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Healthcare-Associated Meningitis in Neonates – A Prospective Study of Epidemiology, Etiology and Risk Factors

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Abstract

Background: The immune system of neonates is considered to be immature, which makes them highly susceptible to acquiring infections. Although meningitis in neonates has been widely studied and is known to be associated with high mortality, the published literature on 'neonatal healthcare-associated meningitis (HAM)', per say is very limited. This one-year prospective cohort study was conducted to generate much-needed epidemiological data on HAM in neonates.

Methods: Using a set of pre-defined inclusion and exclusion criteria, 591 eligible neonates admitted at a tertiary-care hospital nursery in New-Delhi, India were enrolled into the study. Neonatal HAM cases were identified based on the guidelines established by the CDC. Standard diagnostic protocols were followed for microbiological processing of the cerebrospinal fluid (CSF) and blood samples. A series of 28 potential risk factors were also evaluated in the study, using univariate and multivariable logistic regression analyses.

Results: Of 591 neonates enrolled in the study, 32 were diagnosed with HAM (incidence = 5.41 cases per 100 eligible admissions). *Escherichia coli* and *Staphylococcus aureus* were among the most common pathogens isolated from the culture-positive HAM cases. Clinical features were generally non-specific, with lethargy (28%) and irritability (28%) being the most frequently observed signs. Maternal hypothyroidism was found to be a significant risk factor, both on univariate (P = 0.0009; 95%CI: 2.32 - 26.57) and multivariable analyses (P = 0.022; 95%CI: 1.25 - 19.22).

Conclusions: Given the overall high incidence of neonatal HAM, it should be regarded as a major health problem in neonates. Due to its non-specific clinical presentation, a high degree of clinical suspicion is required for timely and accurate diagnosis of neonatal HAM. Our study has identified a unique association between maternal hypothyroidism and neonatal HAM, which needs further exploration with future studies.

Keywords: *Healthcare-Associated Infections; Healthcare-Associated Meningitis; Neonates; Nosocomial; Meningitis*

Abbreviations

CNS: Central Nervous System; HAI: Healthcare-Associated Infection; HAM: Healthcare-Associated Meningitis; LHMC: Lady Hardinge Medical College; NCDC: National Centre for Disease Control; NICU: Neonatal Intensive Care Unit; CDC: Centers for Disease Control And Prevention; CSF: Cerebrospinal Fluid; CLSI: Clinical and Laboratory Standards Institute; OR: Odds Ratio; CI: Confidence Interval; Los: Length of Hospital Stay; GNB: Gram-Negative Bacteria; GPB: Gram-Positive Bacteria; ELBW: Extremely Low Birth Weight; VLBW: Very Low Birth Weight; LBW: Low Birth Weight; TPN: Total Parenteral Nutrition; IDSA: Infectious Diseases Society of America; CVC: Central Venous Catheter

Introduction

It is well established that the newborns' immune system is immature and has several deficiencies in the humoral and cellular immune responses, phagocytic and complement functions, which increases their susceptibility to infections [1]. It is therefore not surprising that infection of the central nervous system (CNS), such as meningitis (inflammation of the meninges) is more common during the neonatal period than in any other phase of life.

Meningitis in neonates has a reported incidence of around 0.2 cases per 1000 live births [2]. Despite the significant advancements in the medical care and availability of broad-spectrum antibiotics, neonatal meningitis continues to be a serious disease with severe long-term sequelae, and has a high mortality rate approaching up to 60% in the developing world [3-5]. A proportion of the total neonatal meningitis cases are due to healthcare-associated infections (HAIs), and this is referred to as, 'neonatal healthcare-associated meningitis (HAM)'. HAIs in neonates are characterized by high morbidity, and are responsible for prolonged hospitalization, increased cost of care and high mortality rates [6].

In the past, neonatal HAM was falsely considered to be an exceedingly rare diagnosis mainly due to the inability to accurately elicit the classical signs of meningitis in infants [7], as well as the difficulty in performing lumbar puncture among sick neonates with multiple co-morbidities [8]. As a result, the literature on HAM in neonates has remained scarce and this disease entity finds only a brief mention in the published studies on neonatal HAIs [6,9-13]. Although infection of the CNS often occurs in the setting of a preceding invasive procedure, emerging data now suggest that these infections can also develop in the absence of such intervention, especially among neonates [14]. Consequently, neonatal HAM is now thought to be a more widely prevalent disease than it was previously believed [8]. Neonatal HAM is also considered particularly important since the morbidity and mortality associated with this disease entity is potentially preventable. However, the true estimates of neonatal HAM incidence and its predisposing risk factors continue to remain elusive.

With this background, we designed this study to generate much-needed epidemiological data on neonatal HAM, with an emphasis on determination of the incidence and etiological profile, and identification of the underlying risk factors.

Material and Methods

Study Design: This is a one-year prospective cohort study conducted in the 23-bedded neonatal nursery of Smt. Sucheta Kriplani Hospital, a major teaching affiliate of Lady Hardinge Medical College (LHMC) in New Delhi, India. The study protocol was approved by the ethics committee and the institutional review board of the Lady Hardinge Medical College, University of Delhi. Informed consent was obtained from the parent/ guardian of every neonate included in the study. The study was conducted in collaboration with National Centre for Disease Control (NCDC), New Delhi, India.

Enrollment Criteria: All neonates admitted to the nursery between February 17, 2010 to February 16, 2011 were screened for the presence of four inclusion criteria: (i) age between 0 to 28 days at the time of admission, (ii) stay in the nursery for > 48 hours, (iii) absence of any signs of sepsis at the time of admission, and (iv) absence of prior hospitalization in the neonatal intensive care unit (NICU). Neonates that fulfilled all the above inclusion criteria were included in the study and further evaluated for identification of HAM cases.

Study Procedure: A detailed birth history was collected from the parent/guardian of all the enrolled neonates, and daily examinations were performed to identify any clinical evidence of sepsis/meningitis until discharge from the nursery or death. In all the clinically suspicious cases of sepsis and/or meningitis that were included in the study, a lumbar puncture was performed using a sterile technique [15]. Approximately 2 mL total cerebrospinal fluid (CSF) was collected in four sterile tubes. Two of the tubes were sent for the evaluation of cell counts and biochemistry (glucose and protein levels). Another CSF tube was sent for identification and isolation of bacterial and fungal pathogens as per the standard protocols [16]. The last tube was sent to the NCDC laboratory at 4°C, where the CSF was inoculated onto HEp-2 cell lines for the isolation of viruses such as Enteroviruses [17]. ELISA for anti- (IgM) Parvovirus B19 [18], and a validated microneutralization assay for Coxsackie viruses B1-B6 were performed on the serum obtained from all suspected meningitis cases. Standard broth-based blood culture technique was used to identify any concomitant bacteremia [19]. Urine culture was performed using

semi-quantitative culture technique, and chest radiographs were obtained for all cases of suspected neonatal sepsis. The antimicrobial susceptibility testing was performed by the Clinical and Laboratory Standards Institute (CLSI) disc diffusion method [20].

The diagnosis of neonatal HAM was established based on the diagnostic criteria established by the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (Table 1) [21]. A total of 28 (7 neonatal, 6 maternal and 15 interventional) risk factors were evaluated to determine any association with the incidence of neonatal HAM. The impact of HAM on outcomes such as the length of hospital stay (LoS) and neonatal mortality was also evaluated.

Diagnostic criteria for HAM in patients ≤ 1 year of age (Must meet at least one of the two criteria)			**Neonates fulfilling the criteria in our study (%)**
1.	Patient has organisms cultured from cerebrospinal fluid (CSF)		5 (16)
2.	At least 1 of the following signs or symptoms with no other recognized cause:	a. Fever (> 38˚C rectal)	7 (22)
		b. Hypothermia (<37˚C rectal)	3 (9)
		c. Apnea	6 (19)
		d. Bradycardia	0 (0)
		e. Stiff neck	0 (0)
		f. Meningeal signs (including vomiting, seizures)	11 (34)
		g. Cranial nerve signs	0 (0)
		h. Irritability	9 (28)
		Total neonates with suggestive clinical signs	32 (100)
	AND Fulfill at least one of the laboratory criteria	a. Positive CSF examination*	32 (100)
		b. Positive Gram's stain of CSF	0 (0)
		c. Organisms cultured from blood	19 (59)
		d. Positive antigen test of CSF, blood, or urine	0 (0)
		Total neonates with supportive laboratory findings	32 (100)

Table 1: *CDC Criteria for Healthcare-Associated Meningitis (HAM) and the Distribution of Cases [21].*

** For preterm neonates: white cells ≥ 10/μL, protein > 170 mg/dL, and/or glucose < 24 mg/dL. For term neonates: white cells > 8/μL, protein > 120 mg/dL, and/or glucose < 20 mg/dL [30]*

Statistical Analyses: The data was compiled and analyzed using the Epi Info™ version 7.1.4 (CDC, Atlanta, USA) statistical software. Univariate logistic regression analyses were performed and variables with a P-value of < 0.05 were entered into a backward step wise regression model in multivariable analysis. All P-values were two sided and values < 0.05 were considered significant. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated for all significant variables.

Results

A total of 899 intramural neonates were admitted to the neonatal nursery during the one-year study period, of which 591 neonates fulfilled the study inclusion criteria. Of these, 103 neonates were clinically suspected to have sepsis and underwent further workup including CSF analysis, leading to subsequent diagnosis of HAM in 32 neonates.

Incidence: The neonatal HAM incidence was determined to be 5.41 cases per 100 eligible nursery admissions (32/591) in our single-institution study. Although the meningitis cases were detected throughout the year, the incidence peaked in the month of March (34.4%; 11/32).

Clinical Profile: The most frequently observed clinical signs in the HAM cases included lethargy and irritability (28.1%), fever (21.9%), seizures (22%) and apnea (18.7%). Other less common signs included vomiting (12.5%), hypothermia (9.4%), respiratory distress (9.4%), decreased cry (6.2%), and decreased oral acceptance (3.1%). Table 1 provides a detailed breakdown of the various criteria fulfilled by the neonates diagnosed with HAM in our study.

Microbial Profile: Of the 21 culture-positive HAM cases in our study, gram-negative bacteria (GNB) were isolated from 13 (62%) neonates, gram-positive bacteria (GPB) from another seven (33%) cases, and *Candida albicans* was isolated from one neonate (Table 2). *Escherichia coli* was the most common (29%; N = 6) pathogen isolated from the culture-positive HAM cases. *Staphylococcus aureus* (N = 5) was the most frequently isolated GPB. Viral etiology was not established in any of the meningitis cases.

Group of Pathogens	Micro-organism	Number of Cases (%)
Gram-negative bacteria (GNB)	*Klebsiella* sp.	5 (24)
	Escherichia coli	6 (29)
	Acinetobacter sp.	2 (10)
Gram-positive bacteria (GPB)	*Staphylococcus aureus*	5 (24)
	Coagulase negative staphylococci	1 (5)
	Enterococcus sp.	1 (5)
Fungi	*Candida albicans*	1 (5)
Viruses	None isolated	0 (0)
Total		21 (100)

Table 2: *Micro-organisms Isolated from Neonates with Healthcare-Associated Meningitis.*

Antimicrobial Susceptibility: All the gram-negative isolates (Table 3) were resistant to two or more antibiotics, most notably to ampicillin (92.3%), gentamicin (53.8%) and third generation cephalosporins (46.1%) while showing good *in-vitro* sensitivity to amikacin (76.9%), ciprofloxacin (84.6%) and imipenem (100%). Gram-positive organisms (Table 3) were mostly resistant to penicillin (85.7%) and ampicillin (85.7%) but majority were sensitive to gentamicin (71.4%), cefuroxime (85.7%), ceftazidime (100%), vancomycin (100%) and teicoplanin (100%).

Antibiotic Tested	Number Tested / Number Resistant (%)		
	Escherichia coli	*Klebsiella sp.*	*Acinetobacter sp.*
Gentamicin	6/2 (33.3)	5/4 (80)	2/1 (50)
Ampicillin	6/6 (100)	5/5 (100)	2/1 (50)
Amikacin	6/0 (0)	5/3 (60)	2/0 (0)
3rd Generation Cephalosporins[a]	6/2 (33.3)	5/3 (60)	2/1 (50)
Ciprofloxacin	6/1 (16.7)	5/1 (20)	2/0 (0)
Imipenem	6/0 (0)	5/0 (0)	2/0 (0)
	Staphylococcus aureus	Coagulase negative staphylococci	*Enterococcus sp.*
Penicillin	5/5 (100)	1/1 (100)	1/0 (0)
Ampicillin	5/5 (100)	1/1 (100)	1/0 (0)

Gentamicin	5/2 (40)	1/0 (0)	1/0 (0)
Cefuroxime	5/1 20	1/0 (0)	0/0
Ceftazidime	5/0 (0)	1/0 (0)	0/0
Vancomycin	5/0 (0)	1/0 (0)	1/0 (0)
Teicoplanin	5/0 (0)	1/0 (0)	1/0 (0)

Table 3: *Antimicrobial Susceptibility Pattern of Bacterial Isolates.*

[a] *Cefotaxime/ Ceftriaxone*

Risk Factors: Out of the 28 potential risk-factors tested, having a 'very low birth weight' (VLBW; 1000 - 1500 grams) (P = 0.033), intubation at birth (P = 0.033), total parenteral nutrition (TPN; P=0.0004), prior antibiotic use (P = 0.040), insertion of peripheral venous catheter (P = 0.0004), maternal hypothyroidism (P = 0.0009) and gestational hypertension (P = 0.015) were found to have a significant association with neonatal HAM incidence on univariate analyses (Table 4). However, on multivariable analysis, the only risk factor that continued to maintain a significant association with neonatal HAM was maternal hypothyroidism (Table 5).

Characteristic	Neonates without HAM N = 559	Neonates with HAM N = 32	*P*-value	Odds ratio	95% Confidence Interval
	Number (%)	Number (%)			
Neonatal Characteristics:					
Male Sex	308 (55.1)	19 (59.4)	0.636	1.19	0.58-2.46
Prematurity	349 (62.4)	24 (75)	0.157	1.81	0.79-4.09
Multiple births	85 (15.2)	4 (12.5)	0.678	0.79	0.27-2.33
Birth weight					
• ELBW [a]	15 (2.7)	0 (0)	0.965	0.00	0.00->1.0E12
• VLBW [b]	118 (21.1)	12 (37.5)	0.033	2.24	1.07-4.72
• LBW [c]	276 (49.4)	17 (53.1)	0.680	1.16	0.57-2.37
Meconium stained liquor	84 (15.0)	8 (25)	0.136	1.88	0.82-4.34
APGAR <4					
• 1 min	61 (10.9)	4 (12.5)	0.780	1.17	0.39-3.44
• 5 min	9 (1.6)	0 (0)	0.973	0.00	0.00->1.0E12
Respiratory distress at birth	330 (59.0)	19 (59.4)	0.969	1.01	0.49-2.09
Maternal Characteristics:					
Multiparity	336 (60.1)	19 (59.4)	0.934	0.97	0.47-2.00
Antepartum hemorrhage	47 (8.4)	1 (3.1)	0.308	0.35	0.05-2.63
Gestational Hypertension	82 (14.7)	10 (31.2)	0.015	2.64	1.21-5.79
Hypothyroidism	10 (1.8)	4 (12.5)	0.0009	7.84	2.32-26.57
Premature rupture of membranes	40 (7.2)	1 (3.1)	0.397	0.42	0.06-3.15
Antenatal steroids	160 (28.6)	6 (18.7)	0.232	0.57	0.23-1.42
Interventional Characteristics:					
Type of delivery					
• Assisted vaginal	16 (2.9)	0 (0)	0.964	0.00	0.00->1.0E12
• Caesarian	182 (32.6)	12 (37.5)	0.563	1.24	0.59-2.60

Resuscitation at birth					
• Bag and mask ventilation	67 (11.9)	3 (9.4)	0.658	0.76	0.23-2.56
• Intubation	54 (9.7)	7 (21.9)	0.033	2.62	1.08-6.34
Vaccination	530 (94.8)	29 (90.6)	0.316	0.53	0.15-1.84
Kangaroo mother care	86 (15.4)	5 (15.6)	0.971	1.02	0.38-2.72
Prior blood transfusion	32 (5.7)	4 (12.5)	0.129	2.35	0.78-7.11
Prior antibiotics	135 (24.2)	13 (40.6)	0.040	2.15	1.03-4.47
Prior H_2 blockers	3 (0.5)	0 (0)	0.976	0.00	0.00->1.0E12
Prior steroids	0	0	-	-	-
Prior surgery	0	0	-	-	-
Total parenteral nutrition	228 (40.8)	24 (75)	0.0004	4.36	1.92-9.87
Orogastric feed	257 (45.9)	16 (50)	0.657	1.17	0.58-2.39
Peripheral venous catheter insertion	285 (50.9)	28 (87.5)	0.0004	6.73	2.33-19.44
Central catheter insertion	17 (3.0)	1 (3.1)	0.979	1.03	0.13-7.98
Mechanical Ventilation	22 (3.9)	0 (0)	0.972	0.00	0.00- >1.0E12
Oxygen hood/prongs	185 (33.1)	13 (40.6)	0.382	1.38	0.67-2.86

Table 4: *Risk Factors for Neonatal Healthcare-Associated Meningitis (HAM).*

[a]ELBW: Extremely low birth weight (<1000 grams); [b]VLBW: Very low birth weight (1000-1500 grams);

[c]LBW: Low birth weight (1500 - 2500 grams).

P-value < 0.05 was considered as statistically significant.

Characteristic	*P*-value	Odds ratio	95% Confidence Interval
Very low birth weight (VLBW)	0.197	1.71	0.76 - 3.89
Intubation at birth	0.106	2.19	0.85 - 5.67
Prior antibiotics	0.793	0.90	0.40 - 2.01
Peripheral venous catheter insertion	0.112	3.38	0.75 - 15.18
Total parenteral nutrition (TPN)	0.267	1.96	0.60 - 6.42
Gestational hypertension	0.061	2.37	0.96 - 5.85
Maternal hypothyroidism	0.022	4.91	1.25 - 19.22

Table 5: *Multivariable Analysis of Risk factors.*

P-value < 0.05 was considered as statistically significant.

Outcomes: The mean duration of hospital stay was 22.7 days (range 5 - 50) for the neonates diagnosed with HAM, in contrast to 9.4 days (range 3 - 77) for the neonates without meningitis. Two (6.25%) out of the 32 neonates that were diagnosed with HAM eventually died of the disease, despite aggressive management with appropriate antimicrobial therapy.

Discussion

This one-year prospective cohort study on neonatal HAM was performed to specifically determine the incidence, microbial profile and the risk-factors for neonatal HAM. The incidence of neonatal HAM was found to be 5.41 cases per 100 eligible nursery admissions, which

is comparable to the incidence rate observed in a similar 15-month study from Brazil (4.9 per 100) that also employed the CDC criteria for the identification of neonatal HAM cases [12]. In two other studies from India [6,11] and a study from Tehran [13], the incidence of neonatal HAM was found to be zero, 1.3 and 0.07 cases per 100 admissions, respectively. The lower incidence rates of neonatal HAM reported in these latter three studies is likely due to the use of different criteria for identifying neonatal HAM cases. In addition, the varying incidence rates of neonatal HAM across studies is likely also contributed by differences in the study population characteristics as well, such as the socio-economic, geographical and environmental factors.

The frequency of HAIs is known to have a direct correlation with LoS, which in turn depends on the severity of the primary illness that resulted in hospitalization of the patient. As a result, an inter-institution comparison of meningitis incidence rates per hospital admission may be misleading due to wide variations in average LoS even for similar appearing illnesses. The incidence density, i.e. the number of infections per 1000 patient hospitalization days, helps to account for this variability [12]. The incidence density of meningitis in our study was 3.6 per 1000 patient days, which was much higher than that reported in studies from Brazil (0.58 per 1000 patient days) and Tehran (0.1 per 1000 patient days) [10,13].

We have determined that the clinical presentation of neonatal HAM is rather nonspecific with lethargy, irritability, fever and seizures being the most commonly observed signs. Similar nonspecific presenting features were also reported in two recent studies on neonatal meningitis from Tunisia and Taiwan [22,23]. This highlights the importance of having a high degree of clinical suspicion in every case of neonatal sepsis, to ensure early diagnosis and prompt management of neonatal meningitis.

CSF analysis remains the gold-standard approach for the diagnosis of meningitis. In our study, CSF cultures were found to be positive in 16% of the neonatal HAM cases, which is considerably lower than the previously reported rate of 26.7% to 72.5% [9,22,24,25]. The lower CSF culture-positivity observed in our study is likely due to early administration of empiric antibiotics, sometimes even prior to CSF analysis. Although bacteremia is a potential risk factor for meningitis, a significant proportion (40%) of neonates diagnosed with CSF culture-positive HAM did not have a concomitant positive blood culture in our study. The exact reason for this remains unknown, however, the rising use of antibiotics during maternal labor has been cited as a possible explanation for a similar observation in another study [26]. This finding reinforces the importance of undertaking CSF examination in every case of suspected meningitis.

Infectious Diseases Society of America (IDSA) has recommended empirical administration of ampicillin plus cefotaxime, or ampicillin plus an aminoglycoside for the treatment of neonatal meningitis [27]. Due to widespread resistance, the empiric antimicrobial policy in our neonatal unit was to administer meropenem plus amikacin for suspected cases of HAM. In our study, the antimicrobial susceptibility testing revealed that all gram-negative isolates were resistant to ≥ two antibiotics, with most strains being resistant to ampicillin, gentamicin and third generation cephalosporins. Likewise, most GPBs were resistant to penicillin and ampicillin. In view of these high rates of emerging resistance to the commonly used antibiotics especially amongst the GNBs, more studies are warranted to determine the etiological and local antimicrobial susceptibility profile of neonatal HAM in the community. This will help choose the most appropriate empiric therapy for neonates and also ensure a rational use of antibiotics.

Risk Factors: Identification of high-risk population is necessary for the implementation of relevant preventive measures and early diagnosis of any disease. This is even more important when it comes to neonatal HAM due to its nonspecific clinical presentation. In our study, among all the neonatal risk factors that were evaluated, VLBW (1000 - 1500 grams) was the only factor that maintained a statistically significant association with the risk of developing meningitis. Prematurity has been previously reported as a risk factor for HAM in neonates [5]. However, the gestational age of the neonate at birth was not found to be a significant risk factor for HAM in our study. Among the maternal risk factors, gestational hypertension and hypothyroidism were found to be significantly associated with neonatal HAM on univariate analyses. Use of invasive devices and procedures can bypass the normal defense mechanisms of the host. In accordance with this concept, intubation at birth, TPN and insertion of peripheral venous catheters were found to be the risk factors that had statistically significant association with HAM on univariate analyses. Surprisingly, we did not find insertion of central venous catheter (CVC) to be

associated with the risk of developing HAM. Our institutional policy to avoid CVC insertion (performed in only 17 out of 591 neonates in our study) or keep it for the minimum possible duration might have contributed to the failure to establish its association with neonatal HAM. Additionally, none of the neonates in our study underwent other invasive procedures that are known risk factors for HAM, such as craniotomy and CSF shunting using ventricular catheters [28]. The statistically significant risk factors identified on univariate analyses were then further evaluated using a multivariable logistic regression model. The only variable that continued to demonstrate a significant association with neonatal HAM was maternal hypothyroidism. The explanation for this association currently remains unknown. A recent study from the U.S. has reported a significant association of both maternal hypo- and hyper-thyroidism with neonatal sepsis [29]; however, the association of maternal thyroid status with neonatal meningitis has not been reported previously. Consequently, there is a need to further explore the relationship between maternal thyroid status and neonatal infections with future studies.

Limitations: We acknowledge that our study is associated with a few limitations. The neonates in our study were not monitored in the post-discharge period to detect any episodes of HAM infections that might be incubating at the time of discharge from the hospital. This could have led to a slight underestimation of the true HAM incidence. Also, in approximately one-third of the neonatal HAM cases, the implicating microorganism could not be identified. Finally, since a large number of risk factors were analyzed in relatively few HAM cases observed in our study, the association that has been observed between some of the risk factors and neonatal HAM could represent a chance finding. Despite these limitations, our study is valuable for generating much-needed epidemiological and microbiological data on HAM in neonates.

Conclusion

To conclude, HAM in neonates is associated with an overall high incidence rate, and it should therefore be regarded as a major health problem in neonates. However, due to the very non-specific clinical presentation, a high degree of clinical suspicion is required for timely and accurate diagnosis of this disease entity. A unique association between maternal hypothyroidism and risk of developing neonatal HAM was identified in this study, which needs further exploration. Future studies on neonatal HAM should utilize the established uniform case definitions, to help refine existing data and gain better understanding of this disease entity. This in turn would facilitate formulation of better infection control policies, leading to a reduction in the incidence of HAM in neonates, worldwide.

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