The Epidemiology, Management, and Outcomes of Bacterial Meningitis in Infants

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abstract

OBJECTIVES: The pathogens that cause bacterial meningitis in infants and their antimicrobial susceptibilities may have changed in this era of increasing antimicrobial resistance, use of conjugated vaccines, and maternal antibiotic prophylaxis for group B *Streptococcus* (GBS). The objective was to determine the optimal empirical antibiotics for bacterial meningitis in early infancy.

METHODS: This was a cohort study of infants <90 days of age with bacterial meningitis at 7 pediatric tertiary care hospitals across Canada in 2013 and 2014.

RESULTS: There were 113 patients diagnosed with proven meningitis (n = 63) or suspected meningitis (n = 50) presented at median 19 days of age, with 63 patients (56%) presenting a diagnosis from home. Predominant pathogens were *Escherichia coli* (n = 37; 33%) and GBS (n = 35; 31%). Two of 15 patients presenting meningitis on day 0 to 6 had isolates resistant to both ampicillin and gentamicin (*E coli* and *Haemophilus influenzae* type B). Six of 60 infants presenting a diagnosis of meningitis from home from day 7 to 90 had isolates, for which cefotaxime would be a poor choice (*Listeria monocytogenes* [n = 3], *Enterobacter cloacae*, *Cronobacter sakazakii*, and *Pseudomonas stutzeri*). Sequelae were documented in 84 infants (74%), including 8 deaths (7%).

CONCLUSIONS: *E coli* and GBS remain the most common causes of bacterial meningitis in the first 90 days of life. For empirical therapy of suspected bacterial meningitis, one should consider a third-generation cephalosporin (plus ampicillin for at least the first month), potentially substituting a carbapenem for the cephalosporin if there is evidence for Gram-negative meningitis.

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WHAT'S KNOWN ON THIS SUBJECT: Before the use of intrapartum antibiotics for group B *Streptococcus* (GBS), common pathogens in bacterial meningitis in the first 90 days of life were GBS and *Escherichia coli*. Ampicillin and cefotaxime were effective for almost all community-acquired cases.

WHAT THIS STUDY ADDS: GBS and *E coli* are still the main pathogens. Three of 60 cases of community-acquired late-onset bacterial meningitis were with Gram-negative pathogens for which a third-generation cephalosporin would be suboptimal therapy.

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There is a paucity of information on the characteristics of neonatal meningitis in the era of infant *Haemophilus influenzae* type B (Hib) and pneumococcal immunization, maternal group B *Streptococcus* (GBS) prophylaxis, and emerging antimicrobial resistance.[1] The primary objective of this study was to describe pathogens in bacterial meningitis in the first 90 days of life in Canada. Secondary objectives were to make inferences about optimal empirical antimicrobial agents, outline the typical duration of treatment, and describe outcomes. The hypothesis was that third-generation cephalosporins may no longer be optimal for empirical therapy of late-onset, community-acquired meningitis.

METHODS

Study results were reported by using The Strengthening the Reporting of Observational Studies in Epidemiology guidelines (https://www.equator-network.org/reporting-guidelines/strobe/). Ethics approval was obtained at 7 pediatric hospitals for a retrospective chart review of infants born January 1, 2013 through December 31, 2014. Cases were identified by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada* diagnostic codes for target discharge (Supplemental Information).

Inclusion Criteria

Infants with onset of bacterial meningitis in the first 90 days of life were included in this study. Proven meningitis was defined as the detection of bacteria from cerebrospinal fluid (CSF) by culture or molecular techniques during life or at autopsy. Suspected meningitis was defined as the detection of a bacteria recognized to cause central nervous system infection from blood or another normally sterile site (including urine) and either sterile CSF pleocytosis or head imaging consistent with bacterial meningitis. CSF pleocytosis was defined as >30 × 10^6/L white blood cells (WBCs) and (1) <100 × 10^6/L red blood cells (RBCs), or (2) WBC:RBC ratio >1:100. Early-onset was defined as diagnosis on day 0 to 6, late-onset as day 7 to 29, and extremely late-onset as day 30 to 90.[2]

Exclusion Criteria

Exclusion criteria were (1) growth of a common skin contaminant (including coagulase negative staphylococci) from a single CSF culture, (2) full recovery despite ≤4 days intravenous antimicrobial agents, or (3) fungal isolate.

Data Collection

Data collected via the Research Electronic Data Capture included demographics, microbiologic results (including susceptibilities, CSF sampling results, and head imaging results from symptom onset until antibiotic completion), duration of antimicrobial agents for meningitis, complications of meningitis (including seizures, hydrocephalus, brain abscesses, suspected ventriculitis, or infarcts), and sequelae at last encounter (seizure disorder, hearing or vision loss, motor deficits, developmental delay, or death).

Data Analysis

Descriptive and comparative statistics were calculated as appropriate, expressing continuous variables by using median and interquartile range (IQR) because data were generally not normally distributed. Comparisons of continuous variables were performed by using nonparametric methods (Mann–Whitney *U* test). Comparisons of proportions were performed by using χ^2 test or Fisher's exact test, as appropriate. Correlations were quantified by using Spearman's rank correlation coefficient (ρ). The Statistical Package for the Social Sciences version 19 (IBM Corporation, Armonk, NY) and GraphPad Prism version 5 (GraphPad Software, La Jolla, CA) were used for statistical analysis and graphical display of data, respectively.

In analyzing antimicrobial susceptibility data, it is an accepted principle that empirical treatment of bacterial meningitis should almost always include an antibiotic to which the pathogen is susceptible.

RESULTS

There were 424 charts with 1 or more target discharge diagnoses, yielding 113 cases of proven bacterial meningitis (n = 63) or suspected bacterial meningitis (n = 50) in 61 boys and 52 girls (68 term; 45 preterm) with a median age of diagnosis of 19 days (IQR 10–33) (Table 1). Sixty-three patients (56%) were presented from home, of which 54 (86%) were term infants (≥37 weeks' gestation). The other 50 patients (44%) presented during their birth hospitalization, of which 14 (28%) were term infants (Table 2).

Pathogens are shown in Table 1 with *E coli* (37/113; 33%) and GBS (35/113; 31%) dominating. Blood cultures performed in 61 of 63 proven cases were positive for the meningitis pathogen in 40 of those cases (66%).

Forty (80%) of the 50 patients with suspected meningitis had bacteremia with CSF sampled only post-antibiotics. Nine of the remaining 10 patients had sterile CSF pleocytosis pre-antibiotics (data missing for 1 patient) with a median CSF leukocyte count of 132 (range 5–545). *E coli* was isolated from 7 patients from blood and urine (n = 2), blood and endotracheal secretions (n = 1), urine and endotracheal secretions (n = 1), and urine alone (n = 3). *E*

TABLE 1 Characteristics of 113 Neonates With Proven or Suspected Bacterial Meningitis

	Proven Cases[a] (n = 63)	Suspected Cases (n = 50)	All Cases (N = 113)	P
GA at birth, wk, n (%)				.55
≥37	38 (60)	30 (60)	68 (60)	
32–36+6	10 (16)	4 (8.0)	14 (12)	
28–31+6	7 (11)	8 (16)	15 (13)	
<28	8 (13)	8 (16)	16 (14)	
Sex, n (%)				1.0
Female	29 (46)	23 (46)	52 (46)	
Male	34 (54)	27 (54)	61 (54)	
Birth weight (kg), median (IQR)	2.9 (1.1–3.4)	2.9 (1.6–3.3)	2.9 (1.4–3.3)	.49
Mode of delivery				.80
Vaginal	44 (70)	36 (72)	80 (71)	
Cesarean delivery	19 (30)	14 (28)	33 (29)	
Congenital abnormality, n (%)	7 (11)	7 (14)	14 (12)	.64
Onset, d				.45
Early (0–6)	8 (13)	7 (14)	15 (13)	
Late (7–29)	33 (52)	31 (62)	64 (56)	
Extremely late (30–90)	22 (35)	12 (24)	34 (30)	
Presentation, n (%)				.025
From home	41 (65)	22 (44)	63 (56)	
During birth hospitalization	22 (35)	28 (56)	50 (44)	
CSF findings (median, IQR)				
WBC × 10^6/L	1100 (350–3200)	250 (140–660)	620 (150–2600)	.011
Percent neutrophils	75 (53–87)	47 (8.5–82)	71 (31–85)	.021
Glucose, mmol/L	1.1 (0.70–2.4)	2.1 (1.5–2.8)	1.7 (0.78–2.6)	.002
Protein, g/L	2.6 (1.6–4.9)	1.9 (1.1–3.2)	2.3 (1.2–4.2)	.057
Organism				.022
E coli	14 (22)	23(46)	37(33)	
GBS	24 (38)	11 (22)	35 (31)	
L monocytogenes	3 (5)	0 (0)	3 (3)	
Streptococcus pneumoniae	1 (2)	0 (0)	1 (1)	
Hib	0 (0)	3 (6)	3 (3)	
N meningitidis	4 (6)	0 (0)	4 (6)	
Other	17 (27)[b]	13 (26)[c]	30 (27)	
Treatment				
Antibiotic duration, d, median (IQR)	23 (15–42)	21 (19–31)	22 (18–36)	.19
Corticosteroids, n (%)	3 (4.8)	1 (2.0)	4 (3.5)	.63
Surgical drainage of abscess, n (%)	2 (3.2)	1 (2.0)	3 (2.7)	1.0
CSF shunt, drain, or reservoir, n (%)	13 (21)	1 (2.0)	14 (12)	.003
Complications				
Seizure	27 (43)	11 (22)	38 (34)	.027
Hydrocephalus	17 (27)	7 (14)	24 (19)	.11
Brain abscess	6 (9.5)	4 (8)	10 (12)	1.0
Suspected ventriculitis	4 (6.3)	8 (16)	12 (12)	.13
Cerebral infarcts	13 (21)	9 (18)	22 (11)	.81
Outcome at last encounter				
Seizure disorder	8 (13)	2 (4.0)	10 (8.8)	.18
Hearing loss	3 (4.8)	2 (4.0)	5 (4.4)	1.0
Vision problem	1 (1.6)	0 (0)	1 (0.9)	1.0
Motor problem (spasticity, paresis)	12 (19)	7 (14)	19 (17)	.51
Developmental delay	11 (18)	1 (2.0)	12 (11)	.011
Death	2 (3.2)	6 (12)	8 (7.1)	.14

[a] A positive CSF culture.

[b] Other bacteria from cases of proven meningitis: *S gallolyticus* (n = 4), *E cloacae* (n = 2), *C sakazakii* (n = 2), *K pneumoniae* (n = 2), coagulase-negative staphylococci (n = 2), *S aureus* (n = 1), *P stutzeri* (n = 1), *S marcescens* (n = 1), *K oxytoca* (n = 1), *Enterococcus* spp. (n = 1).

[c] Other bacteria from cases of suspected meningitis: *E cloacae* (n = 4), *S marcescens* (n = 2), *Bacillus* spp. (n = 2), *K oxytoca* (n = 1), *K pneumoniae* (n = 1), *S gallolyticus* (n = 1), *S anginosus* (n = 1), viridans group streptococci (n = 1).

cloacae was isolated from urine (n = 1) and blood (n = 1) in the remaining patients. The latter patient had prolonged bacteremia and sagittal sinus thrombus leading to treatment of endovasculitis.

Early-Onset Meningitis (Day 0–6)

Early-onset meningitis accounted for 15 cases (13%), with GBS being the leading pathogen (7/15 cases; 47%) followed by *E coli* (4/15; 27%). Other cases were due to *Streptococcus gallolyticus* in a term infant on day 1 of life, *S anginosus* in a term infant the day of birth, *Klebsiella pneumoniae* in a 24 weeks' gestational age (GA) infant day 6, and Hib in a 29 weeks' GA infant day 2. Maternal GBS screening was negative for 3 out of 7 GBS cases, not tested in 3 (all received intrapartum antibiotics), and unknown for one. Twelve of the 15 infants (75%) were term, of which 3 (all term) presented after birth hospital discharge with GBS (n = 2), and *E coli* meningitis (n = 1) on days 2 (n = 1) and 6 (n = 2).

Late-Onset Meningitis (Day 7–29)

There were 64 patients with *E coli* (n = 24; 38%) and GBS (n = 17; 27%) predominating (Table 1). Infants admitted from home were primarily term (28/31; 90%). Six of 32 not yet discharged from the hospital were term (19%).

Extremely Late-Onset Meningitis (Day 30–90)

There were 34 cases of patients with extremely late-onset meningitis, of which 28 (82%) presented from home. Common organisms were GBS (n = 11; 32%), *E coli* (n = 9; 26%), *Neisseria meningitidis* (n = 3), and Hib (n = 2; 6%).

Antibiotic Susceptibilities

Table 3 shows the antibiotic susceptibility patterns. All but 2 of 15 patients with early-onset meningitis (*E coli* on day 1 at 29 weeks' GA and Hib on day 2 at 29 weeks' GA) were susceptible to ampicillin or gentamicin; both exceptions were susceptible to cefotaxime. Another isolate (*E coli* on day 2 in a term infant) was the sole early-onset isolate resistant to cefotaxime

(susceptible to gentamicin and meropenem).

For 64 late-onset cases, 6 isolates were resistant to ampicillin and gentamicin (*E coli* in an infant admitted from home and 5 in infants not yet discharged from the hospital: *E coli* [*n* = 2], *Serratia marcescens* [*n* = 1], and coagulase-negative staphylococci [*n* = 2]). Fifteen isolates were resistant to cefotaxime. Patients admitted from home with cefotaxime resistant isolates had cases of *L monocytogenes* (*n* = 3) on day of life 13, 15, and 21, and *E cloacae* was present on day 24 in a term infant. Patients still in hospital included *E cloacae* (*n* = 5) on day 10, 14, 16, 19, and 20 of life, *S marcescens* (*n* = 2) on day 8 and 15 of life, coagulase-negative staphylococci (*n* = 2) on day 9 and 23 of life, *C sakazakii* on day 17 of life, and *Enterococcus* spp. on day 9 of life.

For the 34 patients with extremely late-onset cases, 31 were reported to be susceptible to ampicillin or a third generation cephalosporin. The remaining 3 isolates included *C sakazakii* (34 weeks' GA infant) and *P stutzeri* (CSF shunt infection) admitted from home on day of life 36 and 37, respectively and *S marcescens* (infant still in hospital).

In total, 13 of 57 Gram-negative bacilli (27%) were resistant to cefotaxime.

CSF Findings

The initial findings in the 63 proven cases are shown in Table 1. Three infants (2.7%) with culture-proven meningitis did not have CSF pleocytosis; CSF WBC count on the day of diagnosis was 1, 2 and 4, and RBC count was 2, 107, and 627 × 10^6/L in infants with GBS, *K oxytoca*, and *S marcescens* in CSF culture, respectively. An additional 4 infants (3.5%) had fewer than 25 × 10^6/L WBC in CSF (a common threshold for pleocytosis in neonates) despite CSF cultures being positive for GBS (*n* = 2), *Staphylococcus aureus*, and *Enterococcus* spp.

Nine patients had persistently positive CSF cultures on antibiotics. The organism and the days of antibiotics when the last positive culture was obtained included GBS (*n* = 3; days 3, 6, and 6), *E coli* (*n* = 2; days 5 and 7), *P stutzeri* (*n* = 1; day 5), *E cloacae* (*n* = 1; day 12), coagulase-negative *Staphylococcus* (*n* = 1; day 8), and *K pneumoniae* (*n* = 1; day 7).

TABLE 2 Comparison of Infants With Meningitis Admitted From Home to Infants Diagnosed With Meningitis During Their Birth Hospitalization

	Admitted From Home (*n* = 63)	In Hospital Since Birth (*n* = 50)	*P*
GA at birth, wk, *n* (%)			<.001
Term (≥37)	54 (86)	14 (28)	
Preterm (<37)	9 (14)	36 (72)	
Birth weight (kg), median (IQR)	3.2 (2.9–3.6)	1.5 (1.0–3.1)	<.001
Sex, *n* (%)			.71
Female	28 (44)	24 (48)	
Male	35 (55)	26 (52)	
Congenital anomaly	7 (11)	7 (14)	.64
Onset, d, *n* (%)			<.001
Early (0–6)	3 (4.8)	12 (24)	
Late (7–29)	32 (51)	32 (64)	
Extremely late (30–90)	28 (44)	6 (12)	
Organism			.029
E coli	20 (31)	17 (34)	
GBS	23 (36)	12 (24)	
L monocytogenes	3 (4.8)	0	
N meningitidis	4 (6.3)	0	
H influenzae	2 (3.1)	1 (2.0)	
S pneumoniae	1 (1.6)	0	
Other	10 (16)[a]	20 (40)[b]	
Antimicrobial resistance			
AMP[c]	15 (24)	25 (50)	.004
AMP+GEN	2 (3.2)[d]	6 (12)[e]	.069
CEF (third)	6 (9.5)[f]	13 (26)[g]	.020
Outcome at last follow-up[h]			
Seizure disorder	5 (8.5)	5 (11)	.68
Hearing loss	2 (3.4)	3 (6.5)	.46
Vision problem	1 (1.7)	0	.38
Motor problem (spasticity, paresis)	9 (15)	10 (22)	.69
Developmental delay	5 (8.5)	5 (11)	.87
Death	4 (6.3)	4 (8.0)	.73
Duration of antibiotics[h]	22 (16–37)	24 (21–41)	.15
Length of hospitalization[h]	18 (12–25)	60 (25–100)	<.001

AMP, ampicillin; CEF (third), third-generation cephalosporin; GEN, gentamicin.

[a] Other bacteria from patients admitted from home include the following: *Klebsiella* spp. (*n* = 3), *Streptococcus bovis* (*n* = 2), *S gallolyticus* (*n* = 1), *E cloacae* (*n* = 1), *C sakazakii* (*n* = 1), *P stutzeri* (*n* =1), and *S aureus* (*n* = 1).

[b] Other bacteria from patients in hospital since birth include the following: *E cloacae* (*n* = 5), *S marcescens* (*n* = 3), *Klebsiella* spp. (*n* = 2), *Bacillus* spp. (*n* =2), coagulase-negative staphylococci (*n* = 2), *S gallolyticus* (*n* = 2), *S anginosus* (*n* = 1), viridians group *Streptococcus* (*n* = 1), *Enterococcus* spp. (*n* = 1), and *C sakazakii* (*n* = 1).

[c] Resistance to AMP includes the following: based on in vitro testing for *E coli* (*n* = 19), *Klebsiella* spp. (*n* = 4), and *H influenza* (*n* = 2); resistance assumed for *E cloacae* (*n* = 6), *S marcescens* (*n* = 3), *C sakazakii* (*n* = 2), and *P stutzeri* (*n* = 1), *S aureus* (*n* = 1), and coagulase-negative staphylococci (*n* = 2).

[d] Resistance to both AMP and GEN (community isolates) was based on in vitro testing for *E coli* (*n* = 1) and resistance assumed for *S aureus* (*n* = 1).

[e] Resistance to both AMP and GEN (hospital isolates) was based on in vitro testing for *E coli* (*n* = 3) and GEN resistant *S marcescens* (*n* = 1); resistance was assumed for coagulase-negative staphylococci (*n* = 2). Of note, all *E cloacae* and *C sakazakii* isolates were GEN susceptible or not tested.

[f] Resistance to CEF (third) (community isolates) includes the following: resistance assumed for *L monocytogenes* (*n* = 3), *E cloacae* (*n* = 1), *C sakazakii* (*n* = 1), and *P stutzeri* (*n* = 1).

[g] Resistance to CEF (third) (hospital isolates) includes the following: based on in vitro resistance testing for *E coli* (*n* = 1); resistance assumed for *E cloacae* (*n* = 5), *S marcescens* (*n* = 3), *C sakazakii* (*n* = 1), *Enterococcus* spp. (*n* = 1), and coagulase-negative staphylococci (*n* = 2).

[h] Among survivors (*n* = 105).

TABLE 3 In Vitro Antimicrobial Susceptibility Testing of Isolates From Cases of Neonatal Meningitis

Organism (*n*)	Antibiotics							
E coli	AMP	GEN	TOB	CEF (third)	MERO	CIP[a]	PIP-TAZ[a]	
(37)	15/34 (44)	27/31 (87)[b]	16/18 (89)[b]	29/30 (97)[c]	12/12 (100)	9/9 (100)	11/13 (85)	
GBS	AMP			CEF (third)				VAN
(35)	32/32 (100)			13/13 (100)				16/16 (100)
Other Gram-negative	AMP	GEN	TOB	CEF (third)	MERO	CIP[a]	PIP-TAZ[a]	
(24)[d,e,f,g,h]	1[d]/4(6)	12/13 (92)[g]	7/8 (95)[g]	12/16 (75)[h]	11/11 (100)	4/4 (100)	5/7 (71)	
Other Gram-positive	AMP			CEF (third)				VAN
(17)[i,j,k,l,m]	9/9 (100)[l]			6/6 (100)[j,k,l]				8/8 (100)

Numbers represent susceptible isolates/isolates tested (% susceptible). AMP, ampicillin; CEF (third), third-generation cephalosporin; CIP, ciprofloxacin; GEN, gentamicin; MERO, meropenem; PIP-TAZ, piperacillin-tazobactam; TOB, tobramycin; VAN, vancomycin.

[a] Not routinely recommended for treatment of neonatal meningitis.

[b] Four isolates of *E coli* (from 4 patients) were resistant to aminoglycosides: 2 GEN resistant (TOB not tested), 1 GEN resistant and TOB intermediate, 1 resistant to both GEN and TOB. All 4 isolates were resistant to AMP and susceptible to CEF (third).

[c] One isolate of *E coli* from a 2-day-old term infant diagnosed with meningitis on the postpartum ward was resistant to AMP, CEF (third), and sensitive to GEN, TOB, and MERO.

[d] Antimicrobial susceptibility testing was availabe for only 1 of 4 *Neisseria meningitidis* isolates. That isolate was AMP and CEF (third) sensitive.

[e] Of 3 cases of *H influenzae*, 2 isolates were resistant to AMP and sensitive to CEF (third) and the third case did not have susceptibility testing available.

[f] Of 5 isolates of *Klebsiella* spp., 4 out of 4 cases tested were resistant to AMP, 3 out of 3 cases were sensitive to GEN, and 4 out of 4 cases were sensitive to CEF (third).

[g] One isolate of *S marcescens* from a 24-week premature male infant diagnosed with meningitis on day 15 of life in the NICU was resistant to AMP, GEN, TOB, CEF (third), and sensitive to MERO and CIP.

[h] *E cloacae* (*n* = 6), *S marcescens* (*n* = 3), *C sakazakii* (*n* = 2), and *P stutzeri* (*n* = 1) may be presumed resistant to AMP and CEF (third) although this was not always tested or reported. All isolates that were tested were sensitive to MERO.

[i] One isolate of *S pneumoniae* and 7 additional isolates of nonGroup B streptococci (*S gallolyticus*, *S anginosus*, viridans group streptococci), were all sensitive to AMP. When reported, all isolates were also sensitive to CEF (third) and VAN.

[j] One isolate of *Enterococcus* spp. was sensitive to AMP and VAN. Presumed resistant to CEF (third).

[k] For 3 isolates of *L monocytogenes* (from 3 patients), in vitro susceptibility testing not performed or reported. Treatment of choice was AMP+GEN. Presumed resistant to CEF (third).

[l] One isolate of *S aureus* (methicillin sensitive) and 2 isolates of coagulase-negative staphylococci would not be adequately treated with AMP+GEN. Testing was not performed or reported for CEF (third). All 3 isolates were sensitive to VAN.

[m] In vitro susceptibility testing not performed or reported for 2 isolates of *Bacillus* spp.

TABLE 4 Neuroimaging Findings in 113 Neonates With Central Nervous System Infection

	Ultrasound, *n* (%)	CT Scan, *n* (%)	MRI, *n* (%)	Any Modality, *n* (%)
No. of patients studied	77 (68)	20 (18)	63 (56)	93 (82)
Normal study	26/77 (34)	3/20 (15)	8/63 (12)	22/93 (24)
Abnormal				
Infarction	4 (5)	7 (35)	18 (28)	22 (24)
Abscess	4 (5)	2 (10)	9 (14)	10 (11)
Calcification	0	1 (5)	0	1 (1.1)
Hydrocephalus	19 (25)	6 (30)	16 (25)	24 (26)
Suspected ventriculitis[a]	7 (9)	1 (5)	6 (10)	12 (13)

CT, computed tomography.

[a] The pathogens associated with suspected ventriculitis included *E coli* (*n* = 5), *S agalactiae* (*n* = 2), *K pneumoniae* (*n* = 1), *P stutzeri* (*n* = 1), *S gallolyticus* (*n* = 1), and coagulase negative staphylococci (*n* = 1).

Head Imaging

Table 4 summarizes the neuroimaging findings. Overall, 93 out of 113 infants (82%) underwent at least 1 imaging study, of which the majority (71/93 = 76%) were abnormal. Infarction and hydrocephalus were common findings. Brain abscess occurred in 3 *E coli* (8%) and 6 GBS cases (17%). Imaging abnormalities were associated with alterations in CSF laboratory parameters, particularly hypoglycorrhachia (*P* = .004) and elevated total CSF protein (*P* = .004). Patients with infarction had lower CSF glucose levels (median 0.70 mmol/L [IQR 0.20–1.1] vs 1.9 mmol/L [IQR 1.1–2.7], *P* = .001), and patients with hydrocephalus had lower CSF glucose levels (0.70 mmol/L [IQR 0.20–1.3] vs 2.0 mmol/L [IQR 1.1–2.7], *P* = .001) and higher CSF protein (5.2 g/L [IQR 2.1–9.8] vs 2.0 g/L [IQR 1.1–3.2], *P* = .001).

Antimicrobial Therapy

Median duration was 23 days for proven meningitis (IQR 19–42) and 21 days for suspected meningitis (IQR 19–30), 21 days for patients who had CSF sampled once, and 26 days for patients with repeat CSF sampling. Treatment duration had a mean of 38 days (median 42) if a repeat CSF sample remained positive.

Proven *E coli* meningitis was treated for median 24 days (IQR 21–42), GBS for median 23 days (IQR 17.3–31.8), and other pathogens for median 24 days (IQR 15–39.8), with 21 of 63 patients (33%) treated for >28 days. Indications for prolonged therapy with *E coli* (*n* = 5) were suspected ventriculitis (*n* = 3), brain abscess (*n* = 1), and positive CSF culture on day 5 of antibiotics (*N* = 1). Indications for prolonged therapy with GBS (*n* = 7) included ventriculitis (*n* = 1), brain abscess (*n* = 3), infarct (*n* = 1), CSF pleocytosis on day 22 of antibiotics (*n* = 1), and persistently low CSF glucose (*n* = 1). Prolonged therapy was given in 9 other patients with the indications being suspected ventriculitis with *K pneumoniae* (*n* = 2) and *L monocytogenes* (*n* = 1), brain abscess with *C sakazakii* (*n* = 1) and *S gallolyticus* (*n* = 2), positive CSF culture on day 7 of treatment of *E cloacae* (*N* = 1), suspected

TABLE 5 Clinical, Laboratory, and Radiographic Predictors of Adverse Outcomes in Infants With Meningitis

Outcome at Last Follow-up	Prognostic Marker, *n* (%)		RR (95% CI)	*P*
	Seizures in Hospital (41)	No Seizures (72)		
No apparent sequelae	4 (9.8)	25 (35)	0.28 (0.088–0.38)	.003
Hearing loss[a]	4 (12)	1 (1.4)	8.4 (1.0–72)	.037
Vision problem[a]	1 (2.9)	0	—	.32
Motor problem (spasticity, paresis)[a]	12 (35)	7 (9.9)	3.6 (1.5–8.3)	.006
Developmental delay[a]	8 (24)	4 (5.6)	4.2 (1.4–13)	.017
Death	7 (17)	1 (1.4)	12 (1.6–96)	.003
	CSF protein >5 g/L (17)[b]	CSF protein ≤5 g/L (72)[b]		
No apparent sequelae	2 (12)	22 (31)	0.39 (0.10–1.5)	.14
Hearing loss[a]	2 (13)	1 (1.5)	9.2 (0.89–95)	.081
Vision problem[a]	0	1 (1.5)	0	1.0
Motor problem (spasticity, paresis)[a]	6 (40)	9 (13)	3.1 (1.3–7.3)	.003
Developmental delay[a]	3 (20)	3 (4.4)	4.6 (1.0–21)	.033
Death	2 (12)	3 (4.1)	2.8 (0.51–16)	.24
	Hydrocephalus on neuroimaging (24)	No hydrocephalus (89)		
No apparent sequelae	3 (13)	26 (29)	0.42 (0.14–1.3)	.12
Hearing loss[a]	3 (14)	2 (2.4)	5.7 (1.0–32)	.028
Vision problem[a]	0	1 (1.2)	0	1.0
Motor problem (spasticity, paresis)[a]	10 (45)	9 (11)	4.2 (1.9–9.0)	<.001
Developmental delay[a]	3 (14)	9 (11)	1.3 (0.37–4.3)	.71
Death	2 (8.3)	6 (6.7)	1.2 (0.27–5.7)	.68

Numbers in table represent *n* (%) or RR (95% CI). RR, relative risk. —, not applicable.

[a] Among survivors (*n* = 105).

[b] Data missing for CSF protein for 24 patients (*n* = 89).

endovascular infection with *Staphylococcus warnerii* (*n* = 1), and CSF shunt infection and ventriculitis with *P stutzeri* (*N* = 1). The 8 infants with the combination of bacteremia, a urinary tract infection, and sterile pleocytosis (before antibiotics) due to *E coli* (*n* = 7) and *E cloacae* (*n* = 1) were treated for median 21 days (range 14–24 days).

Patients treated for <14 days were all *N meningitidis* meningitis treated for 7, 10, and 12 days. The only recurrence was 10 weeks after antibiotics were stopped (*E coli* meningitis treated initially for 54 days for ventriculitis and subdural empyema with sterile CSF on day 18 of antibiotics [WBC count 448 × 10^6/L; glucose 0.6 mmol/L; protein 4.5 g/L]).

Median length of stay for patients admitted from home was 18 days (range 5–53; IQR 12–23).

Outcomes

Tables 1 and 2 show outcomes at the time of last encounter. Clinically significant sequelae were documented in the majority (84/113 = 74%), including 8 deaths (7%) due to GBS (*n* = 5; 14% of 35 GBS cases), *E coli* (*n* = 1; 3% of 37 *E coli* cases), *E cloacae* (*n* = 1), and *S marcescens* (*n* = 1), with meningitis considered to be a significant contributor in all but the latter case. Outcomes were similar between early-, late-, and extremely late-onset cases, and between pathogens (*E coli*, GBS, or other). Motor deficit (spasticity or paresis) was observed in 19 newborns, and was more common among preterm than term infants (12/45 = 27% vs 7/68 = 10%, *P* = .023).

Several clinical, laboratory, and imaging findings predicted adverse outcomes. Hydrocephalus requiring CSF shunt placement was more common in patients with a culture-positive CSF on antibiotics (4/9 = 44%) compared with those with a culture-negative repeat CSF (3/29 = 10%; *P* = .041) and compared with those with a positive initial culture with no repeat CSF (2/25 = 4.0%; *P* = .031). Selected prognostic markers are shown in Table 5 and Supplemental Tables 6 and 7. In addition to associations shown in these tables, the number of leukocytes in the initial CSF was significantly higher in children with hearing loss (median 9000 × 10^6/L [IQR 1600–9000] vs 570 × 10^6/L [IQR 150–2300]; *P* = .006). Neuroimaging finding of infarction was associated with subsequent seizure disorder (6/22 = 27% with infarction versus 4/91 = 4.4% without infarction; *P* = .004).

DISCUSSION

E coli and GBS each accounted for approximately one-third of cases of bacterial meningitis in the first 90 days of life in this Canadian study. GBS was predominant in other recent studies, accounting for 39% of cases from Taiwan (<1 month of age),[3] 52% of cases from the United Kingdom (≤90 days of age),[2] 59% of cases from France (≤28 days of age),[4] and 86% of cases from the United States (<2 months of age).[5] Disparate results may relate to definitions chosen for suspected meningitis and varying GBS prophylaxis strategies although the latter would impact only early-onset cases; GBS guidelines

in Canada and the United States are almost identical to one another.[6,7]

Despite excellent uptake of prophylaxis guidelines, GBS still accounted for approximately half of early-onset meningitis. Maternal colonization status can change between screening and delivery with the sensitivity of cultures being only 51% in 1 study.[8] Rarely, intrapartum prophylaxis fails.[9] The burden of GBS meningitis remains significant with a mortality rate of 14% with the 5 deaths occurring in term and preterm infants with a wide range of age at onset (1–59 days of life). There is a need for additional strategies for prevention of early- and late-onset disease.

There was only 1 case of pneumococcal meningitis in our cohort versus 9% in the 2010–2011 UK cohort in the same age group.[2] Pneumococcal meningitis was always rare in the first month of life, but the low number of cases between 30 and 90 days is presumably from herd immunity with the conjugated pneumococcal vaccine starting at 2 months of age.

Empirical antibiotics for early-onset and/or community-acquired suspected meningitis typically include ampicillin (for at least the first month) and a third-generation cephalosporin. For the 60 community acquired late- and extremely late-onset cases, the 57 cases with data available were susceptible to ampicillin or a third-generation cephalosporin with the other isolates being *E cloacae*, *C sakazakii*, and *P stutzeri*. It therefore seems prudent to consider a carbapenem if CSF parameters suggest bacterial meningitis, the pathogen is unknown, and the Gram-stain is negative or shows a Gram-negative organism (with the addition of ampicillin for at least the first month to cover for *L monocytogenes* unless a Gram-negative is detected on CSF Gram-stain or in the blood), especially if the infant had a complicated birth hospitalization. Typically one will switch to a less broad spectrum agent within 48 hours as culture results become available. The requirement for such a broad-spectrum antimicrobial is not surprising given that community-acquired multiresistant coliforms are becoming more prevalent in Canada.[10] The choice of antibiotic for hospital-acquired cases should be determined by patient-related factors and hospital antibiograms.

Repeat CSF sampling until the cultures are negative, end-of-therapy sampling, and prolongation of antibiotics for persistently abnormal CSF parameters is advocated by some experts for meningitis in the first few months of life,[1] but there are no guidelines as to which pathogens warrant this to or how to interpret the results. A 2001 survey showed that only 18% of physicians in England routinely obtained repeat CSF sampling,[11] whereas it was obtained in 60% of proven cases in the current study. Nine of 38 patients with repeat CSF sampling (24%) had positive cultures and all but one of these infants had a documented complication. A US study of 150 NICUs demonstrated that infants with repeat positive cultures on antibiotics were more likely to die (6/23 [26%] vs 6/81 [7%]; $P = .02$), but did not report on other complications.[12] End-of-therapy sampling appears to be a rare practice in Canada and occurred for only 3 out of 63 infants with proven meningitis.

A recent review article listed the typical duration of antibiotics for meningitis in the first 90 days of life as 14 days for GBS, *L monocytogenes*, or pneumococcus, and 21 days for *E coli* or other enterics with longer courses with delayed clinical response or complications.[1] Most GBS in the current study was treated for ≥21 days. It remains unclear whether prolonged antibiotics improve the prognosis of infants with repeat positive CSF cultures on antibiotics.

Our high complication rate is concordant with a recent study from Taiwan in which 54% had complications.[3] The rate of cerebral infarcts in the current study was especially high among proven GBS meningitis patients (25%). The case fatality rate of 7% compares favorably with that reported in other recent studies, namely 11% in the United Kingdom,[2] 13% in France,[4] and 15% in Taiwan.[3] There are no previous Canadian data for comparison.

In the study from Taiwan, it is striking that only 1 of 156 neonates developed sequelae in the absence of complications. A study from China showed that a high CSF protein both initially and after 2 weeks of antibiotics predicted a low Glasgow Outcome Score at discharge.[13] The study from Taiwan reported that an initial CSF protein >5 g/L predicted a poor prognosis, as did a seizure at admission or during hospitalization.[3] Similarly, poor outcomes in our series were associated with seizures, CSF protein >5 g/L, and hydrocephalus (Table 5). Despite prognostically favorable baseline characteristics (more term infants with higher birth weights), clinical outcomes of community-associated meningitis were as poor as hospital-associated.

This study has the usual limitations of a retrospective chart review. The definitions of suspected meningitis and CSF pleocytosis are not standardized. Maternal intrapartum antibiotics could not be studied as a risk factor for antimicrobial resistance as data were available only for infants with GBS meningitis. Head imaging findings could have been present before meningitis onset. Ventriculitis is a nonspecific term and can occur from intraventricular hemorrhage. Long term outcome data were inconsistently available and not collected by a standardized method. We did not record the age of the child at the time of the most recent

follow-up. Some sequelae will be a result of premature birth. The data are not population-based and the strength of the study is data collected from 7 widely dispersed Canadian centers uniform definitions.

CONCLUSIONS

It appears there have been no major shifts in the bacteria that cause meningitis in the first 90 days of life in Canada. Appropriate empirical antibiotics for early-onset and/or community-acquired suspected meningitis include ampicillin (for at least the first month) and a third-generation cephalosporin. However, especially if the birth hospitalization was complicated, a carbapenem may be a better option than the cephalosporin if the CSF Gram-stain or the blood culture are suggestive of Gram-negative meningitis.

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ABBREVIATIONS

CSF: cerebrospinal fluid
GA: gestational age
GBS: group B *Streptococcus*
Hib: *Haemophilus influenzae* type b
IQR: interquartile range
RBC: red blood cell
WBC: white blood cell

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