Original article

Late and very late onset group B *Streptococcus* sepsis: one and the same?

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Background: **This study aimed to describe the clinical characteristics of group B *Streptococcus* (GBS) sepsis in infants aged 4-90 days [late onset (LO)] compared to infants >90 days of age [very late onset (VLO)].**

Methods: **Microbiology records at Children's Medical Center Dallas were screened. Demographic, clinical, and outcome data were collected for infants with GBS recovered from blood or cerebrospinal fluid culture from January 1, 2006 to July 1, 2012.**

Results: **Totally 48 infants were identified (42 LO, 6 VLO). Infants with VLO sepsis had lower median gestational age (28.5 *vs.* 39 weeks gestation, *P*<0.001) and longer median nursery admissions (8.8 *vs.* 0.5 weeks, *P*=0.004). When gestational age was controlled for, there were no differences in clinical presentation, intensive care unit admission, length of stay, neurodevelopmental outcome, and mortality. Infants with VLO sepsis were more likely to receive vancomycin (83% vs. 33%, *P*=0.02) or third-generation cephalosporins (83% vs. 24%, *P*=0.009), and more likely to continue on those agents even after GBS was identified.**

Conclusions: **Infants with VLO sepsis had lower gestational ages and longer nursery stays than infants with LO sepsis. Beyond age at presentation, there were no significant differences in clinical presentations, hospital course, frequency of neurodevelopmental sequelae, and mortality in infants presenting with LO vs. VLO GBS sepsis. Infants with VLO sepsis were more likely to receive empiric broad spectrum antimicrobials and more likely to continue receiving broad therapy even following GBS identification.**

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Introduction

Group B *Streptococcus* (GBS) remains the leading cause of sepsis in early infancy.[1] Universal screening for maternal carriage of GBS and intrapartum antibiotic prophylaxis (IAP) has reduced the incidence of early onset disease, defined as infection in the first three days of life, to ~0.3/1000 live births.[2] IAP, however, has not impacted the frequency of late onset (LO) or very late onset (VLO) GBS sepsis, resulting in an increased proportion of late presentations among GBS infections in infancy.[3] VLO disease is particularly challenging clinically since, by definition, it occurs in older infants, and the infectious etiologies and the clinical management of these infants change beyond the neonatal period. The pathogenesis of LO GBS sepsis is not well understood.[4] Whether or not LO and VLO GBS sepsis are distinct processes is unclear, and the clinical presentations of VLO GBS sepsis have not been well described. We reported our experience with infants with LO or VLO GBS sepsis at our institution, and compared demographic, clinical, and outcome data between the two groups.

Methods

This was a retrospective study conducted at Children's Medical Center Dallas (CMCD) of children aged <6 months who were cared for as inpatients and had GBS recovered from at least one blood or cerebrospinal fluid (CSF) culture. Study patients were identified by screening the CMCD microbiology laboratory records from January 1, 2006 through July 1, 2012. These records were then cross-referenced against discharge ICD-9 codes for GBS sepsis (038.0, 320.2, 041.0, and 771.81) in an attempt to capture all eligible infants. The institutional review board approved this study.

All infants with GBS obtained from one or more

blood or CSF culture were identified, and their medical records were reviewed for pertinent demographic, clinical, and outcome data. Clinical signs and symptoms, vital signs, and laboratory values from the time of admission were recorded. Imaging studies, microbiologic results, and antibiotic therapy prescribed were collected for the duration of hospitalization. Neurodevelopmental sequelae were defined as mental retardation, cerebral palsy, epilepsy, blindness, or deafness.[5] These outcomes were assessed at the time of discharge and at available follow-up visits within one year, if present.

LO GBS sepsis was defined as a recovery of GBS from a blood or CSF culture between 4 and 90 days of age, with VLO GBS sepsis defined as a recovery of GBS from blood or CSF beyond 90 days of age.[4] A focus of infection was defined as a recovery of GBS from a normally sterile site (i.e. CSF, peritoneal fluid, or bone); infants with clinical signs of sepsis with GBS isolated only from blood culture were defined as having isolated sepsis.

Descriptive analyses were performed using frequency distributions and rates. Medians and interquartile ranges were used to summarize patient demographics and clinical characteristics. LO and VLO groups were compared using the Mann-Whitney *U* test for continuous variables or Fisher's exact test for categorical variables where appropriate. SigmaPlot 11.0 (Systat Software Inc., Chicago, IL, 2008) was used to analyze the data; two-sided statistical tests were conducted with $P<0.05$ considered significant.

Results

From January 1, 2006 to July 1, 2012, 48 infants with LO (n=42, 87.5%) or VLO (n=6, 12.5%) GBS sepsis were admitted to CMCD. No differences were seen in gender or race proportions between infants with LO and VLO sepsis (Table 1). Blood, urine, and CSF cultures were obtained from all infants. One infant with LO sepsis also had GBS identified from a bone aspirate; one infant with VLO GBS sepsis had GBS identified from peritoneal fluid. By definition, infants with VLO GBS sepsis were older at presentation (102 *vs.* 32 days, $P<0.001$). Additionally, infants with VLO GBS had significantly lower median gestational age at birth (28.5 *vs.* 39 weeks, $P=0.006$.). The frequency of GBS infection decreased with increasing age (Fig. 1). When absolute gestational age was controlled by using adjusted gestational age (gestational age at birth plus age in weeks), no significant differences in age at presentation were seen between the LO and VLO groups (41 *vs.* 45 weeks adjusted, $P=0.16$, Fig. 2).

Table 1. Demographics and maternal characteristics at presentation for infants with late-onset group B *Streptococcus* (GBS) sepsis compared with infants with very-late onset GBS sepsis

Parameters	Late onset (n=42)	Very late onset (n=6)	P value
Gender, male (%)	45	60	0.65
Race (%)			
White	26	33	
Black	31	33	
Hispanic	38	33	0.99
Other	5	0	
Age, d (median, IQR)	32 (13-56)	102 (95-110)	<0.001
Preterm birth (%)	29	83	0.017
Gestational age, wk (median, IQR)	39 (35-40)	28.5 (27-31)	0.006
Vaginal delivery (%)	62	33	0.22
Maternal age, y (median, IQR)	24 (20-28)	30.5 (23-32)	0.62
Maternal parity (median, IQR)	1 (1-2)	2 (1-3)	0.37
Maternal GBS colonization (%)			
Positive	5	17	
Negative	14	17	0.68
Unknown	81	66	
Feeding (%)			
Breastfeeding	10	17	
Formula feeding	67	83	0.89
Mixed	23	0	
Duration of nursery stay, wk (median, IQR)	0.5 (0.5-1)	8.8 (0.5-11)	0.007

IQR: interquartile range.

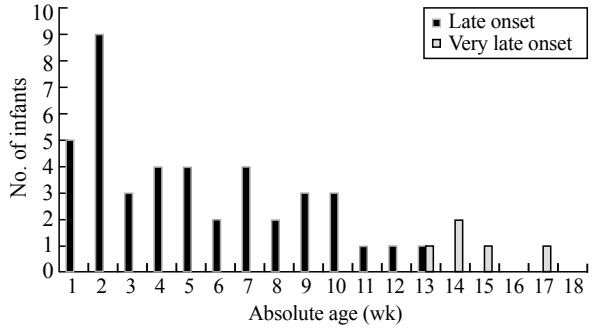

Fig. 1. Cases of group B *Streptococcus* sepsis by absolute age.

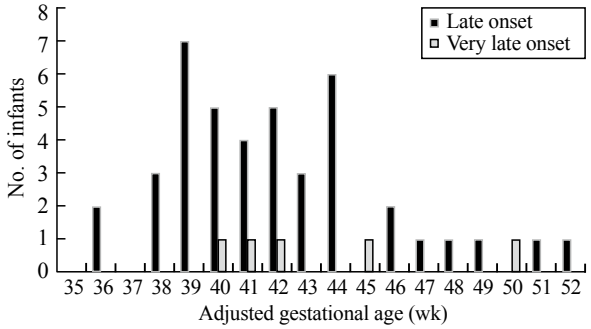

Fig. 2. Cases of group B *Streptococcus* sepsis by adjusted gestational age.

Infants with VLO GBS sepsis had significantly longer median nursery admissions than those with LO GBS (8.8 vs. 0.5 weeks, *P*=0.004, Table 1). The majority of GBS infections (70%) occurred within four weeks of nursery discharge, and no difference in median time from discharge to infection was seen between the LO and VLO groups (*P*=0.96). The birth and maternal characteristics between the two groups were also similar, including frequency of vaginal delivery, maternal age, maternal parity, and maternal GBS colonization (Table 1). No significant difference in breastfeeding was seen between the two groups.

The clinical characteristics of infants presenting with LO and VLO sepsis were similar. No significant differences were found in vital signs, clinical signs of sepsis, and hematologic markers of sepsis (white blood cell count, immature-to-total neutrophil ratio, or acute-phase reactants, Table 2). The hospital courses of infants with LO and VLO GBS sepsis were similar. Site of infection, need for fluid resuscitation, frequency of intubation, frequency of supplemental oxygen, and frequency of consultation with an infectious disease specialist were similar between the two groups (Table 3). Length of hospital stay, including the length of intensive care, was similar between infants with VLO and LO sepsis. Infants with VLO sepsis were significantly more likely to receive empiric antimicrobial therapy that included vancomycin (83% *vs.* 33%, *P*=0.02) or third-generation cephalosporins (83% *vs.* 24%, *P*=0.009) than those with LO sepsis. After GBS was definitively identified in culture, infants in the VLO group were significantly more likely than those in the LO group to continuously receive vancomycin (60% *vs.* 0%, *P*=0.01) or third-generation cephalosporins (100% *vs.* 40%, *P*=0.04).

Adverse neurodevelopmental sequelae occurred with similar frequency between the LO and VLO groups (26% *vs.* 33%, *P*=0.66). There were two deaths in the LO group and none in the VLO group (5% *vs.* 0%, *P*=0.99, Table 3).

Discussion

The results of the study indicate that when prematurity is controlled, demographic, birth and maternal characteristics, clinical presentation, hospital course,

Table 2. Clinical presentations of the infants with late-onset and very late-onset group B *Streptococcus* (GBS) sepsis

Parameters	Late onset (*n*=42)	Very late onset (*n*=6)	*P* value
Duration of illness, d (median, IQR)	1 (1-1)	1 (1-1)	0.91
Appearance (%)			
Well	60	50	0.99
Ill	40	50	
Vital signs (median, IQR)			
Home temperature, ℃	38.3 (37-38.8)	38.8 (38.6-39)	0.51
Admission temperature, ℃	38.8 (37-38.7)	38.0 (37.9-39.6)	0.62
Heart rate, bpm	180 (148-186)	171 (151-189)	0.75
Respiratory rate, bpm	42 (38-53)	38 (29-45)	0.34
Systolic blood pressure, mmHg	91 (85-97)	100 (91-107)	0.67
Clinical signs (%)			
Apnea	24	17	0.99
Seizures	21	0	0.58
Irritability	57	50	0.99
Lethargy	42	50	0.99
Vomiting	12	33	0.21
Decreased oral intake	69	83	0.66
Tachypnea	36	17	0.65
Grunting	21	17	0.99
Cough or rhinorrhea	26	17	0.99
Bulging fontanelle	14	17	0.99
Hematology (median, IQR)			
WBC count ($\times 10^3$ μL)	6.2 (3.8-15.4)	4.5 (3.2-12.9)	0.21
Immature-to-total WBC ratio	26% (14-40%)	38% (16-45%)	0.34
Acute phase reactants (median, IQR)*			
C-reactive protein (mg/dL)	11.9 (6.1-18.6)	8.0 (4.5-16.1)	0.32
Erythrocyte sedimentation rate (mm/h)	36 (12-55)	32 (12-50)	0.71

IQR: interquartile range; WBC: white blood cell. *: *n*=31 for late onset; 5 for very late onset.

Table 3. Hospital course and outcomes for infants with late onset group B *Streptococcus* (GBS) sepsis compared with infants with very late onset GBS sepsis

Parameters	Late onset (*n*=42)	Very late onset (*n*=6)	*P* value
GBS identified from (%)			
Blood	88	83	0.57
Cerebrospinal fluid	55	67	0.67
Urine	12	17	0.57
Clinical diseases (%)			
Isolated sepsis	43	33	0.99
Sepsis with focus	57	67	0.99
Meningitis	55	67	0.99
Osteomyelitis	2	0	0.99
Peritonitis	0	17	0.13
Neurologic imaging findings*			
Normal	16	33	0.87
Cerebritis	21	33	
Meningeal enhancement	21	33	
Hydrocephalus	16	0	
Infarction	42	67	
Empyema	37	33	
Fluid bolus on admission (%)	71	83	0.99
Volume, mL/kg (median, IQR)	20 (0-50)	50 (0-65)	0.83
Intubated (%)	33	33	0.99
Duration, d (median, IQR)	5 (2-8)	6 (6-6)	0.78
Supplemental oxygen, d (median, IQR)	0 (0-3)	1 (0-9)	0.82
Infectious diseases consult (%)	62	83	0.40
Intensive care duration, d (median, IQR)	2 (0-7)	1 (0-7)	0.91
Total length of stay, d (median, IQR)	14 (10-21)	14 (8-23)	0.95
Neurodevelopmental sequelae (%)†	26	33	0.66
Died (%)	5	0	0.99

IQR: interquartile range. *: *n*=19, late onset and *n*=3, very late onset; †: defined as mental retardation, cerebral palsy, epilepsy, blindness, or deafness.

and outcomes between infants with LO and VLO sepsis are similar. This suggests that LO and VLO GBS sepsis represent the same pathogenic process in infants, regardless of time of onset. Prematurity is a well-established risk factor for LO GBS infection. A 6-year review of LO GBS meningitis in France showed that infants with VLO disease had a higher frequency of prematurity (45% *vs.* 21%) and a greater magnitude of prematurity (32% vs. 7% less than 32 weeks gestation).[6] In addition, studies have shown the similarities between GBS serotypes causing LO and VLO disease.[6,7] To our knowledge, this study was the first to compare clinical presentation in a large cohort and supports the hypothesis that VLO GBS sepsis represents the same pathophysiology as LO GBS sepsis, but occurs in infants born more prematurely.

The majority of infections in the study cohort (70%) occurred within four weeks of discharge from the nursery. The serotypes of GBS causing LO sepsis in infants are highly correlated with the colonizing serotype in their mothers, suggesting horizontal transmission.[6] In our cohort, the distribution of GBS sepsis normalized when gestational age was controlled, with a median of 42 weeks post-menstrual age. The median time from nursery discharge to presentation with GBS sepsis, or the time spent at home, was two weeks in the LO and VLO sepsis groups.

Selection of empiric antibiotic therapy was significantly different between infants with LO GBS sepsis and those with VLO GBS sepsis in the study. Infants with VLO sepsis received a higher proportion of empiric vancomycin or third-generation cephalosporins, and were more likely to continue on these agents even after GBS was identified from culture. Empiric therapy for infants outside of the neonatal period often includes third-generation cephalosporins and vancomycin, which are appropriate choices given concerns for penicillin-resistant *Streptococcus pneumoniae* strains.[8] However, once *S. agalactiae* is definitively identified in culture, third-generation cephalosporins and vancomycin are unnecessarily broad for GBS infection. Additionally, *in vitro* evidence suggests that combination therapy with ampicillin and an aminoglycoside synergistically enhances bacterial clearance relative to cephalosporins.[9] Therefore, when an infant has GBS identified definitively from culture, third-generation cephalosporins and vancomycin should be discontinued, and therapy should be completed with ampicillin and gentamicin. The study findings suggest antibiotic use following GBS identification in infants with VLO GBS sepsis can be optimized by appropriately narrowing antibacterial therapy.

Limitations of our study included those inherent to retrospective studies, including the possibility of an incompletely identified cohort, missing or contradictory information in the electronic medical record, and incomplete follow up. Our cohort was small (n=48), most likely due to the relative infrequency of LO GBS disease (~0.3 per 1000 live births),[1,4] and small differences may have been missed. Additionally, only six infants with VLO GBS sepsis were identified. Mortality was able to be assessed with certainty. A minority of the cohort did not have further visits to CMCD and neurodevelopmental outcome was only assessed at the time of discharge for those infants. A majority of the cohort was born to mothers with unknown GBS status, as the primary birth hospital did not routinely perform GBS screening due to universal maternal/infant chemoprophylaxis.[9,10]

Infants with VLO sepsis had a lower gestational age and a longer duration in the nursery than infants with LO sepsis. The demographics and maternal characteristics for the two groups were similar. When gestational age was controlled for, the clinical presentation, hospital course, neurodevelopmental sequelae, and mortality in infants with LO versus VLO GBS sepsis showed no differences. These findings suggest that VLO GBS sepsis represents the same pathophysiology as LO GBS sepsis, but occurs in infants born more prematurely. Additionally, infants with VLO sepsis were more likely to receive empiric broad spectrum antimicrobials and were more likely to continuously receive unnecessarily broad therapy even after GBS was confirmed in culture. In the short term, efforts to minimize LO and VLO GBS sepsis should focus on close attention to hand hygiene;[4] an effective GBS vaccine may provide long-term protection and is needed urgently.[11]

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