ORIGINAL ARTICLE

PREVALENCE OF MENINGITIS IN YOUNG INFANTS 29-90 DAYS WITH SEPSIS IN ADDIS ABABA, ETHIOPIA

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ABSTRACT

Introduction: *Bacterial meningitis is among the most serious infections in infants with high mortality and morbidity. Management of young infants with serious bacterial infections and the need of lumbar puncture (LP) is controversial unlike neonates and older children.*

Objective: *to determine magnitude of meningitis and associated factors in young Infants admitted with suspected sepsis in Addis Ababa.*

Methods*: Cross sectional study was done in young infants admitted to a tertiary center from 2013-2019 for suspected sepsis. Data was abstracted from patient files using structured questionnaire and analyzed by SPSS-20. Logistic regression was used to determine associated factors and independent predictors of meningitis.*

Results*: A total of 230 infants were included with a male to female ratio of 1.2. Most (61%) presented with fever, respiratory symptoms and feeding intolerance. While 3/4th of them have LP performed the prevalence of meningitis was 17 %. Microbiologic tests were rarely used for etiologic diagnosis. Less than 5 % had confirmed bacterial meningitis, mostly gram negative bacteria.*

Conclusion*: Meningitis is common coexisting condition in infants with Systemic Inflammatory Response Syndrome (SIRS) despite low microbiologic confirmation. Complete septic work up with emphasis on microbiology should be the standard of care for all young infants with SIRS.*

Key words: *Young infants, Meningitis, SIRS, Lumbar Puncture.*

INTRODUCTION

Bacterial meningitis is one of the most serious infections in infants associated with high mortality and morbidity especially in neonates and infants. The burden of bacterial meningitis in developing countries is high ranging from 1.1 – 1.9 cases per 1000 live births (1, 2).

Management of young febrile infants is challenging because of high rate of serious bacterial infections (SBI) and inability to discriminate them from simple viral infections. Early diagnosis of meningitis is essential to reduce mortality and to improve outcome. Clinical signs of meningitis are often subtle and overlap with sepsis and current tests do not distinguish sepsis from meningitis (3). As a result LP is recommended for all infants and young children with clinical signs of meningitis like nuchal rigidity, petechiae and abnormal neuro -logic findings (4). Though LP is not routinely needed for all febrile young infants, there is no con-sensus on indications for LP. There is significant variation in the evaluation including LP in young infants with fever worldwide. While blood and urine tests are ordered in the majority of centers, LP and antibiotic treatment differed across centers. Generally LP may be omitted for well-appearing, previously healthy young infants with no focal signs

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of infection, a WBC count between 5,000 and 15,000/mm3, and no pyuria or bacteriuria on urinalysis (5-9).

Prevalence of meningitis in young infants also vary in different studies and settings (10 -15). While the absence of LP may underdiagnose non bacterial meningitis, management of sepsis was carried out without LP in nearly 75% of infants between 29 and 60 days and 90% of infants over 60 days (14).

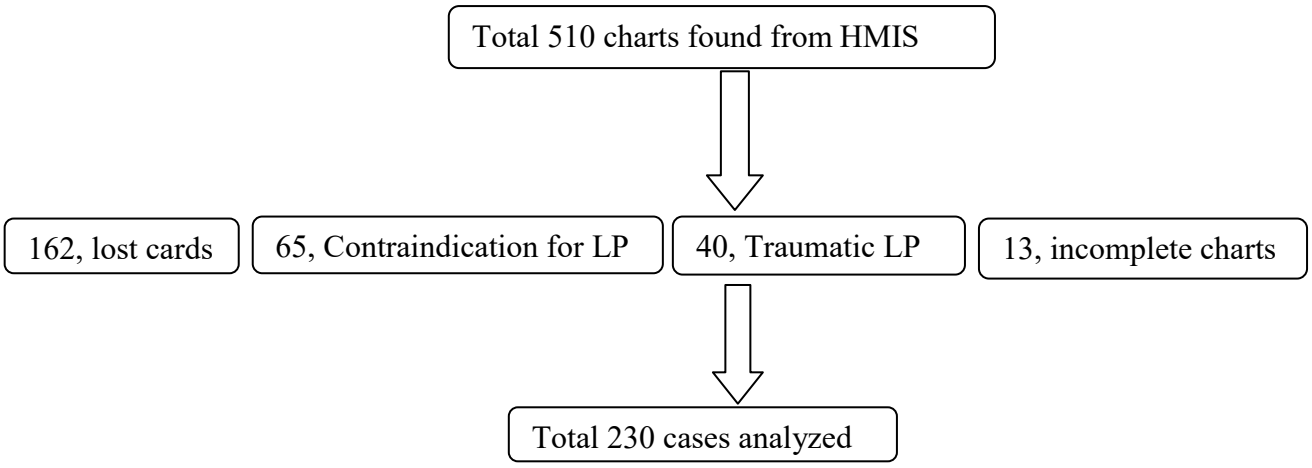
Though data are limited in Africa, a recent Kenyan study found typical clinical signs of meningitis in young infants only in two third of cases and recommended LP in all young infants (16). Located on the eastern part of meningitis belt, Ethiopia is one of the countries most affected with bacterial meningitis (2). Most previous studies in Ethiopia however focused on neonates with late onset infections and to the best knowledge of the authors, no studies assessed evaluation of young infants with possible serious bacterial infections in Ethiopia. This study is thus designed to assess the magnitude of meningitis, associated factors, etiologies and practice in young infants 29-90 days of age presenting with possible sepsis.

MATERIALS AND METHODS

A cross sectional retrospective study was conducted using a 5 years data in St. Paul's hospital millennium medical college department of pediatrics and child health in young infants admitted from 2013-2019.

Study subjects, procedure and analysis

All infants from 29-90 days of age admitted to ward or Pediatric ICU during the study period with clinical diagnosis and treated as sepsis were included. Infants with LP contraindication, incomplete charts and those with failed LP were excluded from the study.



Key: LP – Lumbar puncture, HMIS – Health management information system

Figure 1: Flowchart showing Schematic presentation of sampling procedure

Data was collected using pretested structured questionnaire. The questionnaire includes patient demographic, clinical and laboratory characteristics of patients. Data collectors were two trained General practitioners. Pre-test of questionnaire was done on 10 cases and used to correct and modify the questionnaire.

Data was analyzed using SPSS 20. Descriptive analysis was done by running simple frequencies and proportions. Chi-square test was used to assess statistical significance among the proportions and logistic regression with odds ratio with 95% confidence limits was used to see the strength of association between the presence of meningitis and associated factors. A *P value* <0.05 was considered statistically significant.

Operational definitions

- **Young infants**: infants from 29--90 days of age.
- **Systemic Inflammatory Response Syndrome (SIRS)**: It requires that two or more of the following abnormalities be present, one of which must be either temperature instability or WBC count abnormality:(22)
  - ♦ Temperature > 38.5ºC or <36ºC
  - ♦ Heart rate >2 SD above normal for age (in the absence of external stimulus/ drug)
  - ♦ Respiratory rate >2 SD above normal for age or mechanical ventilation
  - ♦ Leukocyte count elevated or depressed for age(not secondary to other causes)

  Sepsis
  - ♦ SIRS in the presence of or as a result of suspected or proven infection (22).
- Meningitis is diagnosed in a young infants whose CSF findings satisfied all the following criteria:**(**21**)**

1. CSF white cell count >10/mm^3/ < 75% lymphocytes
   1. CSF glucose less than the plasma glucose by ≥50% or < 40 mg/dl.
   2. CSF protein > 75mg/dl.
2. Isolation of organisms on CSF culture or CSF Gram stain as a likely etiology
3. WHO clinical signs of meningitis + blood culture growth or/and imaging suggestive of meningitis

- Based on 2003 WHO Case definitions of bacterial meningitis are**: (** 24**)**
  - Suspected bacterial meningitis: WHO clinical signs of meningitis (sudden onset of fever with one or more typical clinical features (seizures other than febrile seizures, altered consciousness, irritability, other meningeal signs, petechial or purpuric rash) (2, 14).
  - Probable bacterial meningitis: Turbid CSF or cell count > 100 cells/mm^3 ± high CRP and/or elevated WBC count > 15,500 /mm^3
  - Confirmed bacterial meningitis: Clinical signs of meningitis with detectable bacteria on CSF culture and/or gram stain

Ethical considerations

Ethical clearance was given from St. Paul's Hospital Millennium Medical Colleges Institutional Review Board (IRB) before the study.

Results

A total of 510 young infants were treated with a diagnosis of sepsis from 2013 -2019. Among them 230 infants were included in our study (Figure 1). About 123(52%) were male and most (186(80.9%)) were 29-60 days old. Term infants account for 146 (63.5%) of study subjects (Table 1).

Table 1: Mother and infant characteristics among young infants admitted with suspected sepsis.

Characteristics	Category	Frequency	Percentage (%)
Maternal characteristics			
Maternal fever	Yes	15	6.5
	No	215	93.5
ANC follow up	Yes	208	90.4
	No	21	9.1
Duration of labor	Normal(< 24 hrs)	220	95.7
	Prolonged(≥ 24hrs)	10	4.3
Rupture of membrane	< 18 hrs	218	94.8
	≥ 18 hrs	12	5.2
Infant characteristics			
Sex	Male	123	53.5
	Female	107	46.5
Post-natal age	29-60 days	186	80.9
	61-90 days	44	19.1
Birth weight	< 1500 gram	10	4.3
	1500-2500 gram	36	15.7
	>2500 gram	112	48.7
	Unknown	72	31.3
Gestational age	<34 weeks	17	7.4
	34-37 weeks	63	27.4
	>37 weeks	146	63.5
	Unknown	4	1.7
Place of delivery	At home	20	8.7
	At health facility	210	91.3

The commonest presentations were combination of feeding intolerance, temperature instability and respiratory manifestations (140 (61%)). Respiratory symptoms alone accounted for 38(16.5%). About 136(59 %) infants had preceding flu like symptoms. Meningitis specific symptoms including bulged fontanel and seizure were present in 39(17%) infants. Thirty-nine (17%) infants didn't have SIRS despite a diagnosis of sepsis and have LP performed despite the lack of SIRS or neurologic symptoms. All infants had White blood count determined and leukocytosis (WBC > 15,000/ mm3) in 72(31%)) while C Reactive Protein (CRP) was done in 118(51.3) infants and elevated in 54 (24 %). Leukocytosis, elevated CRP and neurologic manifestations (seizure and bulged fontanel) were significantly associated with presence of meningitis on bivariate analysis but only the presence of seizure is independent predictor of meningitis on multivariate analysis (Table 2).

Other demographic, clinical and laboratory parameters were not found to be associated with meningitis. There was no significant association between meningitis and clinical outcome of the study subjects.

Table 2. Logistic regression of factors associated with meningitis in 230 young infants with sepsis in AA

Variable	Category	Meningitis		COR (95% CI)	P-value	AOR (95% CI)	P-value
		Yes	No				
Sex	Male	24	99	1.49 (0.74, 3.01)	0.27*	1.55(0.72,3.33)	0.26
	Female	15	92	1		1	
GA	<34	2	15	0.64(0.14,2.95)	0.563		
	34-37	11	52	1.01(0.46,2.19)	0.982		
	>37	26	124	1		1	
Maternal fever	Yes	3	12	1.24(0.33,4.63)	0.75		
	No	36	179	1		1	
ANC follow up	Yes	36	172	1.26(0.35,4.49)	0.73		
	No	3	18	1		1	
Labor duration	Normal	36	184	0.46(0.11,1.85)	0.27	1.51(0.11,2.48)	0.41
	Prolonged	3	7	1		1	
ROM	< 18 hrs	37	181	1.02(0.22,4.86)	0.98		
		2	10	1		1	
Foul smelling liquor	Yes	0	6	0.00	0.99		
	No	39	185	1		1	
Place of delivery	Home	6	14	2.29(0.84,6.41)	0.11*	1.58(0.53,4.71)	0.41
	Health Facility	33	177	1		1	
Neonatal admission	Yes	7	43	0.75(0.31,1.83)	0.53		
	No	32	148	1		1	
CBC	Yes	19	53	2.47(1.22,4.99)	0.01*	1.89(0.71,5.09)	0.203
	No	20	138	1		1	
CRP	Elevated	17	37	2.52(1.04,6.12)	0.040	2.54(0.93,6.99)	0.07
	Negative	10	55	1		1	
Neurologic symptoms	No	25	102	1		1	
	Seizure*			5.28(2.17,12.82)	<0.001	7.52 (2.05,27.60)	0.002
	Neck stiffness	1	0				
	Fontanel bulge					2.94 (0.23,37.88)	0.408

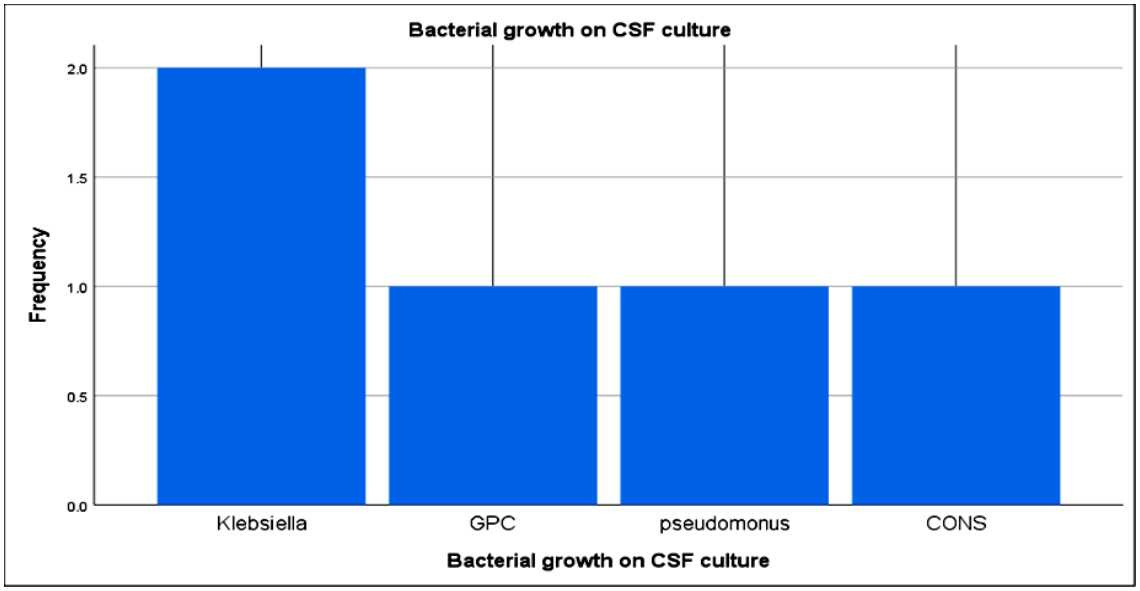
*Key: COR, crude odds ratio, AOR adjusted odds ratio, C.I, Confidence interval, AA Addis Ababa, CBC Complete blood count, CRP C-reactive protein. ROM Rupture of membrane, GA gestational age. * Observed or reported*

LP was performed in 172 (75%) infants. Those who had no LP were because of prior long duration antibiotic, alternate diagnosis with no strong suspicion for meningitis and few of them for undocumented reasons. A quarter of young infants with LP had history of prior use of antibiotics.

Meningitis was present in 39(17 %) infants with suspected sepsis. About 24 (75%) of meningitis occur in infants 29-60 days of age and all but 5 infants with meningitis had SIRS. CSF glucose and protein were done inconsistently with the majority lacking both. The mean CSF cell count was 519 with standard deviation (SD) of 1435. Among those with meningitis, 18 (46 %) had probable bacterial meningitis while only 7 (18 %) had confirmed bacterial meningitis. The remaining 36% didn't fulfill WHO bacterial meningitis definition and are most likely viral infections (24).

Only 3(1.3%) infants had CSF gram stained bacteria (2 gram positive and 1 gram negative) and 20(8.7%) of infants had CSF culture of which 5 (2.2%) had bacterial Growth (Table 3). Klebsiella was identified in 2 patients and streptococcus pneumoniae (also from blood culture in same child), Coagulase negative staphylococcus (CONS) and pseudomonas were the other 3 bacteria. The young infant with CONS infection has also growth on blood culture and we thus considered this as genuine cause of meningitis. The Infants with pseudomonas and klebsiella growth were infants with hospital acquired infections. Blood culture was done only for 55(24%) young infants from which 26 (45.6%) had no growth and 20 (35.1%) of the blood culture results were not documented (not collected from microbiology). Only 11(5%) young infants with suspected

Table 3. Bacteria Isolated From Cerebrospinal Fluid of Study Subjects



Key: GPC Gram positive cocci, CONS Coagulase negative staphylococcus, CSF Cerebrospinal fluid

sepsis had documented blood culture growth. The commonest organisms isolated were CONS 3 (27%), Klebsiella 3(27%) and Staph Aures 2 (18%). The others were streptococcus pneumonia, Neisseria meningitides (had also seizure and CSF pleocytosis but no CSF gram stain and culture not documented), Acinetobacter species each contributing for 1 case. Among young infants with CONS growth on blood culture only 1 patient have proven meningitis with same organism isolated also on CSF culture .The other 2 are likely contaminants. The young infant with Acinetobacter growth has clinical signs of meningitis including seizure but normal CSF profile with negative culture. The patient has however developed complications with hydrocephalus and subdural effusion and was treated as meningitis and sepsis and discharged with complete clinical improvement.

Nine (28%) infants with meningitis developed neurologic complications at discharge. Commonest complications were hydrocephalus and subdural effusion each accounting for 3 cases. About 30 (13%) infants were admitted for more than 3 weeks and 208 (90.4%) of infants were discharged improved, and a total of 16 (7%) young infants died during the study period. While the working diagnosis in those infants was sepsis, the cause of death was not clearly stated.

DISCUSSION

Male to female ratio of 1.2 is in line with previous unpublished study from Ethiopia (3). Clinical features are non-specific and failed to help identify presence or absence of meningitis except for presence of seizure (3,5,14).

Despite higher overall prevalence of meningitis (17%) compared to similar Kenyan study (6.4%), the Kenyan study specifically focused on confirmed bacterial meningitis (3% in our study likely due to poor use of microbiologic tests) and included younger infants unlike ours (16). However, the prevalence of culture proven bacterial meningitis in our study (3 %) is higher than the same study from Florida, USA (19).This is explainable by the difference in the two settings with higher rate of meningitis in our setting. Infants with leukocytosis had 3 times higher rates of developing meningitis than those with normal WBC. Previous studies also have shown increased risk of meningitis in infants with leukopenia and leukocytosis (4).

Our study demonstrated unacceptably poor use of diagnostic microbiologic tests and over reliance on clinical parameters with only about 20 (11.8%) of infants with LP having CSF culture determined. The commonest organisms identified in those minorities with microbiologic study were gram negative organisms unlike previous western data (1) but consistent with similar recent studies in Ethiopian and other African countries as well as in the USA (3, 16, 18, 20, 25). Pseudomonas aeruginosa and CONS are rarely causes of bacterial meningitis and were documented from both blood and CSF cultures in two of our patients.

Previous studies have documented similar findings and we believe these were genuine causes of meningitis in our patients (6, 26).

Looking at the practice in different tiers of the health system in our country, though WHO clinical criteria for pyogenic meningitis is a reasonable compromise for primary and secondary level health systems, tertiary hospitals with specialists should follow evidence based protocols and accurately diagnose and treat CNS infections especially pyogenic meningitis in young infants using strict criteria including microbiologic confirmation. The WHO criteria can however miss a significant number of young infants with meningitis and may not be as sensitive as in older children and require high index of suspicion and CSF analysis should be considered in clinically suspected cases whenever possible.

While this is the first study in our setting, the study is limited by retrospective nature and inability to accurately identify the type of meningitis as bacterial or viral and most might actually be viral in etiology despite being treated as bacterial meningitis. A significant number of patient files (162/510) were also not retrievable during the study period because of poor archiving and sole dependence of the hospital on paper based documentation and it is not known if these files are lost or kept elsewhere.

In conclusion, meningitis is a common infection in young infants with SIRS despite low microbiologic confirmation. Common isolated bacteria were gram negatives and presence of seizure is the only independent predictor of meningitis. In clinical practice, we recommend full septic workup with emphasis on microbiologic studies including blood and CSF culture in all young infants with SIRS as a standard irrespective of the WHO criteria despite the lack of consensus and controversy in the evaluation of those segment of the population. Documentation of laboratory results and chart archiving should be improved with a backup electronic medical recording system for better access and to decrease loss of patient files.

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