Similar low CSF culture positive rates were found in other studies as well, including (65) 9.01%, (14) 7.67%, and (13) 3.8%. Some other studies have shown a slight rise in the isolation rate, such as (11) 11.32% and (9) 13.91%.

There are many factors listed in the literature for a low yield of bacteria on CSF cultures, including clinical misdiagnosis, improper lumbar puncture technique, a delay in transporting specimens to the laboratory, a lack of special media for particular pathogens in the lab setting, autolysis enzymes in the CSF, the pathogen's fastidious nature, viral meningitis, and antibiotic treatment before lumbar puncture (14). In the current study, it was shown that male were 2.4 times more likely than female to have bacterial meningitis. Previous studies have also noted the male predominance that is associated with bacterial meningitis (9,12,14,65). In line with prior studies on bacterial meningitis, the current study also showed that infants were more likely to develop acute bacterial meningitis than children or adults (12,65).

According to our results, Gram-negative bacteria accounted for 13 (76.5%) of the isolated microorganisms, whereas Gram-positive bacteria accounted for 4 (23.5%). In previous studies, the isolation rates of Gram negative bacteria were high from meningitis cases (9,14). On the other side, our result is inconsistent with the results of (65,11) in India who documented the high isolation rates of gram-positive bacteria (66.18%) and (59.9%) compared to gram-negative bacteria (28.86%) and (40.1%) respectively.

In our investigation, the most frequent pathogens causing acute bacterial meningitis were found to be *Pseudomonas aeruginosa* and *Staphylococcus spp*. which together accounted for over 47.1% of all isolates. *Klebsiella pneumoniae* came in second at 17.6%. This result was somewhat consistent with the result of study (11) that documented *Staphylococcus spp*. and *Pseudomonas aeruginosa* as major pathogens of bacterial meningitis.

The majority of bacterial isolates (76.5%) was obtained during the fall and summer and can thus be considered the two peaks of bacterial meningitis in Yemen. This result confirms a similar pattern found in an earlier study (13).

Among Gram negative bacteria, high resistance was seen against beta-lactam antibiotics, cephalosporins, and Cotrimoxazole. In the current investigation, *Staphylococcus spp.* showed high levels of resistance to ampicillin (100%), penicillin (100%), and third-generation cephalosporins (75%). Similar results from earlier studies were reported (12,14,65).

Chapter 6: Conclusion and recommendation

6.1 Conclusion

Identification of the types of organisms that cause the diseases and the choice of an effective antibiotic against the organism in question are necessary for the proper therapy of patients with bacterial infections.

According to the current study, the most prevalent bacteria found in CSF culture were *Pseudomonas aeruginosa, Klebsiella pneumoniae, S. aureus,* and *Acinetobacter baumannii*.

As the isolated bacteria demonstrated significant levels of single and multiple antibiotic-resistance, the prevention and treatment of bacterial meningitis require considerable attention.

6.2 Recommendation

In order to combat the problem of drug resistance and improve institutional diagnostic techniques in the study area, it is reasonable to provide ongoing future updates on local resistance patterns of the most common bacteria associated with meningitis. This is because isolated etiological agents and antimicrobial susceptibility patterns of bacterial meningitis are variable.

It is also necessary to take into account strategies to increase the quality of diagnostic techniques at every level of the health care sector.

The public and private health sector should take life-threatening infectious diseases into account by documenting and reporting them.

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الخلاصة

التصور: التهاب السحايا الجرثومي الحاد هو أحد أخطر الأمراض المعدية التي قد تكون قاتلة. يعد الفهم الحالي للبكتيريا المتورطة في التعاب السحايا ونمط حساسيتها للمضادات الحيوية شائعة الاستخدام في بلد ماة أو منطقة معين أمرًا بالغ الأهمية لضمان العلاج الفعال. **الأهداف**: كان الغرض من هذه الدراسة هو تحديد العزلات البكتيرية ونمط حساسيتها في السائل الدماغي الشوكي لمرضى التهاب السحايا الحاد في مستشفى USTH في مدينة صنعاء. **الطرق**: أجريت الدراسة بأثر رجعي في USTH ، والذي يخدم سكان الحضر والريف في اليمن. والتي شملت سجلات المرضى المشتبه سريريا باصابتهم بالتهاب السحايا في الفترة الممتدة بين يناير 2021 وديسمبر 2022 ، خضعت 187 عينة من السائل الدماغي الشوكي (CSF) من مرضى التهاب السحايا المشتبه بهم سريريًا للفحص الجرثومي. **النتائج**: تم فحص 187 عينة من السائل الدماغي الشوكي خلال فترة البحث. اكدت نتائج زراعة السائل الدماغي الشوكي اصابة 17 مريض بمعدل 9.01٪ بالتهاب السحايا الجرثومي (البكتيري). كان الأطفال أكثر عرضة من البالغين للإصابة بـالتهاب السحيا البكتيري. كانت البكتيريا سالبة الجرام (76.5٪) هي أكثر أنواع البكتيريا عزلا. *Pseudomonas aeruginosa* و *Staphylococcus spp* كانت هي الانواع البكتيرية الكثر عزلا، تلتها *Klebsiella pneumoniae*. أظهرت العزلات البكتيرية سالبة وموجبة الجرام مقاومة عالية للمضادات الحيوية بيتا لاكتام والمضادات الحيوية الأخرى الموصوفة بشكل شائع. **الخلاصة**: العوامل المسببة الثلاثة الرئيسية لالتهاب السحايا الجرثومي في منطقتنا هي *Pseudomonas aeruginosa* و *Klebsiella pneumoniae* و *S. aureus*. من بين العزلات البكتيرية ، كان معدل انتشار المقاومة الفردية والمتعددة للمضادات الحيوية مرتفعًا جدًا عند الانواع البكتيرية المعزولة في دراستنا. وبالتالي ، من الأهمية بمكان إجراء مراقبة ميكروبيولوجية لتحديد العدوى المنتشرة وأنماط حساسية مضادات الميكروبات الخاصة بها من أجل اختيار علاج تجريبي مضاد للميكروبات يعتمد على البيانات المحلية والعالمية لمنع تكوين وانتشار سلالات مقاومة.

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الملامح البكتريولوجية لالتهاب السحايا في صنعاء ، اليمن: دراسة بأثر رجعي لمدة عامين

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مشروع بحث التخرج في استيفاء جزئي لمتطلبات درجة البكالوريوس في المختبرات الطبية

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