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Epidemiology and Outcomes of Culture-proven Neonatal Meningitis in Australian Tertiary Hospitals

A Multicenter Retrospective Cohort Study

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Abstract: We conducted a 5-year multicenter, retrospective cohort study to describe bacterial meningitis in Australian infants (0–180 days). Of 21 culture-positive infections, *Streptococcus agalactiae* (29%, 6/21), *Staphylococcus aureus* (19%, 4/21) and *Escherichia coli* (19%, 4/21) predominated. Four infants died (19%), including 3 with neurosurgical meningitis. In survivors, neurologic sequelae were common. Novel interventions to reduce the morbidity and mortality burden caused by neonatal meningitis are needed.

Key Words: neonatal meningitis, bacterial infections, antimicrobial resistance, preterm infants, CNS infections

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Neonatal meningitis is a rare yet high-consequence pediatric infectious disease, occurring in approximately 1 in every 2000 live births, with a higher incidence evident in preterm neonates.[1] Even with early diagnosis and treatment, up to 1 in 6 neonates with bacterial meningitis will die, and in survivors, there is a high risk of ongoing significant morbidity, including neurologic sequelae, cognitive impairment and seizures.[1–3] Prompt diagnosis and treatment of central nervous system (CNS) infections in infants is crucial to improve survival and reduce morbidity. However, the signs and symptoms of CNS infections in neonates are often nonspecific.[2,4]

There are limited published contemporary data delineating the epidemiology of CNS infections in neonates and young infants globally. In Australia's high-income healthcare system, the resuscitation of extremely preterm infants is often enabled from 23 weeks' gestation. However, the survival and management of these infants are often complicated by a high risk of hospital-acquired infections and complications that may occur secondary to prematurity.[5] As advanced healthcare systems are increasingly capable of resuscitating and supporting extremely preterm infants, there is a rising incidence of neurosurgical interventions due to complications of prematurity (such as intraventricular hemorrhage) that increasingly result in a rising risk of late-onset CNS infections.[2,4,6] This is further compounded by increasing antimicrobial resistance (AMR) globally, as the pathogens causative of neonatal meningitis gradually reveal less susceptibility to commonly used antibiotics to treat CNS infections.[2,6]

As data regarding the clinical presentation, epidemiology and long-term outcomes of meningitis (including neurosurgical meningitis) in young infants are limited, we aim to evaluate the contemporary causes of CNS infections and evaluate for evolving AMR in this vulnerable population, in the context of rapidly advancing technologies that enable the resuscitation and stabilization of extremely preterm infants.

METHODS

We performed a 5-year (January 2015 to December 2019) retrospective cohort study of infants (0–180 days) with culture-positive CNS infections admitted to 3 tertiary pediatric hospitals in New South Wales, Australia. The upper age limit was chosen to capture late-onset and nosocomial infections, particularly in preterm populations who remain hospitalized beyond the neonatal period.

Culture-positive cerebrospinal fluid (CSF) isolates were identified via systematic data extraction from microbiological databases, and corresponding clinical data were extracted from electronic medical records utilizing a standardized proforma to collect deidentified demographic, clinical, laboratory, microbiologic, treatment and outcome data. Data cleaning and descriptive statistical analysis were performed in Microsoft Excel version 2016 V2502. Continuous data were reported as mean or median values (with standard deviations or interquartile ranges [IQRs], as appropriate). Categorical data were compared using χ^2 test for P value, where denominator data were available. Ethics approval was obtained through the Sydney Children's Hospital Network Human Research and Ethics Committee (2020/ETH01847).

RESULTS

We identified 26 culture-positive CSF isolates collected from young infants (≦180 days). Five isolates (*Streptococcus sanguinis* [n = 2], *Streptococcus oralis* [n = 1], *Staphylococcus epidermidis* [n = 1] and *Staphylococcus warneri* [n = 1] were excluded as contaminants, as clinical data and CSF parameters (protein, glucose and cell counts) did not support a diagnosis of meningitis. This resulted in 21 cases of culture-positive CNS infections included in our cohort.

Almost two-thirds of all cases occurred in males (13/21, 62%). The median age of infection was 45 days old (IQR 23–69 days old), and 43% (9/21) of infections occurred in preterm infants (born at <37 weeks' gestation; Table 1). Many of the included infants (11/21, 52%) were admitted as inpatients at the time of their diagnosis, predominantly due to prematurity (9/21, 43%) and/

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TABLE 1. Demographic, Clinical and Microbiologic Features of Infants (0–180 days) With Culture-Positive Meningitis

Total: n = 21	Characteristic		Count (n, %)	Deceased (n, %)	Sequelae at Follow-Up (n, %)
Sex	Male		13 (62)	4 (31)	4 (31)
	Female		8 (38)	0 (0)	6 (75)
Gestation (w)	Extreme	24–27	1 (5)	0 (0)	1 (100)
	Very	28–31	1 (5)	0 (0)	1 (100)
	Moderate	32–36	7 (33)	4 (57)	3 (43)
	Normal	≥37	12 (57)	0 (0)	5 (42)
Days of Life at Diagnosis of Central Nervous System (CNS) infection	Early onset	0–3	1 (5)	0 (0)	0 (0)
	Late onset	4–7	0 (0)		
		8–28	7 (33)	2 (29)	3 (43)
		>28	13 (62)	2 (15)	7 (54)
Prior neurosurgery	Yes		9 (43)	3 (33)	6 (67)
	No		12 (57)	1 (8)	4 (33)
Source of presentation	Community		10 (48)	1 (10)	3 (30)
	Inpatient		11 (52)	3 (27)	7 (64)
CNS pathogen	Gram-positive bacteria (total)		12 (57)	1 (8)	7 (58)
	Streptococcus agalactiae		6 (29)	1 (17)	2 (33)
	Staphylococcus aureus		6 (29)	0 (0)	5 (83)
	Gram-negative bacteria (total)		9 (43)	3 (33)	3 (33)
	Enterobacterales		5 (24)	2 (40)	0 (0)
	Pseudomonas aeruginosa		3 (14)	1 (33)	2 (67)
	Neisseria meningitidis		1 (5)	0 (0)	0 (0)
Investigations	CSF findings			Median (IQR)	
	WCC (× 10^6/L)			141 (6–1845)	
	RBC (× 10^6/L)			145 (28–1215)	
	Protein (g/L)			1.9 (1.2–3.5)	
	Glucose (mmol/L)			2.0 (0.7–3.0)	
	Blood parameters			Median (IQR)	
	WCC (× 10^9/L)			10 (6–14)	
	CRP (mg/L); median (IQR)	Early onset (n = 1)		79 mg/L	
		Late onset (n = 20)		26 mg/L (6–60)	

RBC indicates Red Blood Cell; WCC, White cell count

or congenital anomalies (10/21, 48%; which were primarily neurological in nature—including congenital aqueduct stenosis and myelomeningoceles). Only 1 case had a non-neurologic congenital anomaly necessitating their hospital admission (tracheomalacia) identified. There were 3 cases of neurosurgical meningitis occurring in extremely preterm infants (born at <28 weeks' gestation) who had hydrocephalus secondary to intraventricular haemorrhage as a complication of their prematurity.

Ten of the cases (48%) occurred in neonates (<29 days) presenting to the Emergency Department from a community setting, including 1 ex-premature neonate (born at 34 weeks' gestation) who presented at 5 weeks corrected postnatal age with meningitis and bloodstream infection due to *Streptococcus agalactiae*.

Overall, the most common pathogen identified was *S. agalactiae* (or Group B Streptococcus, GBS) accounting for 29% of all cases (6/21), followed by *Staphylococcus aureus* (4/21, 19%), *Escherichia coli* (4/21, 19%), *Pseudomonas aeruginosa* (2/21, 10%) and *Staphylococcus epidermidis* (n = 2, 10%) (Table 1). In 10 patients (47%), concurrent bacteremia and meningitis occurred, with the same bacterial pathogen isolated in both blood and CSF cultures (Table 1).

All 6 cases of GBS meningitis were in neonates presenting from the community as late-onset infections (presenting at >8 postnatal days of life). Within this cohort, 5 neonates (of 6, 83%) were born at term, to mothers who had undergone GBS screening. Only 2 of these neonates were born to mothers with positive GBS antenatal screening tests; these infants had received intrapartum antibiotic prophylaxis, as per local health guidelines.[6]

The presenting signs and symptoms of bacterial meningitis were diverse, with a median of 9 (IQR 7–10) signs or symptoms evident in each case. The most common presenting symptoms were irritability and/or unsettled behavior (14/21, 67%), followed by lethargy (12/21, 57%), bulging or "full" fontanelle (10/21, 48%) and seizures (7/21, 33%). In infants with neurosurgical meningitis, the incidence of tachycardia (3/21, 33%) and bulging/full fontanelle (2/21, 22%) was significantly lower than for non-neurosurgical meningitis cases (10/21, 83%, $P = 0.02$ and 8/21, 67%, $P = 0.03$).

The most frequently documented abnormal signs were fever (defined as temperature >38.0°C) occurring in 71% of infants (15/21), abnormal color (14/21 67%), tachycardia (defined as heart rate >160 beats per minute) (13/21, 62%), reduced perfusion (11/21, 52%), gastrointestinal symptoms (vomiting or diarrhea; 7/32, 33%), tachypnea (6/21, 29%), hypoxia (3/21, 14%), reduced urine output (2/21, 10%) and hypotension (1/21, 5%). Cell count and biochemistry parameters are summarized in Table 1.

Four neonates died (19%), all of whom were male babies born between 32 and 36 weeks' gestation who had late-onset infections (Table 1). The median age at onset of infection for these infants was 25 days old (IQR 18–35 days old). Three of these infants had a ventricular device *in situ* and were diagnosed with neurosurgical meningitis due to a gram-negative pathogen (*E. coli*, *P. aeruginosa* and *E. cloacae)*. By contrast, only 1 episode of gram-positive meningitis resulted in mortality (of 12, 8%) in an infant with late-onset GBS infection.

CSF pathogen antibiotic susceptibilities were available for 16 of the 21 cases, with high rates of susceptibility to empiric antibiotic regimens evident (Table 1).

DISCUSSION

Our multicenter retrospective observational study has identified that while rare, neonatal meningitis continues to cause a

significant mortality burden that is largely unchanged over recent decades. There were 4 deaths in our cohort, resulting in a mortality rate of 19%. This is slightly higher than that reported in other studies in high-income healthcare settings, although our sample size was small.[4,6] Nevertheless, the inclusion of a population beyond the neonatal period in our cohort enabled our study to identify the high mortality burden caused by late-onset CNS infections, particularly in infants requiring neurosurgical interventions, who constituted 75% (3/4) of the deaths observed in our cohort. This population is frequently not captured by epidemiologic studies evaluating neonatal meningitis.

We found a higher mortality rate in CNS infections caused by gram-negative bacteria (3/9, 33%), which more commonly occurred in preterm infants with neurosurgical meningitis in our study (67%, 6/9 versus 33%, 3/9). This gram-negative meningitis mortality rate aligns with another Australian study conducted 4 decades ago,[4,7] confirming a lack of progress in improving Gram-negative neonatal meningitis morbidity and mortality in infants. There are no known prevention strategies to reduce this ongoing burden of disease caused by gram-negative meningitis; adjunct therapies such as corticosteroids and immunoglobulin may have a role in improving clinical outcomes, yet interventional studies to evaluate these therapies in neonates are required.[4,6,8]

Despite the high mortality revealed by gram-negative neonatal CNS infections in our cohort, GBS remained the predominant pathogen causative of meningitis, followed by *E. coli* and *S. aureus*, aligning with other data from high-income countries.[4,6,8] In our study, all cases of GBS meningitis occurred in young infants presenting with late-onset, community-acquired infections. While GBS screening rates were high, intrapartum antibiotic prophylaxis only prevents early-onset GBS infection, and late-onset GBS infections are consequent to postnatal colonization.[6] Future research is needed to identify strategies to reduce late-onset GBS infections, and the development of vaccine candidates against GBS provides a promising step in reducing this burden of disease.[9]

Our study is limited by its retrospective design and small sample size. Despite a 5-year study period and multicenter involvement, our reliance on culture-based diagnosis likely underestimates the true incidence of bacterial meningitis, as many other infants with suspected bacterial meningitis may have received antibiotics before lumbar puncture.[10] Future research encompassing both culture-positive and -negative meningitis cases, including those increasingly diagnosed via molecular diagnostics, should be conducted to provide a more accurate representation of CNS infections in this age group. While we were unable to perform subgroup analyses by early-onset, late-onset and neurosurgical infections due to the small number of cases, future studies with larger cohorts could investigate potential differences in clinical presentation and outcomes between these groups.

Despite these limitations, our study contributes important findings to the under-reported epidemiology of bacterial meningitis and is unique in its inclusion of infants up to 180 days of age. We have identified the causative pathogens remain unchanged, and there is a high burden of mortality associated with gram-negative infections, particularly in higher-risk populations (including preterm infants and those requiring neurosurgical interventions). Our study also revealed the broad and nonspecific signs and symptoms evident in neonatal meningitis, highlighting the need for clinicians to be astute in considering meningitis in unsettled or lethargic infants, as more obvious signs (such as seizures) are rare, as revealed within our cohort (and other published studies).[8]

As the resuscitation of increasingly premature infants improves worldwide, further research to identify strategies to reduce the ongoing burden of neonatal meningitis is necessary to reduce the persistently high morbidity and mortality associated with this high-consequence infectious disease.

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