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PHILIPPINE CLINICAL PRACTICE GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF ACUTE BACTERIAL MENINGITIS IN INFANTS AND CHILDREN

A joint project of the Pediatric Infectious Disease Society of the Philippines (PIDSP) and Child Neurology Society of the Philippines (CNSP)

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INTRODUCTION

Acute bacterial meningitis is defined as the inflammation of the meninges which is caused by bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. In developed countries, the advent of vaccines for these organisms has significantly decreased the prevalence of bacterial meningitis[1]. For developing countries like the Philippines however, uptake of the vaccines on a nationwide scale has yet to occur, thus a change in the epidemiology has not been seen. From 2001 till 2010, meningitis has always been in the top 10 leading causes of mortality in children[2]. Based on the Philippine Pediatric Society disease registry, out of the 934,633 cases reported from January 1, 2006 to August 31, 2010, there were 5,611 cases of unspecified meningitis. Resistance rates of pathogens to antimicrobials have not declined. The emergence of new resistance for antibiotics have been reported. In 2012, all *S. pneumoniae* isolated were sensitive to levofloxacin. However, in the 2013 Antimicrobial Resistance Surveillance Program (ARSP), 2% resistance to levofloxacin (95% CI: 0.5-5.8) was reported.[4] With varying clinical presentations and rising rates of bacterial resistance, the appropriate management of this disease from its recognition to therapy remains of paramount concern. Thus to address these changes, this guideline was developed.

The first guideline for acute bacterial meningitis was completed in 1998 as commissioned by the Philippine Society for Microbiology and Infectious Diseases (PSMID), however, the guideline was not published. The Pediatric Infectious Disease Society of the Philippines (PIDSP), in line with its 20th anniversary celebration in 2013, saw the need for an update and publication of this guideline, thus, it formed a committee in partnership with Child Neurology Society of the Philippines (CNSP) to develop these current recommendations.

These recommendations are intended for use by pediatricians, general practitioners and emergency medicine physicians to serve as a guide in the management of bacterial meningitis.This guideline serves only as suggestions based on evidences collected that would help lead each clinician to his/her rightful decisions in the management of the patient.

Key questions were formulated for the diagnosis (involving both clinical parameters and laboratory procedures) and treatment protocols which include empiric and targeted therapy, as well as preventive measures by the PIDSP/CNSP Steering Committee. The committee searched for both local and international researches pertaining to the diagnosis, treatment and prevention of acute bacterial meningitis. Workshops were also organized for the critical appraisal of the evidence and were graded using the WHO criteria for strength of evidence. Recommendations were made based on the literature obtained, local data, and expert opinion of committee members. The guideline has been presented to the CNSP and PIDSP. It also has been presented at the Philippine Pediatric Society Annual Convention as well as the PIDSP annual convention. The therapeutic guidelines has also been discussed with the with the National Antibiotic Guideline Committee of the Department of Health, Philippines.The feedback generated were taken into consideration and incorporated in the guideline where appropriate.

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CRITERIA FOR ASSESSMENT OF STRENGTH OF EVIDENCE AND RECOMMENDATION

Evidences obtained and the strength for each recommendation were graded according to the World Health Organization's assessment criteria as shown in the following tables (lifted from the WHO recommendations for management of common childhood conditions: evidence for technical update of pocket book recommendations: newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care, 2012)[5]

Table 1. Grading scheme for level of evidence in assessing articles

Level of Evidence	***Rationale***
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Table 2. Grading scheme for strength of recommendation in assessing articles.

Strength of Recommendation	***Rationale***
Strong	The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional/Weak	The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However, the recommendation is only applicable to a specific group, population or setting OR where the new evidence may result in changing the balance of risk to benefit OR where the benefits may not warrant the cost or resource requirements in all settings.
No Recommendation	Further research is required before any recommendation can be made.

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RECOMMENDATIONS

A. CLINICAL DIAGNOSIS OF ACUTE BACTERIAL MENINGITIS

1. What are the signs and symptoms to suspect acute bacterial meningitis?

There is no single or combination of signs and symptoms that are diagnostic of acute bacterial meningitis.
Level of evidence: MODERATE
Strength of Recommendation: STRONG

Acute bacterial meningitis is characterized by the inflammation of the meninges. This occurs either via direct spread from a para-meningeal focus of infection such as otitis media, brain abscess or via hematogenous spread such as from a respiratory tract infection and sepsis. The disease process is described to involve the invasion of bacteria into the subarachnoid space and its subsequent replication triggers the inflammatory process, mainly the recruitment of activated leukocytes into the cerebrospinal fluid[6].

Bacterial meningitis can affect individuals of all ages. However, extreme of ages are the most susceptible due to the lack of maturity of the immune system for neonates and weakness and suppression of the immune system for the elderly. The course of acute bacterial meningitis is variable. It can be as short as a few days and may last for weeks. Acute bacterial meningitis is a medical emergency and requires immediate attention to prevent death or any significant neurologic impairment such as hearing loss, mental retardation, seizures and behavioral changes which can occur in about 50% of the survivors[7]. Therefore, early detection is key for prompt execution of appropriate management.

Clinically, signs and symptoms of bacterial meningitis vary from being non-specific to having full blown neurological symptoms of nuchal rigidity, abnormal meningeal signs such as positive Brudzinski and Kernig's sign and bulging fontanels. The variability of such clinical presentations depend mainly on the person's age, disease duration and individual response to the infection[8].

Based on a systematic review on neonatal meningitis in developing countries such as Africa, Latin America, Philippines, Thailand, Middle East, Ethiopia, Gambia and Papua New Guinea, frequently reported symptoms for bacterial meningitis were **fever, irritability, poor feeding** and seizures[9]. Another systematic review determined the accuracy of clinical symptoms in the diagnosis of pediatric bacterial meningitis. It has shown that **neck stiffness, bulging fontanel, seizures** (excluding febrile convulsion age range) and **decrease in appetite** all suggest bacterial meningitis[10]. Although fever was commonly reported as a symptom, its absence did not rule out the possibility of meningitis.

The presence of these signs and symptoms increased the probability of the diagnosis of acute bacterial meningitis in different levels. Specifically, the presence of a **bulging fontanel** increased the probability of bacterial meningitis by 3.5 times and **neck stiffness** increased the likelihood of acute bacterial meningitis by eight-fold[11, 12]. Complex seizures double the risk for bacterial meningitis[11,13,14] The presence of irritability does not necessarily mean the presence of the disease, however, the lack of irritability decreased the possibility of bacterial meningitis by half[12]. It is important to note, however, that the results of this systematic review were limited by the lack of precise and standardized definitions of clinical findings that would enable reproducibility. There was also a lack of age specific analysis and geographic variability.

Furthermore, a systematic review of the meningeal signs such as neck stiffness, Brudzinski's and Kernig's signs, as basis for the diagnosis of meningitis proved to be variable in sensitivity and specificity. Thus, these signs of meningeal irritation were not reliably predictive of meningitis if used alone[15].

Therefore, in cases where the signs and symptoms lead to a suspicion of bacterial meningitis, further work up such as a lumbar puncture is definitely warranted unless there are contraindications to the procedure.

2. What is the Definitive Test for Bacterial Meningitis?

Cerebrospinal fluid (CSF) culture is the gold standard for the diagnosis of acute bacterial meningitis.

[Level of evidence: High;
Strength of Recommendation: Strong]

In a retrospective study, 875 patients diagnosed with meningitis (defined in the study as CSF white blood cell count of over 1,000 cells per mm^3 and/or more than 80% polymorphonuclear cells) had a lumbar puncture done prior to antibiotic therapy[16]. In this group of patients, 85% of them had the diagnosis confirmed by a positive CSF culture result. Specifically, 96% of these patients were positive for *Haemophilus influenza*, 87% for pneumococcal meningitis and 80% for meningococcal meningitis. Post treatment cultures were not recommended. Yield of sample substantially decreases if CSF cultures were done in patients with prior antibiotic treatment[16].

Despite technological advances such as PCR and latex agglutination to aid in the diagnosis of meningitis, CSF culture still remains as the definitive test for acute bacterial meningitis.

Table 3. CSF cellular parameters in normal individuals and in patients with different types of meningitis.

	Leukocytes/µL	Pressure (mmH_20)	Protein (mg/dL)	Glucose (mg/dL)	Others
Normal term neonate	0-20	10-14	<1.0	≥0.6 (or ≥2.5 mmol/L)	
Normal (>1 month)	0-5	90-180	<0.4	45-80	
Bacterial meningitis	100-10,000; PMN predominance	Usually elevated; 200-300	100-500, occasionally >1000	<0.4 (may be normal)	Organism seen on smear or recovered on culture
Viral meningitis	10-3000; initially PMNs, then lymphocyte predominate	90-200	50-100	Usually normal; slightly reduces in mumps meningitis and LCM	No organisms seen on stain or recovered on culture
TB meningitis	25-100; Lymphocyte predominance; in early stages PMN	180-300	100-200, may >1000 if block is present	Usually reduced; <40	Acid fast organisms may be seen
Cryptococcal meningitis	10-200, lymphocytes	180-300	50-200	Reduced, <40	Positive India ink

3. How do we differentiate acute bacterial meningitis from other CNS infections?

Quantitative analysis of CSF parameters will help differentiate bacterial meningitis with other CNS infections. (See table 3).

[Level of evidence: High; Strength of Recommendation: Strong]

Since the clinical presentation of acute bacterial meningitis is variable, it cannot be completely differentiated from other CNS infections. This is the reason why lumbar tap with CSF analysis and culture are performed to be able to ascertain the presence of bacterial meningitis and to help direct therapy.

On CSF analysis, parameters indicative of bacterial meningitis include the following: white blood cell count of <100 to >10,000 cells/mm^3 although typically it rests between 1000-5000 cells/mm^3 characterized by a neutrophilic predominance (80-95%), a CSF glucose of <40 mg/dL, and a CSF-serum glucose ratio of ≤0.4 (80% sensitivity, 98% specificity especially for 1 year old children). For term neonates, a CSF-serum glucose ratio of ≤0.6 is deemed to be abnormal[17].

In a prospective cohort study involving 710 patients with suspected CNS infection, WBC counts in the CSF of ≥500/µL indicates a higher chance of having meningitis (LR 15; 95% CI, 10-22) while WBC counts in the CSF of <500/µL decreases the possibility of meningitis (LR 0.3; 95% CI, 0.2-0.4)[18].

CSF protein and neutrophil counts could also be suggestive of bacterial meningitis. A CSF protein of more than 0.5 g/liter (odds ratio of 14) and a neutrophil count of more than or equal to 100 (odds ratio of 12) usually dictates meningitis of bacterial origin[19]. For neonates, the white blood cell count in the CSF may be unreliable if infected with *Streptococcus agalactiae*. According to Georget-Bouquinet *et al*. (2008), the examination of CSF of 276 9children (83% neonates) diagnosed with *Streptococcus agalactiae* meningitis has shown that 6% of these patients had a normal CSF analysis result[20].

4. What are the contraindications to lumbar puncture (LP)?

A lumbar puncture is performed to facilitate cerebrospinal fluid (CSF) analysis, which involves cell count, Gram stain and culture. A successful lumbar puncture is characterized by a collection of an adequate amount of CSF in one attempt without any trauma (CSF sample with less than 1000 red blood cells per high power field), minimum distress to the patient as much as possible, and finally, absence of any serious adverse event[21].

LP must be performed unless any of the following contraindications are present:

- Signs suggesting raised intracranial pressure (papilledema, posturing, depressed sensorium such as stupor and coma
- Shock
- Extensive or spreading purpura
- After convulsions until stabilized
- Coagulation abnormalities: platelet count below 50 x 10^9/L
- Those receiving anticoagulant therapy
- Local superficial infection at the lumbar puncture site
- Respiratory insufficiency
- Radiological evidence of increased intracranial pressure

All must be considered in deciding to do a lumbar puncture but treatment should not be delayed if the procedure cannot be done.

[Level of evidence: Moderate
Strength of Recommendation: Strong]

Absolute contraindications to a lumbar puncture are the following:

1. Signs of elevated intracranial pressure (decreased level of consciousness, fluctuating level of consciousness, relative bradycardia and hypertension, focal neurological signs, abnormal posture or decerebrate posturing, unequal, dilated or poorly responsive pupils, papilledema and abnormal Doll's eye movement)[22,23];
2. Local infection at desired puncture site[22];
3. Radiological signs (in cranial CT or MRI) of obstructive hydrocephalus, cerebral edema or herniation[22], and the presence of an intracranial mass lesion or midline shift warrants postponement of lumbar puncture[22]. On CT scan, signs of increased intracranial pressure reveal coning (the descent of the cerebellar tonsils as well as the brainstem through the foramen magnum), effaced basal cisterns, cerebellar reversal sign, and effaced ventricles and cortical sulci[24].

Relative contraindications (lumbar puncture may be done but only after appropriate diagnostic and therapeutic interventions are done):

1. Signs of shock[23], sepsis[22] or hypotension (SBP: <100 mmHg; DBP <60 mmHg)[22];
2. Coagulation defects [disseminated intravascular coagulopathy (DIC), platelet count <50,000/mm^3, and therapeutic use of warfarin][22];
3. Focal neurological deficit (especially for suspected posterior fossa lesions)[22];
4. Glasgow coma score $\leq$8[22];
5. Epileptic seizures[22].

As observed in a prospective study, the presence of altered mentation (likelihood ratio 2.2; 95% CI 1.5-3.2), focal neurological findings (likelihood ratio 4.3; 95% CI 1.9-10) and papilledema (likelihood ratio 11; 95% CI 1.1-115) increased the odds of having an intracranial lesion[25]. Extensive or spreading purpura, presence of after convulsions until stabilized, as well as respiratory insufficiency are also contraindications to lumbar puncture[23].

There was no data found regarding the safety of performing lumbar puncture in patients with low platelet count[21]. However, in a case series of 66 acute leukemia patients showed that there is an increased risk of a traumatic procedure (defined in the study as having more than 500 red blood cells per high power field in the CSF) when lumbar puncture is done when platelet counts are between 20 to 50x10^3/µL[25]. Furthermore, lumbar puncture done within an hour after anticoagulation therapy poses as a hazard as well since there was a noted increase in the risk of paraparesis (relative risk 11.0; (95% CI 0.60-199)[26] and epidural hemorrhage[21].

5. What are the Ancillary Tests in the Diagnosis of Bacterial Meningitis? What is the Value of each Diagnostic Test?

a. Complete Blood Count (CBC)

> CBC should not be used solely as a basis for starting antibiotics. Signs and symptoms of bacterial meningitis associated with neutrophilia and increased serum CRP are highly suggestive of bacterial meningitis.
>
> [Level of evidence: High; Strength of Recommendation: Strong]

Complete blood count is a basic and routinely requested diagnostic tool in the work up of patients with any sign or symptom of infection. In such cases, the WBC count proves to be an important parameter to consider. In a prospective study a predictive model was created to help rule in bacterial meningitis as a diagnosis wherein CSF parameters are excluded because of cases where lumbar puncture is delayed or

contraindicated[27]. Population in the study was composed of patients with suspected bacterial meningitis aged 1 month and older. Results have shown that peripheral morphonuclear (PMN) leukocyte counts of >16 x 10^9/L, serum CRP level of >100 mg/L, and hemorrhagic rash were highly associated with bacterial meningitis or meningococcal disease. If any one of these factors were present in the patient, the probability for the presence of bacterial meningitis rose to more than 95% and even higher to >99% if there were 2 or more of these variables present[27].

On the other hand, h white blood cell counts are frequently requested, these parameters are of no value in ruling out a serious infection. In a systematic review performed to determine the value of laboratory tests in the diagnosis of serious infections in febrile children, results have shown that the white blood cell count assays have a negative likelihood ratio of 0.61 to 1.14[28]. These white blood cell indicators were shown to have more merit in ruling in a serious infection (positive likelihood ratio (LR) from 0.87 to 2.43). However, compared to inflammatory markers such as CRP or procalcitonin, the inflammatory markers showed more value in ruling in the diagnosis of a serious infection[28].

b. Blood Culture

In patients suspected to have bacterial meningitis, blood culture should be performed prior to starting antibiotic therapy.

[Level of evidence: Moderate;
Strength of Recommendation: Strong]

Suspicion of bacterial meningitis warrants a lumbar puncture and blood culture to correlate the CSF findings with the clinical picture[17]. In instances where lumbar puncture is deferred due to the presence of contraindications, the patient should be started on antibiotic therapy immediately after collection of sample for blood culture[22].

In local practice, blood culture is routinely requested as part of the laboratory work up in febrile children. Not only is blood culture a diagnostic tool, it also serves as a guide in antimicrobial therapy. The drawbacks are that blood culture is expensive and it is not always available especially in remote areas, and the results could take 2-7 days before its release.

c. C-Reactive Protein (CRP)

Serum and CSF CRP are useful in confirming and excluding bacterial meningitis.

[Level of evidence: High
Strength of Recommendation: Strong]

C-reactive protein is an acute phase reactant used in the diagnosis and in monitoring the course of infection[29]. It increases in most microbial infections, making it a reliable and sensitive marker for infection[30,31]. In normal children, serum CRP levels are very low and it quickly rises within 12 to 24 hours in the presence of infection[32].

In a meta-analysis of 5 studies of 1379 children, serum CRP was found to have a pooled positive likelihood ratio of 3.15 (95% CI 2.67-3.71) and a pooled negative likelihood ratio of 0.33 (95% CI 0.22-0.49) for serious infection[28]. In cases of serious infection wherein CSF findings are consistent with meningitis, but the Gram stain turned out negative and antimicrobial therapy is still being considered to be given or not, then serum CRP levels may be of help in decision making since serum CRP level has a high negative predictive value if it turns out to be normal[17].

The serum CRP or CSF CRP can be helpful in the diagnosis of bacterial meningitis

especially for cases where there is difficulty in isolating organisms[32]. In fact, CSF CRP can be useful in the diagnosis of partially-treated meningitis (patients presenting with a history of prior antibiotic intake)[33].

A local study was done to evaluate the value of serum CRP in differentiating various types of CNS infections .[34] There were a total of 103 patients across all ages. Eighteen out of 19 Filipino patients who were diagnosed with bacterial meningitis were found to have elevated serum CRP. The serum CRP was found to be more than 50 mg/L in 17 of these patients, and even beyond 100 mg/L in 14 out of these 17 patients. Of the 18 patients with bacterial meningitis, eight of them received antibiotics prior to hospital admission. Despite pre-treatment with antibiotics, the mean serum CRP concentration (196±91 mg/L) was still comparable to the mean serum CRP level of patients without antibiotic intake prior to admission (204±131 mg/L). Pre-admission antibiotic intake did not affect CRP values significantly[34].

In a hospital-based case control study on CRP as a means to differentiate the different types of meningitis, 140 children were divided into groups of control and different types of meningitis (pyogenic, partially treated, viral, and tuberculous) and blood and CSF analysis were done[35]. Results showed that 31 out of 32 cases of children with pyogenic meningitis (sensitivity 96.87%, specificity 74.73%; positive Likelihood Ratio: 3.83, negative Likelihood Ratio: 0.04) and 18 out of 27 children with partially treated meningitis (sensitivity 66.66%, specificity 63.71%) had positive CSF CRP (Table 4). Comparing the mean CSF CRP among the groups, the mean CSF CRP in patients with pyogenic meningitis (45.75±28.50) and partially treated meningitis (23.11±23.98) were significantly higher (P<0.0001) compared to patients with tuberculous meningitis (1.20±3.79), viral meningitis (4.47±16.93) and the control (2.00±8.84)[35]. Other researchers obtained the following results for CSF CRP in pyogenic meningitis: Sn 84% and 94%, Sp 100%[32,36]; Sn 97% and Sp 98%[37]; Sn 97% and Sp 86%[38].

Table 4. Comparison between CSF and blood CRP among different types of meningitis (Malla *et al.*, 2013).

	Sensitivity (Sn)	***Specificity (Sp)***
CSF CRP		
Bacterial meningitis	*96.87%*	*74.73%*
Partially treated meningitis	*66.66%*	*63.71%*
Tuberculous meningitis	*10%*	*55.38%*
Viral meningitis	*20.58%*	*50.94%*
Blood CRP		
Bacterial meningitis	*90.62%*	*32.40%*
Partially treated meningitis	*88.88%*	*23.68%*
Tuberculous meningitis	*70%*	*26.12%*
Viral meningitis	*64.47%*	*24.52%*

In a prospective study, 63 pediatric patients aged 1 month to 12 years with clinically suspected and laboratory confirmed meningitis had blood and CSF extracted for serum and CSF CRP to determine whether these are useful in the early diagnosis of bacterial meningitis. Of the 63 patients, 38 had bacterial meningitis[32]. CSF CRP was found to be elevated in 33 of the 38 patients with bacterial meningitis, and 12 out of 38 of them had a history of antibiotic use for ≤ 7 days. Serum CRP had a sensitivity of 76% and specificity of 68% (positive Likelihood Ratio: 2.38, -negative likelihood ratio: 0.35) while CSF CRP had a sensitivity of 86.6% and a specificity of 92% (positive Likelihood ratio: 10.8, negative Likelihood Ratio: 0.15). When both serum and CSF CRP were combined, it became 96% sensitive and 100% specific (positive Likelihood Ratio: infinity, negative Likelihood ratio: 0.04) for bacterial meningitis[32].

Despite the promising benefit of serum and CSF CRP in the diagnosis of bacterial meningitis, these are still not routinely done in the Philippines since it is quite expensive.

Serum CRP approximately costs Php 1,100 and CSF CRP is not locally available.

d. Polymerase Chain Reaction (PCR)

PCR may be utilized to amplify DNA from patients with meningitis caused by common meningeal pathogens (*S. pneumoniae*, *N. meningitidis* and *H. influenzae*) especially if the CSF culture is negative.
[Level of evidence: High;
Strength of Recommendation: Strong]

The PCR is used in the field of medicine for various purposes which includes diagnosis of infectious diseases and genetic analyses. It is characterized by the amplification of genomic DNA using specific primer molecules[39]. The polymerase chain reaction is highly sensitive. Based on studies, the sensitivity of PCR does not fall below 90% and its results are not affected by antibiotic administration.

A comparison of the accuracy of real time PCR of CSF against Gram stain and culture in the diagnosis of patients with suspected meningitis caused by *S. pneumoniae*, *N. meningitidis* and *H. influenzae* was performed in Brazil. Real time PCR had a sensitivity of 95% and a specificity of 90% (positive Likelihood Ratio: 9.5, negative Likelihood Ratio: 0.06) based on culture as a reference standard[40]. In another study by Radstrom *et al*. (1994), the sensitivity of a seminested PCR in a verified positive CSF of a patient with bacterial meningitis was 94%, while the sensitivity compared to a culture-positive CSF was 93% and specificity was 96% compared with culture-negative CSF[41].

These observations were also similar to another study in Michigan wherein 74 CSF samples from patients were subjected to broad-range bacterial PCR[7]. Compared to a microbiological standard (positive Gram stain or culture), the sensitivity of the test was 100%, 98.2% specificity, with a 94.4% positive predictive value and 100% negative predictive value[7]. The broad-range PCR may also be used to assist in decision making in initiation, continuation or cessation of antimicrobial therapy. If it has a positive result, this supports the decision to give antibiotics, however, if the result is negative, other possible diagnoses may be considered.

PCR indeed has a high sensitivity and specificity however it still does not replace culture in the isolation of bacteria[7]. In the case of suspected meningococcal meningitis, a whole blood real time PCR test for *Neisseria meningitidis* may be helpful to confirm the disease, but a negative test does not rule out meningococcal disease[23].

CSF PCR testing is available locally at the Research Institute for Tropical Medicine (RITM). For CSF PCR for bacteria (*S. pneumoniae*, *N. meningitidis*, and *H. influenzae*), the cost is Php 3,500 each. For viruses (*HSV*, *Enterovirus* and *Influenza A* and *B*), each costs Php 4,000.

e. Latex Agglutination Test (LAT)

Latex agglutination tests should **NOT** be routinely used in the diagnosis of bacterial meningitis.

[Level of evidence: Moderate
Strength of Recommendation: Conditional]

Latex agglutination test detects bacterial antigens in the CSF. Studies have shown that the sensitivity of CSF bacterial antigen detection test ranges from 0-25%, and this is for cases where culture results are negative. In a study on both adult and pediatric patients at Coney Island Hospital, New York, four out of the thirty CSF specimens from patients with bacterial meningitis were positive in the latex agglutination test (sensitivity of 13.5%) using Wellcogen bacterial antigen kit[42]. For patients with culture negative results in this study, the sensitivity of the latex agglutination test was only 7%. Furthermore, a retrospective study in

adults and children with bacterial meningitis showed that the LAT was not superior compared to Gram stain in screening for bacterial meningitis, even for those with culture negative results[43].

A study on the CSF of 100 children (less than 5 years old) with clinically suspected acute bacterial meningitis was performed to determine the value of latex agglutination test[44]. Out of the 100 patients, 31 were confirmed to have bacterial meningitis via Gram stain, culture and latex agglutination test based on the WHO criteria. Comparing the sensitivity of latex agglutination test to CSF culture as standard, the sensitivity of LAT was only 66.66% and specificity of 87.91% (positive Likelihood Ratio: 5.51, negative Likelihood Ratio: 0.38)[44].

A positive result in latex agglutination test does not alter therapeutic decisions and the course of management. Furthermore, especially for neonates, the LAT is not able to identify bacteria from *Enterobacteriaceae* except for *E. coli*[44], thus CSF culture is still the most important laboratory test to perform. Since the bacterial antigen test does not offer changes in the management, the test is not recommended to be performed regularly for the prompt detection of bacteria in patients with bacterial meningitis[17].Each test costs around 2,100 pesos.

f. Procalcitonin

Procalcitonin may be used differentiate bacterial from viral meningitis. In situations wherein a CSF analysis cannot be performed immediately, it may be used as a basis to start antibiotics. However, it should not replace CSF analysis and culture in the diagnosis of bacterial meningitis.

[Level of evidence: Strong;
Strength of Recommendation: Strong

Procalcitonin is a propeptide of calcitonin and is produced from the C cells of the thyroid gland and peripheral blood leukocytes as well[45]. Production of procalcitonin is also triggered by the presence of bacterial endotoxins and proinflammatory cytokines[46]. Procalcitonin levels in healthy individuals are very low, the levels slightly increase or remain normal in viral infections and substantially increase for bacterial infections[45].

Serum procalcitonin decreases after 72 hours of treatment, making it a valuable parameter for evaluating the efficacy of antibiotic treatment.

[Level of evidence: Moderate
Strength of Recommendation: Strong]

A prospective study involving 40 patients aged 4 months to 12 years old with meningitis was done to determine the role of serum procalcitonin in meningitis and its use in differentiating bacterial versus viral meningitis[45]. Twenty patients were diagnosed with bacterial meningitis while the other half was diagnosed with viral meningitis based on bacterial cultures and CSF profiles. Results have shown that the serum procalcitonin of patients with bacterial meningitis (26.8$\pm$12 ng/mL) at the time of diagnosis was significantly higher than in the viral meningitis (0.4$\pm$0.2 ng/mL) and control groups (0.3$\pm$0.1 ng/mL) ($p<0.001$)[45]. In this study, a procalcitonin level of >2 ng/mL in patients with bacterial meningitis was found to have 100% sensitivity, and 66% specificity with a 68% positive predictive value and a 100% negative predictive value, and this cut off value of procalcitonin may be helpful in differentiating bacterial from viral meningitis[45].

In addition, it was also observed that there was a decrease in the serum procalcitonin level in the bacterial meningitis group after 72 hours of treatment (10.8$\pm$5.3 ng/mL from the initial 26.8$\pm$12 ng/mL), which was statistically significant compared to procalcitonin levels at

the start of treatment ($p<0.05$)[45]. Thus serum procalcitonin may be used in monitoring response to antimicrobial therapy in bacterial meningitis especially in cases where a repeat lumbar tap is not possible.

Results obtained by Taskin *et al*. (2004) were consistent with the results described above[47]. Forty four children were diagnosed with meningitis (22 bacterial, 22 viral) based on clinical presentation, CSF parameters, and Gram stain and culture. Blood were extracted from patients at the time of diagnosis and at 48-72 hours after initiation of treatment. Results showed that the serum procalcitonin level at the time of diagnosis for patients with bacterial meningitis was 75.8 ± 29.8 ng/L compared to the control group of 0.3 ± 0.2 ng/L ($p<0.001$). Serum procalcitonin levels were significantly higher as well at 48-72 hours after onset of treatment in patients with bacterial meningitis (35.7 ± 19.6 ng/L) compared to levels in patients with viral meningitis (0.3 ± 0.1 ng/L) ($p<0.001$). These findings were similar as well by the results obtained from a meta-analysis on studies on serum procalcitonin and CRP levels as markers of bacterial infection. Serum procalcitonin markers were found to be better than CRP markers in distinguishing bacterial from viral infections, with procalcitonin having a positive Likelihood Ratio of 6.05 (95% CI: 4.67–7.82) and negative Likelihood Ratio of 0.10 (95% CI, 0.06–0.15). CRP markers on the other hand had a positive Likelihood Ratio of 3.75 (95% CI: 3.06–4.59) and a negative Likelihood Ratio of 0.20 (95% CI: 0.15-0.27)[48].

Furthermore, procalcitonin was shown to be superior to CRP in terms of distinguishing between bacterial infections from non-infectious inflammatory conditions. The difference was statistically significant ($p<0.05$) in terms of the test's sensitivity (88%, 95% CI: 80-93% for procalcitonin; 75% (95% CI: 62%–84%) for CRP markers) as well as in its specificity (81%, 95% CI: 67%–90% for procalcitonin; 67%, 95% CI: 56%–77% for CRP markers)[48].

Determination of serum procalcitonin level is a good diagnostic test which helps differentiate bacterial from viral infections. In the country, the test is relatively new and available in only a few institutions, plus it is quite expensive.

6. What is the role of imaging tests in the diagnosis of bacterial meningitis?

> Neuroimaging is used to identify the presence of complications of bacterial meningitis and to rule out contraindications in doing a lumbar tap. Neuroimaging is not used to diagnose the presence or absence of a CNS infection.
>
> [Level of evidence: Moderate
> Strength of Recommendation: Strong]

Neuroimaging in acute bacterial meningitis is primarily used to rule out structural lesions and cerebral herniation and also to detect and monitor complications of meningitis. For uncomplicated cases of meningitis wherein there is no doubt on the diagnosis, imaging is not required. Any sign or symptom that suggests an increased intracranial pressure dictates a cranial CT or MRI be done prior to lumbar puncture.

The cranial imaging in bacterial meningitis may show pial enhancement with occasional brain swelling or minimal widening of extra-axial CSF spaces[49]. For uncomplicated cases, imaging is normal in most cases[24]. However, for patients that are not clinically improving or those with new onset neurological signs or symptoms despite therapy, neuroimaging is advised[50].

Based on the four year-surveillance review (July 2011-November 2014) on the clinical practice guideline on bacterial meningitis and meningococcal septicemia of the National Institute for Health and Care Excellence, MRI has no role in the diagnosis of bacterial meningitis[50]. This was based on a systematic review of 5 studies which showed that MRI has low sensitivity in diagnosing bacterial

meningitis[50]; but for detecting and monitoring for complications, MRI may have a role.

The complications of bacterial meningitis are **H**ydrocephalus, **A**bscess, **C**erebritis/ **C**ranial nerve involvement, **T**hrombosis, **I**nfarct, **V**entriculitis/**V**asculopathy, and **E**xtra-axial fluid collections such as empyema or hygroma (HACTIVE)[24]. MRI is preferred over CT scan in monitoring for these complications in patients with bacterial meningitis. A contrast-enhanced brain MRI is said to be the most sensitive in terms of detecting the presence of inflammatory changes in the meninges[51]. One retrospective study in Texas from 2001 to 2011 on infants less than a year old with culture-confirmed bacterial meningitis showed that MRI studies were able to detect and cause changes in the management of these patients. MRI studies evaluated for the presence of leptomeningeal enhancement, cerebritis, choroid plexitis, ventriculitis, hydrocephalus, empyema, abscess, infarct, venous thrombosis and hemorrhage. Eighty one percent of infants with an MRI had abnormal MRI findings, the most common of which was leptomeningeal enhancement (57%), followed by subdural empyema (52%) and brain parenchymal ischemia/infarcts (43%). Of these infants, 45% had a clinical change in management resulting to either extension of antibiotic treatment (30%) or neurosurgical intervention (23%). However, 19% of infants had a normal MRI result despite having a culture-verified bacterial meningitis[52].

Ultrasonography may also be used in monitoring for complications of bacterial meningitis. Aside from its low cost, portability, lack of sedation and radiation, ultrasonography was found to be comparable to CT scan in detecting complications in infants[53]. One prospective study in New Delhi on infants with bacterial meningitis has shown that cranial ultrasound was able to detect complications of bacterial meningitis in infants which resulted to prompt management of such cases. The most common findings seen were echogenic sulci and sulcal separation. Other findings were abnormal parenchymal echoes, ventriculomegaly, ventriculitis, choroid plexitis, exudates, septations, cerebral abscess, subdural empyema and hemorrhagic infarct[53]. However, small subdural effusions were better visualized by CT scan and these may not be detected by ultrasonography especially in those with low frequency transducer[53]. In patients with clinically apparent symptoms hinting possible complications such as the presence of neurologic signs and symptoms, persistent seizures, and deterioration of CSF parameters after 48 hours, cranial ultrasound was found to detect cranial abnormalities in all of these patients[53]. Sonographic findings may include echogenic widening of brain sulci, meningeal thickening; irregular and echogenic ependyma, and intraventricular debris and stranding (ventriculitis); abnormal brain echogenicity; areas with poor margins of increased echogenicity with increased vascularity (early abscess) which may eventually mature to a well-circumscribed, complex solid mass with highly echogenic walls; and ventricular dilatation (hydrocephalus)[54]. Thus, it was suggested that ordering for a cranial ultrasound be done only when complications of bacterial meningitis are clinically suspected since for those without clinically suspicious findings, the cranial sonogram turns out to be insignificant[55]. In contrast, based on a prospective study on infants 3 days to 11 months old with bacterial meningitis, some recommend obtaining a baseline cranial ultrasonography at the time of diagnosis followed by a repeat study the following week if the initial ultrasound findings are abnormal (presence of ventricular or parenchymal abnormalities). It was also advised that a repeat cranial ultrasound be done for cases wherein there is acute clinical deterioration, when CSF parameters show no response to antimicrobial therapy or when new symptoms appear in the infant[56].

7. What are the most common pathogens of acute bacterial meningitis in the different age groups in the Philippines?

In neonates and extended neonates **up to 2 months of age**, the most common etiologic agents are **Gram negative enteric bacilli**.

Among **3 months and older children but less than 5 years of age**, ***Haemophilus influenzae*** **and** ***Streptococcus pneumoniae*** are the predominant bacteria responsible for acute bacterial meningitis.

For children **5 years and older**, ***S. pneumoniae*** is the most common etiologic agent causing bacterial meningitis.

Neisseria meningitidis may occur in **epidemics or sporadically**, 80-90% of cases present as meningitis. In infants, children and young adults, meningococcal meningitis are caused by *Neisseria meningitidis* Serotype A or B.

[Level of evidence: High
Strength of Recommendation: Strong]

Table 5. Summary of pathogens isolated in neonates and extended neonates obtained from data from local and international researches.

Table 5A. Local Researches

(REF)Author and Description	Pathogens isolated
(57)Maramba et al, 2011; Multicenter surveillance and chart review (July-Dec 2006), ≤28 days old	*Gram negative bacteria (94%): Pseudomonas spp.*, *Burkholderia spp.*, and *Klebsiella spp.*
(58)Ignacio et al, 2012; Retrospective, descriptive (July 2004 to June 2006)	*Enterobacter aerogenes (55%)*, *Acinetobacter baumanii* and coagulase negative *Staphyloccoccus*
(59)Quiambao et al, 2007; Prospective (April 1994- May 2000), infants <60 days old	*H. influenzae*, *S. typhi*, *Salmonella* group, *E. coli*, *Pseudomonas*, *Klebsiella sp.*, and *Enterobacter sp.*
(60)Morelos and Gatchalian, 1996; Retrospective, descriptive (July 1982-Dec 1994)	*Gram negative bacteria (69%): E. coli*, *K. pneumoniae*, *Salmonella sp.*, *P.aeruginosa*, *Acinetobacter*, *E. cloacae,* *Group B Strep (9.3%)*
(34)Sutinen et al, 1999; Retrospective, descriptive (Oct 1983 to Nov 1984), Manila, 0-2 months old	3 isolates (*S. pneumoniae*) and 1 isolate *E. coli*

Table 5B. International researches

(REF)Author and Description	Pathogens isolated
(61)Lin et al, 2012; Retrospective, descriptive (1984-2008), Northern Taiwan, <1 month old	Group B *Streptococcus* (39.1%) and *E. coli* (20.5%)
(62)Cho et al, 2010; Retrospective, descriptive (1996-2005), Korea, ≤18 years old	<3 months old: *Group B streptococcus*(47.6%) and *E. coli* (9.6%)

(63)Nigrovic et al, 2008; Retrospective, multicenter (2001-2004), USA, 1 mo-19yrs	I month-3 months old: Gram negative bacilli (32%) and Group B *Streptococcus* (39%)
(64)Gaschignard et al, 2011; Prospective (2001-2007)	*GBS* (59%) and *E. coli* (28%)
(65)Gaschignard et al, 2012; Prospective study (2001-2010)	*GBS* and *E. coli*
(51)Khalifa et al, 2011; Retrospective study (1999-2006), Tunisia, neonates	Enterobacteriaceae and Group B *Streptococcus*

. In Korea, *S. agalactiae* (47.6%) and *E. coli* (9.6%) were the main causes of bacterial meningitis in children less than 3 months old[62]. In the United States, one to 3-month old infants who presented at the emergency department and were diagnosed with bacterial meningitis were found to be mostly because of Gram negative bacilli (32%) and Group B *Streptococcus* (39%) infection[63]. A French national survey conducted from 2001 and 2007 showed that GBS (59%) was the predominant pathogen in neonates with bacterial meningitis, followed by E. coli at 28%[64]. The same is true for early (GBS 84%) and late-onset (GBS 57%) term infants, but for preterm infants, *E. coli* was predominant at 42%[65]. A study in Tunisia on patients with acquired bacterial meningitis in 1999-2006 revealed that Enterobacteriaceae and Group B *Streptococcus* were the most common pathogens identified in neonates[51]. In a systematic review by Furyk *et al*. (2011), 22 reviewed studies describing the etiology of neonatal meningitis in developing countries have shown disparate results mainly due to differences in methodology, quality of the study and study design[9]. There were more studies done in Africa (14 studies) and upon review, the bacterial pathogens found of medical importance in the developing countries studied (Africa, Latin America, Philippines, Thailand, Middle East, Ethiopia, Gambia and Papua New Guinea) were Gram negative bacilli (except *E. coli*), *S. pneumoniae*, *S. aureus* and *H. influenzae*.

Table 6. Summary of pathogens isolated in infants and children obtained from data from local and international researches

Table 6A. Local researches

(REF)Author and Description	**Pathogens isolated**
(70)Galagar et al, (Jan 2010-Dec 2014) >2 mos-18 yrs	*H. influenzae type B* (44%), *S. pneumoniae* (24%)
(69)Espino et al, (2009-2011) 2mos-18yrs, 5 sentinel sites in Luzon and Visayas	*Jap B enceph (34%), Dengue (9.3%), H, influenzae type B (10%), S. pneumoniae (9.3%), N. meningitidis (1.5%)*
(66)Abucejo-Ledesma et al, 2007; Prospective (April-May 2000), Bohol, 0-59 mos	*H. influenzae type B* (37%) and *S. pneumoniae* (18%)
(67)Tam et al, 2001; Retrospective (1994-1999), PCMC	*H. influenzae* and *S. pneumoniae* most common
(34)Sutinen et al, 1999; Retrospective (Oct 1983-Nov 1984), Manila, 3 mo- 15 yrs	5 *H. influenzae type B*, 3 *N. meningitidis*, and 4 *S. pneumoniae*
(68)Abucejo et al, 2000; (Jan 1995-Dec 1998), <5 yrs old	*H. influenzae type B* (43%) and *S. pneumoniae* (16%)

Table 6B. International researches

(REF)Author and Description	Pathogens isolated
(71)Vashishtha et al, 2011; Retrospective (Jan 2009-Dec 2010), Western Uttar Pradesh, 3 mos- 18 yrs old	*S. pneumoniae* (56.67%), *H. influenzae type B* (10%), and *N. meningitidis* (6.67%)
(72)Khorasani and Banajeh, 2006; Retrospective (May 1999 to June 2001), Yemen, 1 mo- 15 yrs old	*S. pneumoniae* (30.1%), *H. influenzae* (15%), *N. meningitidis* (52.9%) plus *S. aureus* (1.3%) and *E. coli* (0.7%)
(73)Ho Dang Trung et al, 2012; Prospective, descriptive (Aug 2007– April 2010), Vietnam, <15 yrs old	*H. influenzae type B* (26%) and *S. pneumoniae* (25%)
(74)Gervaix et al, 2012; Prospective multicenter observational study (Jan 2008 to Dec 2009), Cameroon, 2 mo- 15 yrs old	64 were positive for *S. pneumoniae*, 31 were positive for *H. influenzae type B* and 17 were positive for *N. meningitidis*
(75)Zimba et al, 2009; Prospective (Aug 2007 to March 2008), Mozambique, 1 -20 yrs old	6.52% *H. influenzae type B*, 26.09% *N. meningitidis*, and 6.52% *S. pneumoniae*
(76)Perez et al, 2010; Retrospective (Jan 1998-Dec 2007), Cuba	*S. pneumoniae* 23.6%, *N. meningitidis* 8.2%, *Hib* 6%, bacteria of unknown etiology 55.3% and other bacteria 6.9%
(77)Dickinson and Perez, 2005; Observational study (1998-2003), Cuba, 1 - 18 yrs old	*H. influenzae type B*, *S. pneumoniae*, and *N. meningitidis*
(78)Ceyhan et al, 2008; Prospective (Feb 2005 to Feb 2006), Turkey, 1 mo - <17 yrs old	56.5% *N. meningitidis*, 22.5% *S. pneumoniae*, and 20.5% *Hib*
(79)Mendsaikhan et al, 2009; Prospective (Feb 2002-Jan 2005), Mongolia, 2 months-5 years old	55% *Hib*, 21% *S. pneumoniae* and 23% *N. meningitidis*
(62)Cho et al, 2010; Retrospective, descriptive (1996-2005), Korea, ≤18 years old	< 5years old: *Streptococcus pneumoniae* (32.1%) and *Haemophilus influenzae* (27.8%); 5-18 years old: *S. pneumoniae* (35.9%) and *N. meningitidis* (23.4%)
(80)Dash et al, 2007; Retrospective (2000-2005), Oman, <5 yrs old	*H. influenzae* 22%, *S. pneumoniae* 15%, and *N. meningitidis* 11%
(51)Khalifa et al, 2011; Retrospective (1999-2006), Tunisia	3 months to 5 years old: *H. influenzae* (36.3%) and *S. pneumoniae* (28.8%); >5 years old: *S. pneumoniae* (47%)
(81)Franco-Paredes et al, 2008; Retrospective (1993-2003), Mexico, 1 mo- 18 yrs old	H. influenzae type B (50%), *S. pneumoniae* (31%), and *N. meningitidis* (2%)
(82) Salih et al, 2010; Prospective (2003-2004), Sudan, <5 yrs old	*N. meningitidis* (48.49%), *H. influenzae* (30.30%) and *S. pneumoniae* (21.21%)
(83)Theodoridou et al, 2007; Retrospective, Athens, 1 mo- 14 yrs old	*N. meningitidis*, *Haemophilus influenzae type B* and *S. pneumoniae*
(84) Mani et al, 2007; Retrospective (Jan 1996 to Dec 2005), South India	0-5 yrs of age: *S. pneumoniae* (44.12%), *H. influenzae* (17.65%), *Pseudomonas* (8.82%) and *E. coli* (2.94); 5-12 years old: *S. pneumoniae* (76.47%) and *H. influenzae* (5.88%); >12 yrs old: *S. pneumoniae* (62.99%), *Klebsiella* (1.62%), alpha hemolytic *Streptococcus* (1.62%), *S. aureus* (1.62%), *N. meningitidis* (1.30%) and *E. coli* (0.97%)
(63)Nigrovic et al, 2008; Retrospective, multicenter s (2001-2004), USA, 1 mo-19 yrs old	*S. pneumoniae* (33% in between 3 months and 10 years old) and *N. meningitidis* (54% in 11 years old and above)
(85)Sakata et al, 2010; Retrospective study (April 2004-Jan 2007), Japan, ≤15 years of age	*H. influenzae* (63.5%), *S. pneumoniae* (15.2%), *S. agalactiae* (6.7%) and *E. coli* (2.6%)

A local study in Bohol on children with bacterial meningitis revealed that for children 0-59 months old, *H. influenzae type B* (37%) and *S. pneumoniae* (18%) were very common[66]. *H. influenzae* was the most common organism observed while *S. pneumoniae*, *Pseudomonas*, *Salmonella* and *E. coli* were less frequently seen in the CSF culture in a retrospective study of 90 patients at Philippine Children's Medical Center (PCMC) from 1994 to 1999[67]. The same pathogens were isolated in 3-month old to 15 year old children with CNS infection in Manila (out of 15 bacterial isolates within this age group, there were five *H. influenzae type B*, three *N. meningitidis*, and four *S. pneumoniae*)[34]. *H. influenzae type B* (43%) and *S. pneumoniae* (16%) were also the common microorganisms identified in a study in children less than 5 years old with bacterial meningitis in a provincial hospital in the Philippines, the data were collected from 1995 to 1998[68]. In a multicenter study with sites in Luzon and the Visayas, patients with symptoms of CNS infection had *H. influenzae type B* and *S. pneumoniae* as the most common bacterial pathogens, although viral etiologies (Japanese encephalitis and Dengue) were found to be more common[69].

A recent study at the Philippine General Hospital included 68 patients aged 2 months to 5 years with bacterial meningitis from 2010-2014[70]. Only 36% had an identified pathogen in the CSF. The dominant bacteria were H. influenzae B (44%) and S. pneumoniae (24%). In the same study, there was only 1 positive isolate in a patient more than 5 yrs which was identified as S. pneumoniae. The dominance of these pathogens is not surprising since the Hib and pneumococcal conjugate vaccines were only included in the National Expanded Program for Immunization in 2013 and has not been implemented nationwide.

The type of microorganisms obtained from CSF cultures was consistent even with studies from other countries. Confirmed cases attributed to *S. pneumoniae* (56.67%), *H. influenzae type B* (10%), and *N. meningitidis* (6.67%) were isolated in children 3 months old to 18 years old in a retrospective study of hospitalized children in Western Uttar Pradesh[71]. Similar isolates were obtained as well in a study in Yemen from 1999-2001 on children 1 month to 15 years old with clinical features of acute bacterial meningitis[72]. There were 153 cases with positive cultures of *S. pneumoniae* (30.1%), *H. influenzae* (15%), *N. meningitidis* (52.9%) plus *S. aureus* (1.3%) and *E. coli* (0.7%). In Vietnam, a prospective study revealed that in children younger than 15 years old with bacterial meningitis, the most common bacteria seen were *H. influenzae type B* (26%) and *S. pneumoniae* (25%)[73]. This was also observed in a prospective multicenter observational study in Cameroon involving 170 children aged 2 months to 15 years, with bacterial meningitis. The CSF PCR was positive in 112 children (64 were positive for *S. pneumoniae*, 31 were positive for *H. influenzae type B* and 17 were positive for *N. meningitidis*)[74]. The pneumococcal and *Hib* meningitis were frequently seen in children aged 9 to 15 months while meningococcal meningitis were found more often in 72-month old children. Furthermore, in Mozambique, a study including patients more than a month old showed similar microbiological isolates as well[75]. There were 330 CSF samples but only 46 had a positive culture result out of which 6.5% grew *H. influenzae type B*, 26% *N. meningitidis*, and 6.5% grew *S. pneumoniae* in patients aged 1 year to 20 years. More studies from different countries are listed in Table 6B which shows the etiology of bacterial meningitis in patients 2 months and older.

8. Are there signs and symptoms suggestive of a specific etiology?

There are no signs and symptoms suggestive of a specific etiology except for meningococcal meningitis. Classic symptoms include a hemorrhagic rash, impaired consciousness and meningism.
[Level of evidence: High
Strength of Recommendation: Strong]

A retrospective study compared the clinical profile of 300 pediatric patients with meningitis secondary to *H. influenzae* and *S. pneumoniae* infections[86]. Nuchal rigidity as well as prolonged fever were associated with *H. influenzae meningitis* (p=0.05), whereas a bulging fontanel and frequent seizures were more likely to be found in patients with pneumococcal meningitis. However, in a study by Panlilio and Lee from 1984 to 1989 in pediatric patients with bacterial meningitis at PCMC, there was no significant difference found between patients with *H. influenzae* or pneumococcal meningitis in terms of the clinical picture of those patients who developed subdural effusion[87]. The only difference observed was that those with *H. influenzae* infection had a more prolonged clinical course. Since children with bacterial meningitis usually have non-specific signs and symptoms (fever, vomiting, irritability, headaches, muscle pain or joint pains) that may be indistinguishable to other illnesses, signs and symptoms alone are not sufficient as basis for diagnosis of the disease.

In the case of meningococcal disease, some children may present with more specific signs and symptoms such as rash and altered mental status which may become more severe and specific over time[23]. A local retrospective study in Baguio city described the profile of 217 patients infected with *Neisseria meningitides*. One hundred of these patients comprised of children from 0-18 years of age. All of the patients had a history of fever; majority of them (90%) had rashes, 39% of which was purpuric in character[88]. Leg pain, cold hands and feet and abnormal skin color were noted to be important features of meningococcal disease and signify early sign of the disease (occurs within 12 hours of onset of illness) in children and adolescents[89]. These were observed in the review of data gathered from parents of children 0-16 years old who died from meningococcal disease from 1997-1999 in England, Wales and Northern Ireland. Symptoms of meningism, rash and impaired consciousness were said to occur later in the course of illness.

9. **What are the empiric antibiotics for acute bacterial meningitis?**
a. in neonates? (0-28 days old)

For neonates with acute bacterial meningitis, the recommended empiric therapy is the combination of an
Ampicillin* OR Cefotaxime* OR Ceftriaxone* PLUS
an **aminoglycoside***.
*depending on the local resistance pattern
[Level of evidence: Moderate
Strength of Recommendation: Strong]

In developed countries, the recommended empiric therapy includes an ampicillin plus cefotaxime OR an ampicillin plus an aminoglycoside. This was based on the fact that most of the organisms affecting neonates were Group B *Streptococci*, *Escherichia coli*, *Listeria monocytogenes*, Gram negative enterics and *S. pneumoniae*[90,91,92,93,94,95].

However, in developing countries such as the Philippines, the isolated organisms differ from those in developed countries because of multiple factors such as population characteristics, genetics and the individual's immune response, and techniques in the laboratory including pathogen isolation and reporting[96,97], not to mention varying microbial resistance patterns as well.

Bacterial pathogens causing meningitis can also cause sepsis as well. A multicenter

surveillance and chart review of neonates diagnosed with sepsis in five hospitals in the Philippines has shown that the predominant organism isolated in cultures was Gram negative bacteria (94%) (*Pseudomonas spp., Burkholderia sp., Klebsiella spp.*). No Group B *Streptococci* were seen[57]. Four out of the five hospitals used the combination of ampicillin and aminoglycoside (amikacin or gentamicin) as first line therapy for neonatal meningitis, however, in about half of these patients, the antibiotics were shifted due to either inadequate response to therapy or because the results of culture and antibiotic susceptibility testing showed a different but more appropriate drug to use.

With regard to early onset and late onset sepsis, no particular antibiotic regimen can be recommended as of this time. For early neonatal sepsis, a review of two randomized, controlled trials comparing monotherapy to combination therapy has shown to have no significant difference in mortality, treatment failure or bacteria resistance. According to the reviewers, there is not enough evidence to support any particular antibiotic regimen over another, thus more studies regarding this matter are needed[98]. The same goes for late onset neonatal sepsis as there is still lacking evidence to justify treatment protocols. In the review by Gordon and Jeffrey (2005), although there were thirteen studies identified for inclusion in the review, in the end, only one small study on 24 neonates was reviewed because majority of these studies did not differentiate data for early and late onset sepsis[98]. The study compared beta-lactam monotherapy with the combination of beta-lactam plus an aminoglycoside and there was no significant difference noted for mortality (relative risk 0.17, 95% CI 0.01-3.23) or treatment failure (relative risk 0.17, 95% CI 0.01 to 3.23). There were no documented cases of antibiotic resistance in either group. However, it is important to note that since the study was small, the small population size might have significantly affected the outcomes of the study.

The empiric treatment of neonatal meningitis must be adjusted accordingly based on onset of disease, local epidemiology, bacterial resistance patterns and available resources[42]. Currently, Group B *Streptococci* is not common. As for resistance patterns, if bacterial resistance of Gram negative bacilli to ampicillin is high, a third generation cephalosporin PLUS an aminoglycoside may be given. If the resistance is low, ampicillin PLUS an aminoglycoside would suffice. Also, consider the price of medications. The ampicillin plus an aminoglycoside is less expensive than a third generation cephalosporin plus an aminoglycoside.

Ceftriaxone is contraindicated in neonates who are hyperbilirubinemic, particularly in premature babies[99]. Ceftriaxone can displace bilirubin from serum albumin thus aggravating the condition which in turn may lead to kernicterus. Ceftriaxone is also contra-indicated in neonates who are less than 28 days of age who are receiving treatment with Calcium-containing intravenous solutions[99]. This is due to the risk of precipitation of the Ceftriaxone-calcium salt and deaths have been reported due to this. When Ceftriaxone is contraindicated in the neonate, Cefotaxime should be used.

b. 1month to 18 years old

For children 1 month-18 years old with acute bacterial meningitis, the recommended empiric therapy is **Ceftriaxone OR Chloramphenicol**.
[Level of evidence: Moderate
Strength of Recommendation: Strong

Empiric antibiotic therapy must take into consideration the antibiotic resistance pattern of the locality. In the Philippines, *S. pneumoniae* does not show the same

sensitivity pattern as surrounding nations with high penicillin resistance. Using meningitis breakpoints, 7% of *S. pneumoniae* isolate were resistant to penicillin in 2014[100]. Other antibiotics, namely Cotrimoxazole, Erythromycin and Chloramphenicol showed 17.2, 4.3 and 4% resistance respectively. For *H. influenzae type B*, the resistance for ampicillin, chloramphenicol and cotrimoxazole were 12%, 13.4% and 42.9% respectively. All the ampicillin isolates were β lactamase positive. But for CSF Hib isolates, the resistance for the mentioned antibiotics were 25%, 0% and 60% respectively.

In 1984 to 1986, a multicenter study in Finland was done on patients 3 months to 15 years old with bacterial meningitis. They were randomized to treatment groups of 4 different intravenous antimicrobial therapy, namely chloramphenicol (53 cases), ampicillin (46 cases), cefotaxime (51 cases) and ceftriaxone (50 cases), for 7 days. Results showed that in patients with *Hib* meningitis, ceftriaxone was found to significantly hasten CSF sterilization compared to the other antibiotics ($p<0.01$). In terms of adverse effect, mild to moderate cases of diarrhea were observed in all groups but was significantly more common in patients treated with ceftriaxone (19 out of 50 patients; $p<0.01$). However, in terms of mortality, there was no significant difference found among treatment groups[101].

A systematic review was done to determine the difference between conventional antibiotic treatment [ampicillin plus chloramphenicol (majority), ampicillin plus chloramphenicol plus gentamicin, benzylpenicillin plus chloramphenicol, ampicillin alone, benzylpenicillin alone, and oily injection of chloramphenicol] and third generation cephalosporins [ceftriaxone (majority), cefotaxime alone and ceftazidime alone] in terms of efficacy and safety in treating patients with community acquired acute bacterial meningitis[102]. Nineteen studies were reviewed and results showed that there was no statistically significant difference between conventional antibiotics and 3rd generation cephalosporin in terms of risk for treatment failure (defined as presence of either death or deafness) (risk difference of -1%; 95% CI -4% to 2%). The only statistically significant result was the higher culture positivity of CSF after 10 to 48 hours (risk difference of -6%; 95% CI -11% to 0%) in the conventional antibiotics group and increased occurrence of diarrhea in the cephalosporin group (risk difference of 8%; 95% CI 3% to 13%).

In a local study, the combination of ampicillin and chloramphenicol was compared retrospectively to a third generation cephalosporin as first line drug in treating children with pneumococcal meningitis[103]. There were a total of 34 patients divided into 3 groups: ampicillin/chloramphenicol (15 patients), third generation cephalosporin (5 patients), and those who were initially treated with ampicillin/chloramphenicol then shifted to a third generation cephalosporin (14 patients). Reasons for shifting therapy were mainly due to absence of changes in the CSF parameters and deterioration in clinical condition. In the ampicillin/chloramphenicol group, 12 out of 15 were discharged improved (80%), 4 out of 5 for third generation cephalosporin (80%), and 11 out of 14 (78.6%) recovered in those who had their initial antibiotic shifted from ampicillin/chloramphenicol to a third generation cephalosporin.

In a retrospective cohort study in PCMC, the cure rates of ampicillin, chloramphenicol, a third generation cephalosporin, and the combination of ampicillin and chloramphenicol as initial antibiotic therapy for children diagnosed with *H. influenzae type b* infection (sepsis and meningitis) were compared[104]. Sixty seven percent of the patients treated initially with ampicillin did not improve, for chloramphenicol it was 11%, in third generation cephalosporin it was 38% and for the combination of ampicillin and chloramphenicol, 61%.

Based on the above data, patients on ampicillin had poor responses in spite being sensitive in the time period stated. Patients treated with chloramphenicol and 3rd generation cephalosporins had higher cure rates, thus these are still being recommended at the moment.

10. What is the drug of choice for a specific etiologic agent?

a. *Haemophilus influenzae*

The drug of choice for *Haemophilus influenzae* meningitis is **Ceftriaxone for 7-10 days**. Alternative treatment would be chloramphenicol.
[Level of evidence: Moderate
Strength of Recommendation: Strong

In developed countries, the antibiotic of choice for beta-lactamase negative *H. influenzae* is ampicillin, alternatively, ceftriaxone, cefotaxime, cefepime, chloramphenicol or fluoroquinolone may be used. For beta-lactamase positive *H. influenzae*, drug of choice is a third generation cephalosporin. Cefepime, chloramphenicol, or fluoroquinolone may be used as alternatives[17]. On the other hand, for *Haemophilus influenzae type B* (*Hib*) meningitis, the recommended initial antibiotic treatment is either a ceftriaxone or cefotaxime with alternatives such as the combination of chloramphenicol/ampicillin or chloramphenicol/amoxicillin for 7 to 14 days[22]. In the NICE guidelines of 2010, for children at least 3 months old, ceftriaxone IV for is recommended for *H. influenzae type B* meningitis[23]. Local surveillance data shows that for H. influenzae type B, the resistance for ampicillin, chloramphenicol and cotrimoxazole were 12%, 13.4% and 42.9% respectively. All the ampicillin isolates were β lactamase positive[100]. But for CSF Hib isolates, resistance rates were 25%, 0% and 60% respectively for the previously mentioned antibiotics.

Although there is no difference between cephalosporin and conventional antibiotics in the clinical outcome, ceftriaxone provides an advantage over chloramphenicol because of lower culture positivity after 10-48 hours, lower levels of resistance and twice daily dosing of ceftriaxone compared to the 4 times daily injection of chloramphenicol.

b. *Streptococcus pneumoniae*

The drug of choice for *Streptococcus pneumoniae* meningitis is **penicillin for 10-14 days**. Alternative agents are chloramphenicol and ceftriaxone.
[Level of evidence: Moderate
Strength of Recommendation: Strong]

According to the Practice Guidelines for the Management of Bacterial Meningitis by the Infectious Diseases Society of America, the recommended treatment of meningitis caused by penicillin sensitive-*S. pneumoniae* based on microbial susceptibility is either a penicillin, third generation cephalosporin or a vancomycin plus third generation cephalosporin combination[17]. If the penicillin minimum inhibitory concentration (MIC) is <0.1 ug/mL, penicillin G or ampicillin is recommended.

Based on the ARSP 2014, the penicillin resistance rate for *Streptococcus pneumoniae* isolates was 7% based on meningeal breakpoints[100]. There was no report of resistance to ceftriaxone. Invasive isolates obtained were subjected to susceptibility testing with ceftriaxone and cefotaxime using meningitis and non-meningitis breakpoints at the reference laboratory. Resistance of *S. pneumoniae* to chloramphenicol was 4%. Our local antibiotic sensitivity pattern is very different from other developed countries. In the United States (2013) data shows that pneumococcal bacteria are resistant to one or more antibiotics in 30% of cases[105].This is the reasons for different recommendations for

empiric and definitive therapy for bacterial meningitis in different countries.

c. *Neisseria meningitidis*

Penicillin is the drug of choice for *Neisseria meningitidis* meningitis for 7 days. Alternative agents are ampicillin, ceftriaxone, chloramphenicol, and cefotaxime.
[Level of evidence: Strong
Strength of Recommendation: Strong

According to the NICE guideline for bacterial meningitis and meningococcal septicemia in children (2010), treatment for children with confirmed meningococcal disease or clinically suspected meningococcal disease is intravenous ceftriaxone for 7 days[23]. In the IDSA guideline, N. meningitides isolates with a MIC of <0.1 ug/mL, penicillin G or ampicillin is recommended (alternative: ceftriaxone, cefotaxime, chloramphenicol). If MIC is between 0.1-1.0 ug/mL, ceftriaxone or cefotaxime is advised (alternative: chloramphenicol, fluoroquinolone, meropenem)[17]. The EFNS guideline on the management of community acquired bacterial meningitis (2008) has a similar recommendation: benzyl penicillin or ceftriaxone or cefotaxime (alternative: meropenem or chloramphenicol or moxifloxacin) for 5 to 7 days[22].

A local retrospective, descriptive study was done in Baguio city involving patients with a discharge diagnosis of either meningo-coccemia, meningococcal meningitis or meningococcal disease in a tertiary government hospital from 2004-2006[88]. Out of the 217 patients, 51% was diagnosed with meningococcemia and 46.08% was composed of children 18 years old and below, and this event was considered by the WHO as an outbreak. The pathogen isolated was *Neisseria meningitidis* Serogroup A subtype A1.9. During the outbreak, *N. meningitidis* remained to be sensitive to penicillin, and had good outcomes in their patients. In 2013, local resistance rates did not have any resistance to penicillin, Ceftriaxone or chloramphenicol (personal communication with Dr. Celia Carlos, Head ARSP) The resistance rate for *Neisseria meningitidis* was not included in the 2014 ARSP data.

d. *Escherichia coli*

For *E. coli*, **cefotaxime** is the specific treatment to be given for at least 21 days. Ceftriaxone may be used as an alternative to cefotaxime but it is contraindicated for use in premature babies or in babies with jaundice, hypoalbuminemia or acidosis as it may exacerbate hyperbilirubinemia. Treatment needs to be individualized on the basis of patient's clinical response.
[Level of evidence: Moderate; Strength of Recommendation: Strong]

According to the NICE guidelines, infants less than three months of age with meningitis caused by Gram negative bacilli are recommended to be given intravenous cefotaxime for at least 21 days until antibiotic sensitivity results come out with a more specific drug[23]. For complicated cases such as presence of effusion or abscess, poor response to antimicrobial therapy and concurrent intraventricular hemorrhage in premature infants, extending the duration of treatment as well as consultation with an infectious disease specialist is advised. The EFNS guideline on management of community acquired bacterial meningitis has recommended either ceftriaxone, cefotaxime or meropenem for Gram negative Entero-bacteriaceae in general. There was no specific drug mentioned for *E. coli*[22]. Third generation cephalosporin was also the recommended treatment for *E. coli* meningitis by the Infectious Disease Society of America guideline for the management of bacterial meningitis[17]. Alternatives include aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole and ampicillin.

In 2014, local resistance rates of *E. coli* for antimicrobials are as follows: 81.4% for ampicillin, 24.8% for ampicillin-sulbactam, 32% for cefuroxime, 32.2% for ceftriaxone, 67.7% for cotrimoxazole, 4% for amikacin, 41% for ciprofloxacin and 2% for imipenem and meropenem[9]. Although these isolates are from all ages and from different types of isolates (e.g. blood, urine, CSF, etc).

e. Group B Streptococcus (GBS)

Treatment recommendation for GBS is third generation cephalosporin, **cefotaxime OR ceftriaxone** to be given for at least 14 days. Ceftriaxone may be used but it is contraindicated for use in premature babies or in babies with jaundice, hypoalbuminemia or acidosis as it may exacerbate hyperbilirubinemia. But once the culture sensitivity results are available, antibiotics should be adjusted or shifted according to the susceptibility data. The duration of therapy may need to be individualized on the basis of the patient's clinical response.
[Level of evidence: Low;
Strength of Recommendation: Conditional

A prospective, descriptive, observational, hospital-based study was done in two separate locations (which includes the Philippines) from 2012-2013. Among 11,768 births reported in hospitals in Manila and Bohol, there were 3 cases of early onset GBS infection, two of which were fatalities. There were no cases of late onset GBS disease observed. The incidence rate was 0.3% per 1,000 live births (95% CI: 0.1-0.8)[106].

According to the NICE Guidelines, in infants younger than 3 months old, intravenous cefotaxime is recommended for at least 2 weeks in patients with GBS meningitis[23]. For complicated cases, duration of therapy may be extended and consider consultation with an infectious disease expert. The European Federation of Neurological Societies (EFNS) guideline on management of community acquired bacterial meningitis did not specify any treatment for *GBS*, instead they recommended medication for penicillin-sensitive pneumococcal meningitis including other sensitive *Streptococcal* species which includes benzyl penicillin or ampicillin/amoxicillin or ceftriaxone or cefotaxime[22]. As an alternative, meropenem or vancomycin plus rifampicin or Moxifloxacin can be used.

Currently, there are no local data available for susceptibility patterns against GBS. More studies are recommended with focus on the improvement of the yield of microbial pathogens from CSF samples of patients with acute bacterial meningitis.

11. What is the recommended duration of treatment for acute bacterial meningitis in patients wherein the organism was not isolated?

The recommended duration of empiric therapy for acute bacterial meningitis is **10-14 days**. The duration of therapy may need to be individualized on the basis of the patient's clinical response.
[Level of evidence: Moderate;
Strength of Recommendation: Strong]

The empiric therapy recommended for infants younger than 3 months of age with unconfirmed but clinically suspected meningitis is at least 14 days[107]. Children 3 months of age and older with suspected uncomplicated bacterial meningitis must be treated for at least 10 days. Bear in mind as well the presenting signs and symptoms and the course of the illness and adjust treatment accordingly[23]. This recommendation is also consistent with WHO's recommendation for the empiric treatment of acute bacterial meningitis which is 10-14 days with a third generation cephalosporin (cefotaxime or ceftriaxone)[5]. In addition, 10-14 days long of antimicrobial therapy for

unspecified bacterial meningitis was also mentioned in the European Federation of Neurological Societies guideline[22].

Empiric antimicrobial treatment of 10-14 days will most likely benefit patients. Until more supporting evidence becomes available, empiric therapy is recommended to be given intravenously to achieve optimal concentration of the antimicrobial drug in the CSF.

12. **What are the indications to shift to another antibiotic agent?**

Modification of the antimicrobial regimen should be made after careful assessment of both clinical and microbiological parameters which include but not limited to the following:
1. Absence of or limited improvement despite adequate antibiotic coverage (e.g. persistent fever after 36-48 hours of adequate antibiotics);
2. Clinical deterioration
3. Drug intolerance
4. Resistant isolate based on cultures and clinically compatible with the clinical course.

Level of Evidence: Moderate
Strength of Recommendation: Strong

With appropriate antimicrobial therapy, microbiologic evidence of CSF sterilization occurs within 48 hours of treatment. Currently, there is no hard and fast rule that governs this topic since there are no randomized controlled trials or prospective trials available that serves as evidence to address this issue. The recommendations as stated above are solely based on clinical experience and expert opinion. The decision to shift antibiotics rests on the physician's clinical judgment, as supported by microbiological evidence when available.

13. Is it appropriate to step down to oral therapy?

1. Switching from intravenous to oral antibiotic therapy for bacterial meningitis is generally not recommended due poor penetration of most oral antibiotics into the CSF.
2. Chloramphenicol is the only antibiotic which could be used orally for treating community acquired CNS infections. If necessary, IV chloram-phenicol can be switched to oral form after 3 to 4 days of initial therapy in children ≥ 3 months old and are well nourished.
3. Antibiotic resistance patterns should be considered when chloramphenicol is used due to reports of resistant strains of *H. influenzae*.
4. Drug interactions should be monitored when there is concomitant use of chloramphenicol and phenobarbital or phenytoin.

[Level of evidence: Moderate; Strength of Recommendation: Strong]

There is currently very limited evidence to support the use of oral antibiotics for the treatment of bacterial meningitis. Most of the antibiotics used intravenously have oral equivalents which have poor penetration into the CSF. The studies available on oral antibiotics for meningitis involve chloramphenicol. The oral form of chloramphenicol has good bioavailability and CNS penetration. Based on a pharmacokinetic study on the use of oral and intramuscular chloramphenicol on Filipino children less than 3 months old, chloramphenicol was found to have an unpredictable metabolism[108]. Oral chloramphenicol is should not be given in infants below 3 months old as well as in malnourished children because the drug has an unpredictable absorption and may accumulate to toxic levels. The injectable form is preferred. For bacterial meningitis, the

recommended dose is 100 mg/kg/day in four equally divided doses. In addition, the drug interacts along with other administered drugs such as phenobarbital, phenytoin, rifampin or acetaminophen. Also, chloramphenicol is not effective in the treatment of resistant strains of *Haemophilus* and multidrug-resistant *pneumococci*.

Chloramphenicol is locally available and is relatively cheaper compared to third generation cephalosporins. The test to determine serum levels of chloramphenicol, however, is not readily available. Furthermore, there is a large percentage of Filipino children with concomitant nutritional problems which complicates management.

14. What is the value of using steroids for acute bacterial meningitis?

Dexamethasone has **NO role** in treating **neonatal meningitis**.

In children 2months to 5 years of age wherein *Hib* meningitis is suspected, give dexamethasone 0.15 mg/kg (maximum of 10 mg) every 6 hours for 4 days. Administer dexamethasone **along with or shortly before** the first parenteral dose of antibiotic.

Note: If dexamethasone was not given before or along with the 1st dose of antibiotics despite its indication, try to administer the first dose within 4 hours of starting antibiotics, but do not start dexamethasone >12 hours after starting antibiotics.

[Level of evidence: Moderate; Strength of Recommendation: Strong]

Corticosteroids may be beneficial in CNS infections since they reduce the inflammation that worsen damage in the nervous system, as shown in experimental animal studies[108]. With corticosteroid treatment in animal studies, there was an observed reduction in the inflammatory response in the CSF, reduction of edema in the brain and improvement in outcomes[109,110].

In acute bacterial meningitis, dexamethasone was found to decrease hearing loss and other neurologic sequelae in high income countries[110]. A systematic review of 16 randomized controlled trials of community acquired bacterial meningitis showed that children treated with the corticosteroid had significantly fewer occurrences of hearing loss compared to the placebo group (any hearing loss: risk ratio 0.73, 95% CI 0.61-0.86; severe: risk ratio 0.67, 95% CI 0.49-0.91). In particular, for *H. influenzae* meningitis, corticosteroid therapy reduced the incidence of severe hearing loss in children (risk ratio 0.34, 95% CI 0.20 to 0.59), however, no significant effect was seen in children with non-*Haemophilus* meningitis.

This result was in contrast to the findings from a prospective, randomized, double blind study on 383 children aged 2 months to 16 years old with bacterial meningitis[111]. The study determined whether IV dexamethasone or oral glycerol or the combination of IV dexamethasone and oral glycerol had any effect on sequelae of bacterial meningitis such as hearing impairment. Bacteria isolated from the CSF of patients were *Hib* (146), *S. pneumoniae* (70), *N. meningitidis* (54), other bacteria (7), and the rest had undisclosed etiology. Results showed that neither of the three treatment groups prevented hearing impairment in children with bacterial meningitis at hearing threshold levels of 40, 60, and 80 dB.

Neurologic sequelae such as focal neurologic deficits, epilepsy (after onset of bacterial meningitis), severe ataxia, significant impairment in memory and concentration were also assessed in the systematic review of Brouwer *et al*., (2013) and divided into short and long term neurologic sequelae (short term: between date of hospital discharge and six weeks after discharge; long term: between six weeks to 1 year after hospital discharge)[112]. Results showed that corticosteroid treatment offers protection from short term neurologic

sequelae in children from high income countries (risk ratio 0.67, 95% CI 0.46 to 0.97) but no long term decrease in neurological sequelae was observed (risk ratio 0.90, 95% CI 0.74 to 1.10).

As for mortality, giving corticosteroids in patients with *S. pneumoniae* meningitis significantly reduced mortality (risk ratio 0.84, 95% CI 0.72 to 0.98), the case is different with *N. meningitidis* meningitis since no significant reduction in mortality was observed (risk ratio 0.71, 95% CI 0.35 to 1.46). In addition, corticosteroids had no effect on mortality for patients with *H. influenzae* meningitis[112]. Corticosteroids had no significant effect for children in low income countries.

In the systematic review by Furyk *et al*., (2011) on neonatal meningitis in the developing world, steroids were mentioned as adjunctive therapy[9]. There were two non-randomized studies which suggested some benefit by steroid therapy. However, there was one note of a small randomized controlled trial in Jordan with a small sample size of 52 which showed no significant difference in morbidity or mortality with steroid treatment[113]. The use of steroids in neonatal meningitis was discouraged.

The European Federation of Neurological Societies (2008) recommended dexamethasone to be given with the first dose of empiric antimicrobial drug for patients whom *pneumococcal* or *Hib* meningitis is suspected[22]. In adult patients with pneumococcal meningitis who are either previously well or not immunocompromised, dexamethasone is advised to be given together or shortly prior to the first parenteral dose of the antibiotic. The recommended dosage is 10 mg every 6 hours for 4 days. For children with *Hib* and pneumococcal meningitis, the dosage is 0.15 mg/kg every 6 hours for 4 days. The authors also discouraged giving dexamethasone routinely to patients who have non-pneumococcal or non-Hib meningitis.

According to the NICE clinical guideline for bacterial meningitis and meningococcal septicemia in children[23], dexamethasone (0.15 mg/kg, maximum dose of 10 mg, every 6 hours for 4 days) should be given as soon as possible to patients with either suspected or confirmed bacterial meningitis if the lumbar puncture shows any of the following laboratory results: purulent CSF, CSF WBC count >1000/microliter, increased CSF WBC count with CSF protein > 1 g/liter, and presence of bacteria in Gram stain. However, children below 3 months of age with suspected or confirmed bacterial meningitis should not be given corticosteroids. If there is an indication to give dexamethasone but it was not given together with or prior to the first dose of antibiotics, give the first dose of dexamethasone within 4 hours of starting the antibiotic. However, defer administration of dexamethasone if antibiotics were given for more than 12 hours already.

The NICE center for clinical practice-surveillance program made a 4-year surveillance review of the 2010 guideline for bacterial meningitis. After the review, there was still insufficient evidence of benefit of corticosteroid therapy in neonates. Therefore, the recommendation which prohibits the administration of corticosteroids in children below 3 months of age is sustained[114]. Further research is necessary regarding the routine use of corticosteroid as an adjuvant therapy.

15. What are the supportive management for acute bacterial meningitis?

Give **full volume maintenance fluids** and do not restrict unless there is evidence of increased intracranial pressure OR increased antidiuretic hormone secretion.
[Level of evidence: Strong
Strength of Recommendation: Strong]

Fluid therapy for patients with acute bacterial meningitis should be carefully managed since excessive fluids or the lack thereof could lead to severe outcomes. A meta-analysis was done comparing the different volumes of initial fluid therapy (up to 72 hours since clinical onset of disease) in patients with acute bacterial meningitis and its effect on neurologic outcomes (short term: first 4 weeks of illness; long term: persistence beyond 4 weeks of illness) and mortality[115]. Three trials were reviewed which included 415 children. The 3 studies implemented the fluid management as follows: 1st trial: milk-based fluids (60% of required amount) vs. maintenance fluids (defined in the study as 100 ml/kg/day for the first 10 kg of body weight, 50 ml/kg for the second 10 kg, and 20 ml/kg for over 20 kg); 2nd trial: two thirds of the maintenance fluids vs. full maintenance fluids; 3rd trial: restricted fluids (65% of calculated maintenance fluid requirement) vs. the maintenance fluid requirement. Results showed that there were no significant difference with regard to mortality between the fluid restricted groups and the maintenance fluid group (risk ratio 0.82, 95% CI 0.53-1.27). Short term neurologic outcomes such as hemiparesis/hemiplegia (risk ratio 0.97, 95% CI 0.52-1.81), visual impairment (risk ratio 0.77, 95% CI 0.44-1.35) and response to sound (risk ratio 0.60, 95% CI 0.25 to 1.41) were not clinically significant between fluid restriction and maintenance fluids groups. On the other hand, spasticity (risk ratio 0.50, 95% CI 0.27-0.93), and seizures at 72 hours (risk ratio 0.59, 95% CI 0.42-0.83) and at 14 days (risk ratio 0.19, 95% CI 0.04-0.88) were all statistically significant. Children who were given maintenance fluids had significant reductions in the rate of occurrence of spasticity and seizures. There was also a notable significant reduction as well in the rate of long term neurologic sequelae at the three-month follow up (risk ratio 0.42, 95% CI 0.20-0.89) in the maintenance groups.

Fluid administration is the first line management in patients with acute bacterial meningitis. Give full volume maintenance fluids unless patient presents with increased intracranial pressure or increased levels of ADH.

16. Is there a need for follow up antibiotics to eradicate the carrier state of a patient?

There is a need to administer a follow up antibiotic to eradicate the carrier state in the index case to reduce secondary cases among household members and daycare contacts. For *meningococcal* meningitis, if the patient was not treated with ceftriaxone, give prophylaxis just prior to hospital discharge.
For invasive *Hib* disease, children younger than 10 years old who acquire the infection must receive rifampicin chemoprophylaxis to eliminate carriage.
[Level of evidence: Moderate
Strength of Recommendation: Strong]

The carrier state is more common in children than adults. Since children always have caretakers when they are stricken with illness, risk of disease transmission increases as well. Compared to the general population, household members and daycare contacts of index patients have a higher risk for developing invasive *Hib* disease.

The carriage rate of *H. influenzae* is about <5% and may be higher in young children and those in hospitals and day care centers[116,117]. Based on randomized controlled studies, a

four-day course of rifampicin (20 mg/kg/day) eliminated 92-97% of *Hib* pharyngeal carriage in contacts[118,119,120,121,122,123,124,125,126]. But for children less than 3 months of age, it was advised that the dose of rifampicin should be halved at 10 mg/kg/day for 4 days to eradicate *Hib* carriage[127].

Hib vaccination has just been included in the Expanded Program of Immunization (EPI) 2013 in the Philippines. The pathogen, *H. influenzae type B* is still a significant invasive organism that causes severe illnesses, therefore, prophylaxis and vaccination could help lower infection rates secondary to this pathogen.

As for *N. meningitidis*, nasopharyngeal carriage in asymptomatic, healthy individuals is <35% during a single year and rise especially among close contacts of index cases[128]; however, at any one time, only a handful of individuals will be carrying the pathogen likely to cause an epidemic[129]. *N. meningitidis* is transmitted via respiratory droplets through close contacts especially in crowded areas such as dormitories. The highest nasopharyngeal carriage rates were noted among adolescents and young adults[130,131], thus adolescents may be the prime source for disease transmission to other age groups[132].

Nasopharyngeal carriage can be eliminated via prophylaxis with antimicrobial drugs: rifampicin for *Hib* and rifampicin, ceftriaxone or ciprofloxacin for *N. meningitidis* (discussed further below).

17. What are the indications of prophylaxis among close contacts? What is the drug of choice?

Prophylaxis is an important measure to help prevent spread of infection. In the case of meningitis, the risk for a secondary case peaks immediately after contact with the index patient and it usually occurs within the first week after the index case. Prophylaxis is mainly given to individuals living in the same quarters as the index case or those with history of body fluid exchange with an infected patient (i.e. kissing). The administration of prophylaxis aims to eradicate nasopharyngeal carriage in household contacts, prevent secondary cases from occurring and hopefully to treat individuals currently incubating the disease[133].

a. *Haemophilus influenzae*

Rifampicin prophylaxis is recommended for all household contacts or child care contacts in cases of *H. influenzae type B* meningitis, especially if there is an infant of <2 years old or an immunocompromised person in the house.

[Level of evidence: Moderate; Strength of Recommendation: Strong]

Chemoprophylaxis is essential since there are numerous children who lack vaccinations especially those who live in far-fetched rural areas. The dosage used for chemoprophylaxis with rifampicin is 20 mg/kg orally once a day for 4 days, maximum dose of 600 mg/day[127]. Children below 2 years old are the most susceptible for secondary *Hib* disease, and the risk decreases after 4 years of age[127]. For children in the household below 5 years old with exposure to an infected person, within a month after the exposure, the secondary attack rate would be 500-800 times more than the endemic attack rate for invasive *H. influenzae*[134,135].

b. Neisseria meningitidis

Chemoprophylaxis for *N. meningitidis* for high risk groups is a necessity.

Prophylactic regimens are as follows:
Rifampicin:
<1 month old: 5mg/kg orally every 12 hours x 2 days
≥1 month old: 10mg/kg (max 600 mg) orally every 12 hours x 2 days;
Ceftriaxone:
<15 years old: 125 mg, IM single dose
≥15 years old: 250mg, IM single dose;
Ciprofloxacin:
≥18 years old: 20mg/kg (max 500 mg) orally, single dose
[Level of evidence: High; Strength of Recommendation: Strong]

High risk groups include individuals who are close contacts of the index case, as described below[136]:

1. Household contacts especially children below 2 years old;
2. Child care contacts within 7 days prior to onset of illness of index patient
3. People with direct exposure to oral secretions of the index patient (kissing, sharing personal items such as toothbrush and utensils) within 7 days prior to onset of illness of index patient;
4. Individuals who performed mouth to mouth resuscitation to an infected patient or unprotected contact during an endotracheal intubation at any time prior to the onset of illness of index patient;
5. Persons who often shared the same living quarters as the patient within 7 days prior to the onset of illness of index patient;
6. Passengers in transportation vehicles (buses, trains, airplane) who were seated next to the index case for at least 8 hours.

Ceftriaxone, rifampicin and ciprofloxacin are the most effective prophylactic drugs for *N. meningitidis*[137]. Rifampicin is the drug of choice for most children but must not be given to pregnant women. Ceftriaxone and ciprofloxacin are also effective in eradicating nasopharyngeal carriage of *N. meningitidis*. Furthermore, both allow ease in the administration of prophylaxis since they only require a single dose. Ciprofloxacin is also avoided in pregnancy and in persons younger than 18 years old. Ceftriaxone on the other hand is safe to use during pregnancy.

In 2007, a Cochrane systematic review on antibiotics for preventing meningococcal infections was performed. Twenty three randomized and two quasi-randomized trials were included in the systematic review. Study population were composed of household contacts, army recruits, students, volunteers and children[137]. Assessment of the trials revealed that ciprofloxacin (relative risk 0.04, 95% CI 0.01-0.12), rifampicin (relative risk 0.17, 95% CI 0.12-0.24), minocycline (relative risk 0.30, 95% CI 0.19-0.45) and ampicillin (relative risk 0.41, 95% CI 0.25-0.66) were effective against *N. meningitidis* (compared to placebo) 1 week after treatment. Between 1-2 weeks after treatment, rifampicin (relative risk 0.20, 95% CI 0.14-0.29) and ciprofloxacin (relative risk 0.03, 95% CI 0.00-0.42) were still effective. Minocycline and penicillin were effective as well but the confidence intervals were quite wide. Ceftriaxone was found to be more effective than rifampicin (stated in one study; relative risk 5-93, 95% CI 1.22-28.68) but rifampicin was still effective even 4 weeks after treatment compared to placebo, although there were resistant isolates obtained as well.

During meningococcal outbreaks, ceftriaxone or ciprofloxacin is recommended instead of rifampicin[137]. If ceftriaxone or ciprofloxacin will be used, the index patient must receive the chemoprophylaxis prior to hospital discharge to eradicate nasopharyngeal carriage of *N. meningitidis*[136].

Various institutions have different protocols for meningococcal prophylaxis, some give it

after a secondary case, while others give it after an index case. A systematic review was done on the effectiveness of antibiotics in preventing meningococcal disease after a case, which evaluated the occurrence of succeeding meningococcal disease cases 1-30 days after onset of disease in the index patient[138]. There were a total of five studies reviewed (4 retrospective cohort studies and one small trial) upon which meta-analysis revealed that chemoprophylaxis offers 89% significant reduction in risk of subsequent meningococcal disease in household contacts of the index patient (risk ratio 0.11, 95% CI 0.02-0.58). The authors recommend the use of chemoprophylactic drugs against meningococcal disease since antimicrobials to be taken are those known to eliminate meningococcal carriage.

18. What is the role of vaccines in the prevention of acute bacterial meningitis?

a. *Haemophilus influenzae type B*

Haemophilus influenzae type B (*Hib*) vaccine is safe and effective against *Hib*-invasive disease including acute bacterial meningitis, pneumonia and bacteremia. Also, nasopharyngeal Hib colonization has declined after introduction of Hib conjugate vaccines.

[Level of evidence: High;
Strength of Recommendation: Strong]

In all countries that have used the Hib conjugate vaccine in their national immunization program have reported reduction in reported Hib diseases. Several randomized controlled trials and observational studies on the conjugated Hib vaccine have shown its efficacy as well as effectiveness in preventing Hib meningitis, pneumonia, bacteremia and other invasive diseases[139, 140] After the introduction of Hib vaccination in national programs there has been also substantial decreases in nasopharyngeal Hib colonization and even greater reduction in diseases which may have resulted from her protection[141].

b. Pneumococcal conjugate vaccine

Pneumococcal conjugate vaccine is safe and effective against *invasive pneumococcal disease* including acute bacterial meningitis, pneumonia and bacteremia. Also, nasopharyngeal colonization has declined after introduction of Pneumococcal conjugate vaccines.

[Level of evidence: High;
Strength of Recommendation: Strong]

Many countries have adopted the use of the pneumococcal conjugate vaccine in routine immunization of infants. Surveillance of disease have shown that this intervention has dramatically reduced the incidence of invasive pneumococcal disease caused by vaccine serotypes, which includes acute bacterial meningitis and sepsis[142]. Herd immunity has been evident as manifested in reductions in invasive pneumococcal disease even in age groups not targeted by immunization programs. Decrease nasopharyngeal carriage is seen as the cause of herd immunity.

c. Meningococcal vaccine

Vaccines against N. meningitides have a limited role in outbreak situations
For control of meningococcal outbreaks caused by vaccine preventable serogroups (A,C,Y, W 135) MPSV4 or MCV4 vaccines may be used.
The reactive vaccination strategy relies on early detection of outbreaks followed by mass vaccination with the vaccine adapted to the circulating serogroup.
Further research is required on the use of vaccines to control transmission of the disease during outbreaks.
Strength of evidence: Moderate
Strength of recommendation: Conditional/Weak.

[Level of evidence: Moderate;
Strength of Recommendation: Conditional/Weak]

The two meningococcal vaccines used are the Meningococcal polysaccharide vaccine (MPSV4) and the Meningococcal conjugate vaccine (MCV4). The MPSV4 contains purified meningococcal capsular polysaccharides, given as a single dose of 0.5 mL subcutaneously[143]. Antibody concentrations offering immune protection are attained within 7-10 days after immunization[144]. On the other hand, the MCV4 contains capsular polysaccharides from serogroups A, C, Y, and W-135 conjugated to a diphtheria toxoid. MCV4 is given also as a single dose of 0.5 mL but intramuscularly, achieving protective antibody concentration within 8 days after immunization[143].

Recommendations for routine immunization with meningococcal vaccines are usually prescribed for specific groups populations such as adolescents, since 75% of meningococcal disease caused by serogroups (A, C, Y, or W-135) occur in children age 11-18 years old[145]. As such, outbreaks might then occur in age groups not routinely vaccinated. Mass vaccination might then be of help in protecting population at risk during outbreaks[132]. An outbreak is defined as the *"occurrence of at least three confirmed or probable primary cases of meningococcal disease caused by the same serogroup in ≤3 months, with a resulting primary attack rate of ≥10 cases per 100,000 population"*[132]. In instances of outbreaks caused by *N. meningitidis* serogroups A, C, Y or W-135, MPSV4 or MCV4 are recommended for people of at least 11 years of age (MCV4 for ≥11 years old, MPSV4 for 2-10 years old[143]. Take note, however, that vaccines have no role in *N. meningitidis* serogroup B outbreaks since the available vaccines do not cover this serogroup. This highlights the importance of preventive measures since in children less than a year old, *N. meningitidis* serogroup B causes more than 50% of meningococcal disease[146].

During suspected outbreaks, the decision to vaccinate the population at risk must be considered when the disease attack rate is more than 10 cases per 100,000 people based on the following factors: 1) the comprehensiveness of reported cases and the number of suspected meningococcal cases without bacteriologic confirmation or serogroup data; 2) the appearance of additional meningococcal cases after the suspected outbreak was recognized; and 3) logistics and financial resources[132].

19. What are the infection control measures necessary to prevent transmission?

The current Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines should be implemented to prevent transmission of pathogens causing bacterial meningitis.

[Level of evidence: Moderate; Strength of Recommendation: Strong]

The general standard precautions include the following[146]:

- Hand hygiene with proper hand washing using soap and water before and after handling the patient;
- Wear personal protective equipment especially for procedures that may involve contact with blood or body fluids;
- Respiratory etiquette: symptomatic patients are advised to wear masks to prevent spread of infected respiratory droplets; as well as to maintain separation distance of at least 3 feet from nearby people in waiting areas;
- Dispose of wastes accordingly in their proper bins;
- In pediatrics patients who bring toys to hospitals, avoid furry ones, only bring those that are easy to clean;
- Aseptic technique in all procedures to be done;
- Proper placement: patients who pose risk of disease transmission to others (e.g. those who require droplet precaution) should be

placed in a single-patient room; if there are insufficient rooms available, patients with the same infection and isolated pathogen may be roomed in together; in patients sharing rooms, separate them using curtains and make sure that they are physically spaced more than 3 feet apart from each other;

- Limit the transport of patients outside the room for only medically necessary procedures;

The preventive maneuvers must be performed by all involved persons in the care of the patient including patient watchers and visitors to help prevent disease transmission. For those with droplet precautions, placing the patient in a single-patient room would suffice, isolation rooms are not necessary.

This guideline shall be updated as necessary, but not later than 5 years from the time of publication.

Appendix A

Table 7. Antibiotic Dosages for Neonatal Bacterial Meningitis, Adjusted by Weight and Age

Antibiotic	**Route**	**Dosage**			
		BW < 2000 g, Age 0-7 Days	**BW >2000 g, Age 0-7 Days**	**BW < 2000 g, Age >7 Days**	**BW >2000 g, Age >7 Days**
Penicillins					
Ampicillin	IV, IM	50 mg/kg q12h	50 mg/kg q8h	50 mg/kg q8h	50 mg/kg q6h
Penicillin G	IV	50,000 U/kg q12h	50,000 U/kg q8h	50,000 U/kg q8h	50,000 U/kg q6h
Oxacillin	IV, IM	50 mg/kg q12h	50 mg/kg q8h	50 mg/kg q8h	50 mg/kg q6h
Ticarcillin	IV, IM	75 mg/kg q12h	75 mg/kg q8h	75 mg/kg q8h	75 mg/kg q6h
Cephalosporins					
Cefotaxime	IV, IM	50 m mg/kg g q12h	50 mg/kg q8h	50 mg/kg q8h	50 mg/kg q6h
Ceftriaxone	IV, IM	50 mg/kg q d	50 mg/kg q d	50 mg/kg q d	75 mg/kg q d
Ceftazidime	IV, IM	50 mg/kg q12h	50 mg/kg q8h	50 mg/kg q8h	50 mg/kg q8h

Table 8. Dosages and Dosing Intervals for Intravenous Antimicrobials in Infants and Children With Bacterial Meningitis

Antibiotic	**IV Dosage**	**Maximum Daily Dose**	**Dosing Interval**
Ampicillin	400 mg/kg/day	6-12 g	q6h
Vancomycin	60 mg/kg/day	2-4 g	q6h
Penicillin G	400,000 U/kg/day	24 million U	q6h
Cefotaxime	200-300 mg/kg/day	8-10 g	q6h
Ceftriaxone	100 mg/kg/day	4 g	q12h
Ceftazidime	150 mg/kg/day	6 g	q8h
Cefepime*	150 mg/kg/day	2-4 g	q8h
Meropenem	120 mg/kg/day	4-6 g	q8h
*Experience with this agent in pediatric patients is minimal; it is not licensed for treatment of meningitis.			

Table 9. Chemoprophylaxis for Bacterial Meningitis Caused by *Haemophilus influenzae* or *Neisseria meningitidis*

Causative Organism	Drug Name	Age of Contact	Dosage
Haemophilus influenzae	Rifampin	Adults	>600 mg PO q d for 4 days
		≥1 month	20 mg/kg PO q d for 4 days; not to exceed 600 mg/dose
		< 1 month	>10 mg/kg PO q d for 4 days
Neisseria meningitidis	Rifampin	Adults	600 mg PO q12h for 2 days
		≥1 month	10 mg/kg PO q12h for 2 days; not to exceed 600 mg/dose
		<1 month	>5 mg/kg PO q12h for 2 days
	Ceftriaxone	≥15 years	250 mg IM once
		<15 years	>125 mg IM once
	Ciprofloxacin	>18 years	>500 mg PO once

Appendix B. Definitions of Terms for Prevention of Infection

Definition of terms:

Index case: the index case is the individual who presents with the disease in absence of known exposure to another patient with the disease[79].

Secondary case: presentation of the disease in close contacts of the index case patient which occurs 24 hours or more after the onset of illness in the index case[79].

Household contacts*: individuals inside the household who had a prolonged close contact with the index case within 7 days prior to the index case' development of clinical symptoms of the disease. For instance, people living or sleeping within the same house, people involved in romantic relationships (boyfriend/girlfriend), and sharing a dormitory or flat with the index case[49].

Child care contacts*: any individual sharing a space or in constant exposure to the index case wherein other children are also present and cared for within 7 days prior to the index case' development of clinical symptoms of the disease[29].

Contacts within the hospital setting*: includes individuals with direct exposure to the index case' respiratory secretions (such as healthcare workers in direct care of the index case and close contacts of the index case such as those individuals who share a hospital room with the index case) prior to the index case's completion of 48 hours of clearance antibiotics[29].

*As defined for Hib cases

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