EFFECT OF HAEMOPHILUS INFLUENZA VACCINATION

ON ADMISSION FOR PNEUMONIA AND MENINGITIS IN HOSPITAL USM

DR SITI AISYAH IDRIS

DISSERTATION SUBMITTED

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE MASTER OF MEDICINE

(PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2018

ACKNOWLEDGEMENT

My highest gratitude to Allah S.W.T. The Most Gracious and The Most Merciful. Alhamdulillah, thanks to Him with his will, has given me the opportunity to complete this dissertation as part of partial fulfilment of Master of Medicine (Paediatrics). Without his help, nothing is accomplished.

I would like to thank the Head of Paediatric Department, HUSM, Associate Professor Dr Norsarwany Mohamad for all her support. Also to the Head of Paediatric Department, Hospital Raja Perempuan Zainab II, Kota Bharu Kelantan, Dr Mariana binti Daud for her support and understanding. Not to forget my supervisors, Associate Professor Dr Ariffin bin Nasir and Associate Professor Dr Sarimah binti Abdullah for their time and effort and also to Professor Dr Suhaimi Ab. Wahab who introduced me to this study. Another very important person is Encik Mohd Anizan Bakhtiar Abdullah, Penolong Pengarah Seksyen Maklumat Kesihatan (Kod Penyakit & Statistik) from Medical Records Office HUSM who provided me all the necessary data. Without any of them, this study will be very difficult to pursue.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS, ABBREVIATIONS OR NOMENCLATURE

Hib	*Haemophilus influenza*e type b
WHO	World Health Organization
DTP	Diphtheria-tetanus-pertussis
HIV	Human immunodeficiency virus
US	United States
CAP	Community acquired pneumonia
bpm	beats per minute
INR	International Normalized Ratio
CPAP	Continuous Positive Airway Pressure
BIPAP	Bilevel Positive Airway Pressure
GI	Gastrointestinal
CNS	Central nervous system
WBC	White blood cell
CSF	Cerebrospinal fluid
DIC	Disseminated intravascular coagulation
LP	Lumbar puncture
PCR	Polymerase chain reaction
CT	Computed tomography
MRI	Magnetic resonance imaging
FBC	Full blood cell
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
IV	Intravascular
ICP	Intracranial pressure
PRP	Polyribosylribitol phosphate

HUSM	Hospital Universiti Sains Malaysia
HRPZII	Hospital Raja Perempuan Zainab II
AOR	At own risk

ABSTRAK

Objektif – Untuk mengkaji impak pelalian Haemophilus influenza b (Hib) ke atas jumlah kemasukan pesakit untuk pneumonia dan meningitis di Hospital Universiti Sains Malaysia dari tahun 2000 sehingga tahun 2017.

Tatacara – Kajian retrospektif berdasarkan kod ICD-10 diagnosis yang direkodkan oleh Unit Rekod Perubatan Hospital USM daripada ringkasan pelepasan (discaj) pesakit. Pesakit yang dimasukkan di dalam kajian ini adalah yang berumur lingkungan usia 3 sehingga 60 bulan semasa dimasukkan untuk penyakit pneumonia and meningitis. Poisson regression digunakan untuk menentukan sama ada wujudnya kaitan antara jumlah kemasukan pesakit sebelum dan selepas imunisasi Hib dilaksanakan dan berapa lama pesakit ditahan di dalam wad untuk menerima rawatan sebelum dibenarkan dibenarkan pulang.

Keputusan – analisa menunjukkan bahawa kemasukan untuk pneumonia (RR = 3.5, 95% CI: 1.3, 13.6) dan jumlah hari berada di dalam wad (RR = 2.7, 95%CI: 1.2, 7.2) menunjukkan peningkatan yang ketara seiring dengan bermulanya imunisasi Hib. Walaubagaimanapun, semua model menunjukkan poor goodness-of-fit.

Kesimpulan - berdasarkan analisis data, kita tidak boleh membuat kesimpulan bahawa imunisasi Hib adalah mempengaruhi jumlah kemasukan pesakit untuk pneumonia dan meningitis, dan juga jumlah hari berada di dalam wad. Terdapat banyak data yang hilang dalam kajian ini memandangkan ini merupakan kajian retrospektif. Lebih banyak kajian diperlukan untuk mengenalpasti perkara di atas.

ABSTRACT

Objective – To study the impact of implementation of Haemophilus influenzae b (Hib) vaccination on the total number of hospital admission for pneumonia and meningitis in Hospital Universiti Sains Malaysia from year 2000 up to 2017.

Methods – retrospective study based on diagnosis recorded by Medical Records Unit Hospital USM from the patients' discharge summaries. Patients included in this study are those within age of 3 to 60 months during admission and when the diagnosis was made and admitted for pneumonia and meningitis. Poisson regression was used to determine the association between number of admission before and after immunization.

Results – Analyses showed that number of admission for pneumonia (RR = 3.5, 95% CI: 1.3, 13.6) and lengths of stay in days (RR = 2.7, 95% CI: 1.2, 7.2) significantly increased with the starting of Hib immunization. However, all models had poor goodness-of-fit (predicted count did not fit the data).

Conclusions – Based on the analyses of the data, we cannot correlate between the implementation of Hib vaccination with current incidence of pneumonia and meningitis as there are many other factors that influence both the illness. In addition, there were many missing data as this is a retrospective study. Further studies are warranted.

BIODATA ABSTRAK PENYELIDIKAN

EFFECT OF HAEMOPHILUS INFLUENZA VACCINATION ON ADMISSION FOR BACTERIAL PNEUMONIA AND MENINGITIS IN HOSPITAL USM

Dr Siti Aisyah binti Idris

MMed Paediatrics

Department of Paediatrics

School of Medical Sciences, Universiti Sains Malaysia

Health Campus, 16150 Kelantan, Malaysia

Introduction: *Haemophilus influenza*e is one of the commonest pathogen causing pneumonia and meningitis. There are 6 serotypes of Haemophilus influenza, and serotype b (Hib) is the most virulent. The introduction of routine vaccination has led to substantial declines in the incidence of Hib disease. *Haemophilus influenzae* vaccine has been introduced into the immunization program in Malaysia since 2002. However, published national data about impact of *Haemophilus influenza* vaccine on cases of pneumonia and meningitis is still lacking. This study mainly aims to look at the impact of implementation of *Haemophilus influenzae* vaccination to the number of cases admitted for pneumonia and meningitis in Paediatric wards in Hospital USM

Objective: To study the impact of implementation of Haemophilus influenzae b (Hib) vaccination on the total number of hospital admission for pneumonia and meningitis in Hospital Universiti Sains Malaysia from year 2000 up to 2017.

Methods: retrospective study based on diagnosis recorded by Medical Records Unit Hospital USM from the patients' discharge summaries. Patients included in this study are those within age of 3 to 60 months during admission and when the diagnosis was made and admitted for pneumonia and meningitis. Poisson regression was used to determine the association between number of admission before and after immunization.

Results: Analyses showed that number of admission for pneumonia (RR = 3.5, 95% CI: 1.3, 13.6) and lengths of stay in days (RR = 2.7, 95% CI: 1.2, 7.2) significantly increased with the starting of Hib immunization. However, all models had poor goodness-of-fit (predicted count did not fit the data).

Conclusions: Based on the analyses of the data, we cannot correlate between the implementation of Hib vaccination with current incidence of pneumonia and meningitis as there are many other factors that influence both the illness. In addition, there were many missing data as this is a retrospective study. Further studies are warranted.

Associate Professor Dr Ariffin bin Nasir: Supervisor

Associate Professor Dr Sarimah binti Abdullah: Supervisor

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

*Haemophilus influenza*e is an infectious bacterium cause of meningitis, pneumonia, epiglottitis and other severe infectious diseases (such as septic arthritis, cellulitis, purulent pericarditis and bacteremia). Both capsulated (types a, b, c, d, e, or f) and noncapsulated *Haemophilus influenzae* can cause invasive disease especially among children under five years of age and immunosuppressed patients (Domenico *et al*., 2017). Without proper vaccination plans, capsulated *Haemophilus influenza*e type b (Hib) has unquestionably the highest incidence.

The World Health Organization (WHO) recommends that all countries introduce Hib conjugate vaccine in to their routine infant immunization programs (Salvador *et al*., 2012). Hib vaccines are commonly given as a three-dose primary series at the same time as diphtheria-tetanus-pertussis (DTP) vaccination, and several combination vaccines are available. Hib conjugate vaccine has been shown to be highly effective in preventing invasive Hib disease after a three-dose primary series.

Several studies found the Hib conjugate vaccines to have a clear value in reducing meningitis incidence worldwide. Local influences including type of Hib vaccine, prevalence of human immunodeficiency virus (HIV) infection and vaccine coverage may be responsible for some of the variation in results. However, the vaccine impact remains high regardless of these influences.

Surveillance systems in resource-poor settings also demonstrated Hib vaccine effectiveness by documenting vaccine effectiveness against purulent meningitis as well as declines over time in this outcome. Studies in Rwanda, Uganda, and Indonesia all showed that the Hib vaccine prevented approximately 50% of purulent meningitis cases. Asian countries had low documented incidences which presented particular difficulties with using surveillance data to estimate vaccine impact. Past studies of Hib in Asia demonstrated varied disease incidence rates, with the great majority of earlier surveillance-based studies finding low rates.

In addition to meningitis, Hib causes a substantial proportion of paediatric bacterial pneumonia. However, most Hib pneumonia is non-bacteremic making it difficult to evaluate vaccine impact using data based on microbiologically confirmed cases no matter how good the surveillance system is.

Previous studies suggested that Hib conjugated vaccine showed marked impact on the incidence of Hib diseases (William *et al*., 1993). In the United States (US), a study done showed that the vaccine preventing an estimated 10,000 to 16,000 cases of Hib disease in 1991. The age-specific incidence of Hib disease among children less than 5 years old decreased by 71% (from 37 per 100,000 persons in 1989 to 11 per 100,000 persons in 1991). The surveillance data showed that *Haemophilus influenzae* meningitis incidence decreased by 82% between 1985 and 1991.

Study in The Gambia, which is the first country in Africa to introduce conjugate Hib conjugated vaccine, also showed an effective disease control up to 14 years after introduction. The incidence of Hib meningitis remained low as did the oropharyngeal carriage rate.

Almost similar finding was also noted by a study done in Italy which looked on the impact of Hib conjugate vaccination on hospitalization for invasive disease in children fifteen years after its introduction. A significant decline of hospitalization rates was observed among children 1-4 years over the study period.

1.2 PNEUMONIA

Pneumonia is one of the commonest causes of admission of the patients especially in Paediatric Wards. It is frequently but not always caused by infection. The infection may be bacterial, viral, fungal, or parasitic.

The WHO guidelines define pneumonia as an acute disease episode with cough or difficult breathing combined with fast breathing with age specific cut-off values for increased respiratory rate (Taneli *et al*., 2008). Pneumonia often starts with symptoms of upper respiratory tract infection followed by fever, chills and cyanosis. Children who presented with lower chest wall in-drawing are classified as severe pneumonia and will be referred for evaluation and possible in-patient care.

Pneumonia caused substantial morbidity and mortality in all age groups. In the USA, pneumonia and influenza combined are the greatest infectious case of death. Pneumonia accounts for 3-18% of all childhood hospital admissions (Carlos *et al*., 2007). Community acquired pneumonia hospitalization causes an important health and cost burden to the country. One study shows that the total median direct medical cost of bacterial-acquired-pneumonia-related hospitalization in our country was 375.80 USD, per episode (Tan *et al*., 2017). Lots of

money could be saved if we able to prevent children from having severe pneumonia subsequently requiring hospital admission with simple way of providing adequate immunization.

1.2.1 Etiology

Over the past century, findings of pneumonia etiology studies in children have swung from detection of only bacteria to a preponderance of viruses (Daniel *et al*., 2017). *Streptococcus pneumoniae* was first identified in 1881 from samples of human saliva. Early access to antibiotics presented a difficulty for research on pneumonia etiology as prior treatment with antibiotics is associated with a 30% reduction in blood culture positivity in children with pneumonia. The history of pneumonia etiology studies over the last century also shows several trends: from the use of highly specific tests on specimens from the lung itself to highly sensitive tests on samples of body fluids distant from the lung; from detection of single pathogens to detection of multiple pathogens; and from an exclusive focus on bacteria to enhanced detection of viruses.

The most frequently detected bacterial agents for pneumonia were *Klebsiella pneumoniae (5.4%), Streptococcus pneumoniae (5.2%), Escherichia coli (5.2%), Staphylococcus aureus (3.9%), Haemophilus influenza* (3.6%) and *Haemophilus parainfluenzae* (3.3%) (2c). The most frequently detected viruses were human rhinovirus (20.3%, in just 2 studies), respiratory syncytial virus (RSV, 17.3%), human bocavirus (9.9%), parainfluenza virus (5.8%), human metapneumovirus (3.9%) and influenza (3.5%). *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were identified in 9.5% and 2.9%, respectively, of children less than 5 year of age with community acquired pneumonia (Guijun *et al*., 2017).

1.2.2 Epidemiology

Approximately 120 – 156 million cases of acute lower respiratory infections occur globally, with approximately 1.4 million resulting in death (Rodrigo *et al*., 2016). Of these, pneumonia kills an estimated 1 million children under the age of 5 every year and accounts for 15% of deaths in children less than 5 years of age, with 90 – 95% of these deaths occurring in the developing world. The majority of pneumonia episodes in children less than 5 years of age occur in just 15 countries, with South Asia and Sub-Saharan Africa collectively enduring the largest burden of more than half the worldwide total cases of pneumonia in children. Risk factors for community-acquired pneumonia (CAP) include age (less than 1 year), malnutrition, prematurity, immunosuppression, overcrowding, passive tobacco exposure, indoor fuel exposure, inadequate housing and the winter season. The burden of disease has been worsened by the human immunodeficiency virus (HIV) epidemic. Other co-existing illnesses, like malaria and diarrhea, are also important contributing factors to the increased CAP burden of disease in African and South Asian settings.

1.2.3 Pathophysiology

Pneumonia is an infectious process resulting from the invasion and overgrowth of microorganism in the lung parenchyma, breaking down defenses and provoking intra-alveolar exudates. The development of pneumonia requires that the pathogen reach the alveoli and that host defenses are overwhelmed by microorganism virulence or by the inoculum's size. Intrusion of bacteria into the lower respiratory tract usually is the result of aspiration of organism from the upper respiratory tract. Underlying disease, loss of mechanical respiratory defenses with the use of sedatives, tracheal intubation and antibiotic treatment are determinant factors for change in the

normal flora of the upper respiratory tract. Nasal, oropharynx, biofilm and respiratory tract colonization have been related to the risk for pneumonia, especially in “late-onset” pneumonia. Aspiration of normal oropharynx flora in a comatose patient and during intubation seems to be the pathogenesis of “early-onset” pneumonia.

1.2.4 Clinical manifestation

The clinical presentation of bacterial pneumonias varies (Justina, 2018). Sudden onset of symptoms and rapid illness progression are associated with bacterial pneumonias. Chest pain, dyspnea, hemoptysis, decrease exercise tolerance, and abdominal pain from pleuritis are also highly indicative of pulmonary process.

The presence of cough, particularly cough productive of sputum, is the most consistent presenting symptom. Nonspecific symptoms such as fever, rigors and malaise are common. Other nonspecific symptoms that may be seen with pneumonia include myalgia, headache, abdominal pain, nausea, vomiting, diarrhea, anorexia and weight loss, and altered sensorium.

Physical examination findings may vary, depending on the type of organism, severity of infection, coexisting host factors, and the presence of complications. Signs of bacterial pneumonia may include the following:

- Hyperthermia (fever, typically > 38°C) or hypothermia (< 35°C)
- Tachypnea
- Use of accessory respiratory muscles
- Tachycardia (> 100 bpm) or bradycardia (< 60 bpm)

- Central cyanosis
- Altered mental status

Physical findings may include the following:

- Adventitious breath sounds, such as rales / crackles, rhonchi and wheezes
- Decreased intensity of breath sounds
- Egophony
- Whispering pectoriloquy
- Dullness to percussion
- Tracheal deviation
- Lymphadenopathy
- Pleural friction rub

1.2.5 Diagnosis and investigation

The following investigations are useful not only for diagnostic purposes but also for classifying illness severity:

- Blood studies
    - Full Blood Count with differential
        - Leukocytosis with a left shift may be observed in any bacterial infection
        - Leucopenia may be an ominous clinical sign of impending sepsis
    - Coagulation studies

        - An elevated International Normalized Ratio (INR) has been associated with more severe illness. This finding may herald the development of disseminated intravascular coagulation
    - Blood cultures
        - Should be obtained before the administration of antibiotics
        - When blood cultures are positive, they correlate well with the microbiologic agent causing the pneumonia. Their yield may be higher in patients with more severe pneumonia / infection
        - Unfortunately, blood cultures show poor sensitivity in pneumonia; findings are positive in approximately 40% of cases
- Sputum evaluation
    - Sputum Gram stain and culture should be performed before initiating antibiotic therapy. A single predominant microbe should be noted at Gram staining. Mixed flora may be observed with anaerobic infections.
    - However, often, patients cannot produce an adequate specimen. Many specimens produced are so contaminated by oral materials that the results of stains and cultures are unreliable
- Chest radiography
    - Considered the standard method for diagnosing the presence of pneumonia, that is, the presence of an infiltrate is required for the diagnosis
    - However, the accuracy of plain chest radiography for detecting pneumonia decreases depending on the setting of infection

- In H influenza pneumonia, pleural effusion is present in an approximately half of infected individuals.

1.2.6 Treatment

- Respiratory support
  - For patients with mild shortness of breath, only supplemental oxygen with a nasal cannula may be required for ventilator support
  - Ventilator support becomes necessary when supplemental oxygen is not sufficient or when the patient cannot maintain the increased work of breathing
  - Moderate dyspnea requires high oxygen concentrations, such as those provided by Venti-mask or partial rebreathing face mask
  - Patients in respiratory failure may require endotracheal intubation and ventilation
  - An alternative to intubation for refractory hypoxemia may be use of continuous positive airway pressure (CPAP)
  - Bilevel positive airway pressure (BIPAP) may be employed as a means of noninvasive ventilation in patients with hypercarbia
- Fluid resuscitation
  - Many individuals with pneumonia also have volume depletion
  - Patients with hypotension and/or tachycardia may benefit from an intravenous crystalloid

- Empiric antibiotic therapy
    - Empiric therapy for the hospitalized patient should be initially broad and cover the likely causative organisms
    - Maximum time from door to antibiotics administration should be within four hour or less. Failure to abide by these time parameters may be associated with poor outcome
    - The goals of pharmacotherapy for bacteria pneumonia are to eradicate the infection, reduce morbidity, and prevent complications
    - With appropriate antibiotic therapy, improvement in the clinical manifestations of pneumonia should be observed in 48 – 72 hours
    - Antibiotics should not be changed within the first 72 hours unless marked clinical deterioration occurs or the causative micro-organism is identified with some certainty
- Supportive measures
    - Analgesia and antipyretics
    - Chest physiotherapy
    - Intravenous fluid (or diuretics) if indicated
    - Monitoring (pulse oximetry with or without cardiac monitoring
    - Oxygen supplementation
    - Positioning of patient to minimize aspiration risk
    - Respiratory therapy, including treatment with bronchodilators if indicated
    - Suctioning and bronchial hygiene
    - Mechanical ventilator support (if necessary) with low tidal volumes

- Systemic support – proper hydration, nutrition, early mobilization to create a positive host milieu to fight infection and speed recovery

1.2.7 Complication and prognosis

Potential complications of bacterial pneumonia include the following:

- Destruction and fibrosis / organization of lung parenchyma with scarring
- Bronchiectasis
- Necrotizing pneumonia
- Frank cavitation
- Empyema
- Pulmonary abscess
- Respiratory failure
- Acute respiratory distress syndrome
- Ventilator dependence
- Superinfection
- Meningitis
- Death

1.3 MENINGITIS

Meningitis is a clinical syndrome characterized by inflammation of the meninges. Microbiologic causes of meningitis include bacteria, virus, fungi and parasite. The classic triad

of bacterial meningitis consists of fever, headache and neck stiffness. Other symptoms can include nausea, vomiting, photophobia, sleepiness, confusion, irritability, delirium and coma.

Over the years, significant advances have been made in developing approaches to management of meningitis. Although admission for meningitis is not as common as pneumonia, prompt and accurate diagnosis and adequate treatment of bacterial meningitis in children is still a major challenge. Until now, bacterial meningitis is still an important cause of childhood mortality. Those who survive are at high risk of developing neurological disability.

1.3.1 Etiology

Causes of meningitis include bacteria, viruses, fungi and parasites. There are seven bacterial types known to cause meningitis: *Escherichia coli*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *group B Streptococcus agalactiae*, *Staphylococcus aureus*, and *Listeria monocytogenes* (Oordt-Speets *et al*., 2018).

1.3.2 Epidemiology

The incidence of meningitis varies according to the specific etiologic agent, as well as in conjunction with a nation's medical resources (Rodrigo, 2017). The incidence is presumed to be higher in developing countries because of less access to preventive services, such as vaccination. In these countries, the incidence has been reported to be ten times higher than that in developed countries.

Meningitis affects people of all races. In the United States, black people have a higher reported rate of meningitis than white people and Hispanic people.

With almost 4100 cases and 500 deaths occurring annually in the United States, bacterial meningitis continues to be a significant source of morbidity and mortality. The annual incidence in the United States is 1.33 cases per 100,000 population. The reported attack rate for bacterial meningitis is 3.3 male cases per 100,000 population, compared with 2.6 female cases per 100,000 population.

Meningococcal meningitis is endemic in parts of Africa, India, and other developing areas. Periodic epidemics occur in the so-called sub-Saharan "meningitis belt," as well as among religious pilgrims traveling to Saudi Arabia for the Hajj. In parts of Africa, widespread epidemics of meningococcal meningitis occur regularly. In 1996, the biggest wave of meningococcal meningitis outbreaks ever recorded arose in West Africa. An estimated 250,000 cases and 25,000 deaths occurred in Niger, Nigeria, Burkina Faso, Chad, and Mali.

N meningitidis causes approximately 4 cases per 100,000 children aged 1-23 months. The risk of secondary meningitis is 1% for family contacts and 0.1% for daycare contacts. The rate of meningitis caused by *S pneumoniae* is 6.5 cases per 100,000 children aged 1-23 months.

Previously, Hib, *N meningitidis*, and *S pneumoniae* accounted for more than 80% of cases of bacterial meningitis. Since the late 20th century, however, the epidemiology of bacterial meningitis has been substantially changed by multiple developments.

The overall incidence of bacterial meningitis in the US declined from 2.0 to 1.38 cases per 100,000 population between 1998 and 2007. This was partially because of the widespread

use of the Hib vaccination, which decreased the incidence of *H influenzae* meningitis by more than 90%. Routine Hib vaccination has nearly eliminating this pathogen as a cause of meningitis in many developed countries.

BACTERIA	1978 - 1981	1986	1995	1998 - 2007
Haemophilus influenza	48%	45%	7%	6.7%
Listeria monocytogenes	2%	3%	8%	3.4%
Neisseria meningitidis	20%	14%	25%	13.9%
Streptococcus agalactiae	3%	6%	12%	18.1%
Streptococcus pneumoniae	13%	18%	47%	58%

Table 1.1 Changing Epidemiology of Acute Bacterial Meningitis in United States

H influenzae meningitis primarily affects infants younger than 2 years. *S agalactiae* meningitis occurs principally during the first 12 weeks of life. Among the bacterial agents that cause meningitis, *S pneumoniae* is associated with one of the highest mortalities (19-26%).

1.3.3 Pathophysiology

Most cases of meningitis are caused by an infectious agent that has colonized or established a localized infection elsewhere in the host. Potential sites of colonization or infection include the skin, the nasopharynx, the respiratory tract, the gastrointestinal (GI) tract, and the genitourinary tract. The organism invades the submucosa at these sites by circumventing host defenses (e.g., physical barriers, local immunity, and phagocytes or macrophages).

An infectious agent (i.e., a bacterium, virus, fungus, or parasite) can gain access to the central nervous system (CNS) and cause meningeal disease via any of the 3 following major pathways:

1. Invasion of the bloodstream (ie, bacteremia, viremia, fungemia, or parasitemia) and subsequent hematogenous seeding of the CNS
2. A retrograde neuronal (eg, olfactory and peripheral nerves) pathway (eg, *Naegleria fowleri* or *Gnathostoma spinigerum*)
3. Direct contiguous spread (eg, sinusitis, otitis media, congenital malformations, trauma, or direct inoculation during intracranial manipulation)

Invasion of the bloodstream and subsequent seeding is the most common mode of spread for most agents. This pathway is characteristic of meningococcal, cryptococcal, syphilitic, and pneumococcal meningitis.

Rarely, meningitis arises from invasion via septic thrombi or osteomyelitic erosion from infected contiguous structures. Meningeal seeding may also occur with a direct bacterial inoculate during trauma, neurosurgery, or instrumentation. Meningitis in the newborn may be

transmitted vertically, involving pathogens that have colonized the maternal intestinal or genital tract, or horizontally, from nursery personnel or caregivers at home.

Local extension from contiguous extracerebral infection (eg, otitis media, mastoiditis, or sinusitis) is a common cause. Possible pathways for the migration of pathogens from the middle ear to the meninges include the following:

1. The bloodstream
2. Preformed tissue planes (eg, posterior fossa)
3. Temporal bone fractures
4. The oval or round window membranes of the labyrinths

The brain is naturally protected from the body's immune system by the barrier that the meninges create between the bloodstream and the brain. Normally, this protection is an advantage because the barrier prevents the immune system from attacking the brain. However, in meningitis, the blood-brain barrier can become disrupted; once bacteria or other organisms have found their way to the brain, they are somewhat isolated from the immune system and can spread.

When the body tries to fight the infection, the problem can worsen; blood vessels become leaky and allow fluid, white blood cells (WBC) and other infection-fighting particles to enter the meninges and brain. This process, in turn, causes brain swelling and can eventually result in decreasing blood flow to parts of the brain, worsening the symptoms of infection.

Depending on the severity of bacterial meningitis, the inflammatory process may remain confined to the subarachnoid space. In less severe forms, the pial barrier is not penetrated, and

the underlying parenchyma remains intact. However, in more severe forms of bacterial meningitis, the pial barrier is breached, and the underlying parenchyma is invaded by the inflammatory process. Thus, bacterial meningitis may lead to widespread cortical destruction, particularly when left untreated.

Replicating bacteria, increasing numbers of inflammatory cells, cytokine-induced disruptions in membrane transport, and increased vascular and membrane permeability perpetuate the infectious process in bacterial meningitis. These processes account for the characteristic changes in CSF cell count, pH, lactate, protein, and glucose in patients with this disease.

Exudates extend throughout the CSF, particularly to the basal cisterns, resulting in the following:

1. Damage to cranial nerves (eg, cranial nerve VIII, with resultant hearing loss)
2. Obliteration of cerebrospinal fluid (CSF) pathways (causing obstructive hydrocephalus)
3. Induction of vasculitis and thrombophlebitis (causing local brain ischemia)

1.3.4 Clinical manifestation

The younger the child, the less likely he or she is to exhibit the classic symptoms of fever, headache, and meningeal signs (Martha, 2017). A child younger than three months may have very nonspecific symptoms, including hyperthermia or hypothermia, change in sleeping or eating habits, irritability or lethargy, vomiting, high-pitched cry, or seizures. After the age of three months, the child may display symptoms more often associated with bacterial meningitis,

with fever, vomiting, irritability, lethargy, or any change in behavior. After the age of two to three years, children may complain of headache, stiff neck, and photophobia.

The clinical course may be brief and fulminant with rapid progression of symptoms or may follow a more gradual course with several days of upper respiratory infection progressing to more severe symptoms.

Physical examination findings vary widely, depending on the infecting organism and the patient's age. The younger the child is, the less specific the symptoms. As the child grows older, the physical examination becomes more reliable.

Kernig and Brudzinski signs are helpful indicators when present, but they may be absent (along with nuchal rigidity) in very young, debilitated, or malnourished infants. Skin findings range from a nonspecific blanching, erythematous, maculopapular rash to a petechial or purpuric rash, most characteristic of meningococcal meningitis.

Patients may also have other foci of infection. Presenting symptoms may point toward those foci, causing unnecessary delay in diagnosis of bacterial meningitis.

Approximately 15% of patients have focal neurologic signs upon diagnosis. The presence of focal neurologic signs predicts a complicated hospital course and significant long-term sequelae.

Generalized or focal seizures are observed in as many as 33% of patients. Seizures that occur during the first three days of illness usually have little prognostic significance. However, prolonged or difficult-to-control seizures, especially when observed beyond the fourth hospital day, are predictors of a complicated hospital course with serious sequelae.

In later stages of the disease, a few patients develop focal CNS symptoms and other systemic signs (eg, fever) indicating a significant collection of fluid in the subdural space. Incidence of subdural effusion is independent of the bacterial organism causing meningitis. Approximately 6% of affected infants and children show signs of disseminated intravascular coagulation (DIC) and endotoxic shock. These signs are indicative of a poor prognosis.

1.3.5 Diagnosis and investigation

Bacterial meningitis must be the first and foremost consideration in the differential diagnosis of patients with headache, neck stiffness, fever, and altered mental status. Acute bacterial meningitis is a medical emergency, and delays in instituting effective antimicrobial therapy result in increased morbidity and mortality.

A firm diagnosis is usually made when bacteria are isolated from the cerebrospinal fluid (CSF) and evidence of meningeal inflammation is demonstrated by increased pleocytosis, elevated protein level, and low glucose level in the CSF. Timely collection and processing of CSF and isolation of an organism allows optimization of choice of antimicrobial agent and duration of therapy. CSF chemistries and cytology vary, depending on the age of the patient.

A lumbar puncture (LP) may be contraindicated in some of the following conditions: unstable patients with hypotension or respiratory distress who may not be able to tolerate the procedure, brain abscess, brain tumors or other cause of raised intracranial pressure, and occasionally infection at the lumbar puncture site.

The Bacterial Meningitis Score, a clinical decision rule developed by Nigrovic et al, has shown high accuracy and usability and continues to be evaluated with respect to its effectiveness as an aid to identify those children with CSF pleocytosis who are at low risk for bacterial meningitis. The components of the score include the following:

- Positive CSF Gram stain
- CSF absolute neutrophil count of 1000/µL or higher
- CSF protein level of 80 mg/dL or higher
- Peripheral blood absolute neutrophil count of 10,000/µL or higher
- History of seizure before or at the time of presentation

Perform total and differential cell counts, chemistries (ie, glucose and protein), Gram stains, and cultures on all CSF specimens. In a setting of antibiotic pretreatment, rapid bacterial antigen testing may be considered. Note that patients with both fulminant disease and poor immune response may not show cytologic or chemical changes in CSF. In about 2-3% of bacterial meningitis cases, bacterial cultures may be positive even when the Gram stain is negative and the cell counts and glucose and protein levels are normal.

White blood cell (WBC) counts higher than 1000/µL are usually caused by bacterial infections. Counts of 500-1000/µL may be bacterial or viral and call for further evaluation. Lower counts are usually associated with viral infections.

The CSF protein concentration is usually elevated in bacterial meningitis (greater than 50 mg/dL), but it is also elevated by a traumatic lumbar puncture. The CSF glucose concentration is usually reduced in bacterial meningitis. A normal CSF glucose level should be higher than two thirds of the serum glucose level; a CSF level lower than 50% of the serum level is suggestive of

bacterial meningitis. In patients with very early disease, however, CSF protein and glucose values may be within the reference range.

Several tests based on the principle of agglutination are available for the detection of bacterial antigens in body fluids. Bacterial antigen detection can be carried out in samples of CSF, blood, and urine. A negative result, however, does not rule out bacterial infection. Antigen detection tests are most helpful in patients with partially treated meningitis in whom bacteria may not grow from CSF but antigens persist in body fluids.

Many children receive antibiotics before definitive diagnosis is made. As a rule, a few doses of oral antimicrobial agents, or even a single injection of an antibiotic, do not significantly alter CSF findings, including bacterial cultures, especially in patients with Hib disease. Oral antibiotics have never convincingly been shown to render patients with bacterial meningitis CSF culture–negative.

In cases where antibiotic administration leads to CSF sterilization, polymerase chain reaction (PCR) testing may have a role to play in identifying the pathogen. PCR testing is able to identify the pathogen quickly and accurately and does not require a large number of organisms; however, it does require further validation in this setting.

Nigrovic *et al*. (2018) found that Gram stain results (WBC count and absolute neutrophil count) in CSF were not affected by pretreatment with antibiotics; however, the rates of positive CSF culture and blood culture were lower with antibiotic pretreatment. After pretreatment with antibiotics for 12 hours or longer, the patients had higher CSF glucose levels and lower CSF protein levels.

A concern regarding LP is that the lowering of CSF pressure from withdrawal of CSF could precipitate herniation of the brain. Herniation can sometimes occur in acute bacterial meningitis and other CNS infections as the consequence of severe cerebral edema or acute hydrocephalus. Clinically, this is manifested by an altered state of consciousness, abnormalities in pupil reflexes, and decerebrate or decorticate posturing. The incidence of herniation after LP, even in patients with papilledema, is approximately 1%.

A screening computed tomography (CT) scan of the head may be performed before LP to determine the risk of herniation. The decision to obtain a brain CT scan before LP should not delay the institution of antibiotic therapy; such delay can increase mortality. It should be also noted that herniation can occur in patients with bacterial meningitis who have a normal brain CT scan. The most reliable clinical signs that indicate the risk of herniation include deteriorating level of consciousness, brainstem signs, and a very recent seizure.

Computed tomography (CT) of the head and magnetic resonance imaging (MRI) of the brain generally do not aid in the diagnosis of meningitis. Some patients may show meningeal enhancement, but its absence does not rule out the condition. Neuroimaging may yield normal results or demonstrate small ventricles, effacement of sulci, and contrast enhancement over convexities. Late findings include venous infarction and communicating hydrocephalus. Brain abscess, sinus or mastoid infection, skull fracture, and congenital anomalies must be ruled out.

Other laboratory tests, which may include blood cultures, are needed to complement the CSF culture. These bacterial cultures are used for identification of the offending bacteria and occasionally its serogroup, as well as for determination of the organism’s susceptibility to antibiotics. Other blood investigations that may be indicated include the following:

- Full blood count (FBC) with differential
- Blood cultures
- Coagulation studies
- Serum glucose
- Electrolytes

Measurement of the serum glucose level close to the time of CSF collection is helpful for interpreting CSF glucose levels and assessing the likelihood of meningitis.

Some data suggest that procalcitonin may be a useful biomarker for distinguishing bacterial meningitis from aseptic meningitis. Its use may enhance the sensitivity of the Bacterial Meningitis Score. In a retrospective analysis of admitted patients with meningitis, Dubos et al found procalcitonin at a level of 0.5 ng/mL to have a sensitivity of 99% and a specificity of 83% for differentiating bacterial from aseptic meningitis.

1.3.6 Treatment

Management of acute bacterial meningitis in infants and older children involves both supportive measures and appropriate antimicrobial therapy.

Closely monitor patients' fluid and electrolyte status. Check vital signs and neurologic status, and ensure that an accurate record of intake and output is maintained. By prescribing the correct type and volume of fluid, the risk of brain edema can be minimized. The child should receive sufficient amounts of fluid to maintain systolic blood pressure at around 80 mm Hg, urinary output at 500 mL/m2/day, and adequate tissue perfusion. Although it is important to

avoid syndrome of inappropriate antidiuretic hormone secretion (SIADH), it is equally important to avoid underhydration of the patient and the risk of decreased cerebral perfusion.

Bacterial meningitis (including *Meningococcal meningitis, Haemophilus influenzae meningitis*, and *Staphylococcal meningitis*) is a neurologic emergency that is associated with significant morbidity and mortality. Initiation of empiric antibacterial therapy is therefore essential for better outcome. The choice of agents is usually based on the known predisposing factors, initial CSF Gram stain results, or both. Once the pathogen has been identified and antimicrobial susceptibilities determined, the antibiotics may be modified for optimal targeted treatment. All antibiotics should be administered intravenous (IV) to achieve adequate serum and CSF levels. An intraosseous route is acceptable if venous access is not an option.

Primary treatment is with either Cefotaxime (50 mg/kg IV every 6 hours, up to 12 g/day) or Ceftriaxone (50 mg/kg every 12 hours, up to 4 g/day). Treatment with Dexamethasone (0.4 mg/kg IV every 12 hours for 2 days or 0.15 mg/kg IV every 6 hours for 4 days) should be strongly considered, starting 15-20 minutes before the first dose of antibiotics. Experimental studies have revealed a correlation between outcome and the severity of the inflammatory process in the subarachnoid space. In animal models of bacterial meningitis, the use of dexamethasone has been associated with decreased inflammation, reduced cerebral edema and intracranial pressure (ICP), and lesser degrees of brain damage. Subsequent controlled, double-blind clinical trials demonstrated the beneficial effects of adjunctive dexamethasone in infants and children with Hib meningitis. The incidence of neurologic and audiologic sequelae was significantly decreased on follow-up examination; clinical benefit was greatest for overall hearing impairment.