

The Many Faces of Late Onset Group B Streptococcus Infection

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Abstract

Overall early onset Group B Streptococcus (GBS) infection in the United States has decreased because of preventive protocols. However, late onset GBS remains fairly common disease and can be difficult to diagnose. This paper displays the wide range of presentations of late onset GBS and the possible dire ramifications of the disease.

Keywords: Group B streptococcus (GBS); Streptococcus agalactiae; Late onset disease; Sepsis; Bacteraemia; Osteomyelitis; Meningitis

Introduction

Group B streptococcus (*Streptococcus agalactiae*; GBS) disease continues to be a tremendous burden to high-income countries. Particularly worrisome is GBS sepsis, which is divided into three categories. Early onset disease caused by GBS (EOD-GBS) occurs during days 1-6 postpartum, late onset disease (LOD-GBS) occurs on days 7-89 postpartum and very-late-onset disease occurs beyond 3 months of life [1,2]. While great strides have been made in the prevention EOD-GBS resulting in significantly decreased rates, LOD has not benefited much from the prevention protocols for EOD-GBS. LOD-GBS rates remain at 0.3 to 0.4 per 1000 live births since 1990 despite changes in intrapartum antibiotic prophylaxis and decreases in early onset disease [3-5]. The lack of progress in the prevention of LOD-GBS is complicated by lack of certainty for not only the acquisition of LOD-GBS, but also the risk factors which predispose infants to LOD-GBS. This lack of progress is troubling, especially with the potential severity of the disease. In infants less than two months of age, GBS was found to be the culprit in 86.1% of all bacterial meningitis cases and up to 27% of LOD GBS sepsis cases have associated meningitis [2,4]. We report another intricacy in the problem: the wide range in presentation within the spectrum of LOD-GBS. All of these factors play a significant role in the diagnostic challenge presented by GBS disease.

Case 1

A 6-week-old African American female born at 39 weeks gestation by spontaneous vaginal delivery was seen in the emergency department (ED) with a two-hour history of crying, fussiness and feeling warm to touch. Temperature at home was 38°C and she was given acetaminophen before she was brought to the ED. There was a maternal history of GBS vaginal colonization, which was adequately treated with 3 doses of peripartum ampicillin. The pregnancy, labour and delivery were uncomplicated. Notably, this patient had been evaluated and empirically treated with ampicillin and cefotaxime for sepsis 2½ weeks earlier when she had presented with a fever. On examination, rectal temperature was 39.2°C, Blood Pressure (BP) 103/59 mm Hg, Pulse 175/min, respiratory rate 40/wmin and SpO2 on pulse oximetry was 100%. She was consolable and had a mild reticular diffuse erythematous rash. The rest of the physical examination was unremarkable. She again underwent a sepsis evaluation, including blood and urine cultures; a chest radiograph was normal. Patient was empirically started on acyclovir, ampicillin, and cefotaxime. A lumbar puncture (LP) was attempted but failed to produce cerebral spinal fluid (CSF). A repeat LP on day one of the hospital stay showed increased glucose of 83 mg/dL, and increased protein of 5360 mg/dL. The CSF specimen was not enough for any other CSF studies. The blood culture grew GBS 12 hours later. A blood culture repeated on day two of hospitalization was sterile. Cefotaxime was discontinued. She showed clinical improvement, and received a total of 14 days of treatment.

Case 2

An 8-week-old African American male infant who was born at 31 weeks gestation by spontaneous vaginal delivery presented to the ED with apnoea and bradycardia. Maternal history was significant for recurrent HSV with no active lesions and an unknown GBS status. His 5 weeklong neonatal ICU course was notable for hypothyroidism. On examination his temperature was 38.2°C, Pulse 214/min, BP 97/43 mm of Hg, respiratory rate 56/min and SpO2 by pulse oximetry was 100%; he was in

distress with pupils nonreactive and the left pupil dilated greater than right. There was also nasal flaring, intercostal retractions, bilateral coarse breath sounds, and abdominal tenderness, poor capillary refill of 3-5 seconds, copious white oropharyngeal secretions, and head bobbing.

He was emergently intubated and a sepsis evaluation was completed, including blood and urine cultures. His complete blood cell count on a peripheral smear demonstrated a white blood cell (WBC) count of 1,700/mm³ with haemoglobin 9.4 g/dL and haematocrit 28.4% (Table 1). An LP was attempted, but was unsuccessful. A non-contrast CT of the head and a chest X-ray were unremarkable. He was initially started empirically on intravenous ampicillin and cefotaxime and later gentamicin was added. Other laboratory tests including a complete metabolic panel, magnesium, phosphorous, TSH, T4 and T3, ammonia, levels of ethyl alcohol, acetaminophen, and salicylate, urinalysis, and an arterial blood gas were all unremarkable. A respiratory viral panel by PCR (testing for Influenza A and B, Parainfluenza, Adenovirus, RSV, Rhinovirus, Influenza H1N1, Human Metapneumovirus, H1, H3) was positive for rhinovirus. The blood culture grew GBS after 10 hours. On day one he began having subclinical seizures captured by EEG and he was started on levetiracetam. The LP was repeated successfully and the CSF culture also grew GBS. An HSV PCR on the CSF specimen was negative so acyclovir was discontinued.

Magnetic resonance imaging (MRI) of the brain was performed on day 2. T1-weighted coronal MRI image (Figure 1) after injection of intravenous gadolinium based contrast agent shows diffuse meningeal enhancement consistent with meningitis. Diffusion weighted Figures (Figure 2, Figure 3) of the brain showed multiple areas of restricted diffusion. Figure 2 shows restricted diffusion in bilateral subdural space (arrowheads) representing small empyema. Restricted diffusion was also noted in the left frontal lobe (Figure 3, arrow) due to cerebritis. Restricted diffusion was noted in the distribution of bilateral posterior circulation (Figure 2, Figure 3) suggestive of ischemic infarct from vasospasm of the arteries of the posterior circulation related to meningeal irritation. Ischemic infarcts involved bilateral thalami, bilateral posterior limb of internal capsule, and head of the right caudate nucleus, splenium of the corpus callosum, brainstem and bilateral hippocampi. The vasospasm was confirmed on magnetic resonance angiogram (MRA) on day 6 as described below.

Later, on the day 2, the patient began having decerebrate posturing. On day three he became hypotensive and seizures persisted. Repeat CSF analysis demonstrated WBCs 110 (uL), RBCs 785 (uL), neutrophils 52%, lymphocytes (L) 32%, monocytes 16%, protein 298 mg/dL, and glucose 298 mg/dL. On day 6, a brain MRI with and without intravenous contrast as well as MRA was performed. MRA (Figure 4) showed vasospasm of the terminal basilar artery (arrow) and bilateral P1 segment of the posterior cerebral arteries (arrowheads). Post-contrast MRI image (Figure 5) showed dural venous sinus thrombosis involving the superior sagittal sinus, left sigmoid sinus, left jugular bulb and bilateral transverse sinus (arrow). There was enhancement of ependymal lining of bilateral lateral ventricles consistent with ventriculitis (Figure 6, arrowheads).

Table 1: Initial Laboratory Findings.

	Case 1	Case 2	Case 3
CBC			
WBC (thou/mm ³)	9.5	1.7*	9.3
Hb (g/dL)	10.3*	9.4*	6.8*
Hct (g/dL)	30.5*	28.4*	22.2*
Plt (thou/mm ³)	402	392	clumped
Neut (%)	64.3*	10*	46*
Lymph (%)	28.2*	81*	34*
Band (%)	0	2	3
Blasts (%)	0	1	0
BMP/LFT's			
Na/K/Cl/HCO ₃ (mmol/L)	139/4.6/103/19*	138/4.5/105/19*	137/5.0/105/23
Glucose (mg/dL)	103	160*	73
BUN/Cr (mg/dL)	7/0.28*	14/0.21*	8/0.2*
ALT/AST/Alk Phos (U/L)	24/33/344	12/19/206	N/A
Bilirubin (T/I/D) (mg/dL)	0.2*/0.1*/0.1	1.2*/0.7/0.5*	N/A
TSH (uIU/mL)	N/A	4.07	N/A
T3/T4 (ng/mL)	N/A	1.1/1.0	N/A
Ammonia (umol/L)	N/A	53.3*	N/A
Albumin/Total Protein (g/dL)	3.9/5.9*	3.7*/5.4*	N/A
Mg/Ph (mg/dL)	N/A	2.2*/5.3	N/A
Arterial Blood Gas	N/A		N/A
pH		7.20*	
pCO ₂ (mmHg)		56*	
pO ₂ (mmHg)		69	
HCO ₃ (mmol/L)		23.5	
Base Excess (mmol/L)		-5.9	
O ₂ sat (%)		96*	
CSF			
RBC (/uL)	Failed Obtain	Failed Obtain	N/A
WBC (/uL)			
Protein (mg/dL)			
Glucose (mg/dL)			
Color			
CRP (mg/L)	N/A	N/A	33.2*

Urinalysis	Small Blood*	150* glucose (mg/dL)	N/A
Resp Viral Panel			
Influenza	N/A	N/A	Negative
Parainfluenza			Negative
RSV			Positive
H1N1			Negative
Hu Metapneu			Negative
* indicates abnormal value			

Axial (Figure 7) and coronal (Figure 8) post-contrast T1-weighted Figures showed patchy enhancement in the left frontal lobe, bilateral thalami, basal ganglia and brainstem. A small subdural haemorrhage was noted in the posterior fossa. Lovenox was initiated for the thrombosis. The patient developed scalp swelling most likely associated with subdural haemorrhage in the posterior fossa on day seven. Gentamicin was discontinued after seven days of treatment.

A follow-up MRI with and without contrast and magnetic resonance venography (MRV) on day 10, showed improvement of the thrombosis, and with haemorrhagic products in the subarachnoid space. Pre contrast T1-weighted Figure showed development of multifocal curvilinear hyper intense signal consistent with cortical laminar necrosis at the site of prior ischemia in the brainstem, thalami and basal ganglia (Figure 9, arrows). He was extubated on day 10 and gradually recovered. On day nineteen a repeat CSF culture was sterile and antibiotics were discontinued after completing 21 days of treatment. A repeat MRI with and without contrast and MRV was performed on day 23 which showed further improvement. The patient was discharged on day 26 after home nursing services were set up and the family received extensive training for his continued care.

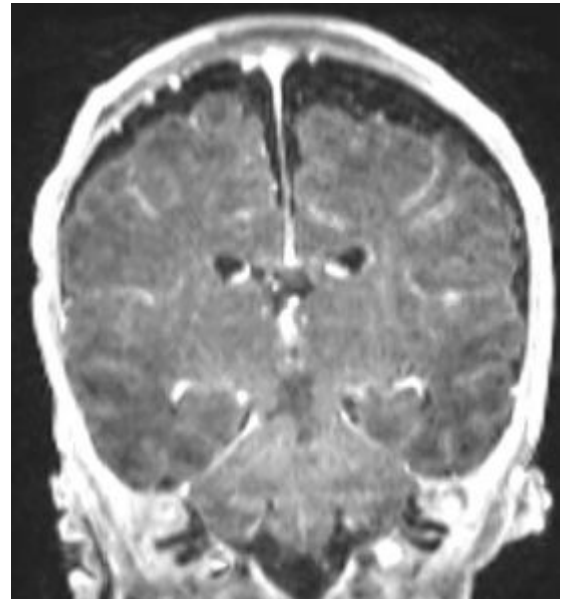


Figure 1: Post-contrast T1-weighted coronal MRI image shows bilateral diffuse meningeal enhancement.

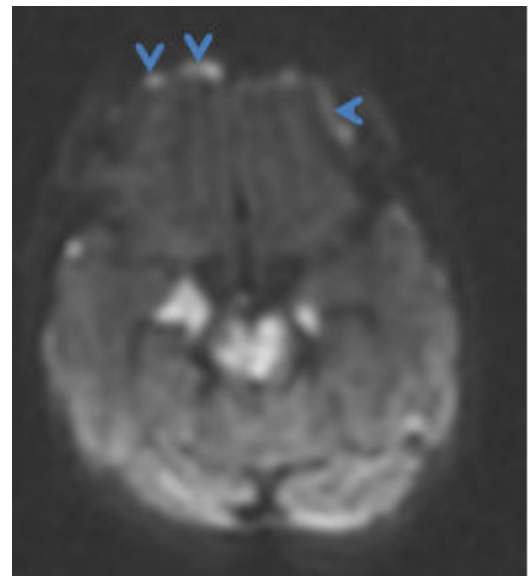


Figure 2: Diffusion weighted MRI image shows restricted diffusion in bilateral subdural space (arrowheads), bilateral medial temporal lobes including hippocampi and brainstem.

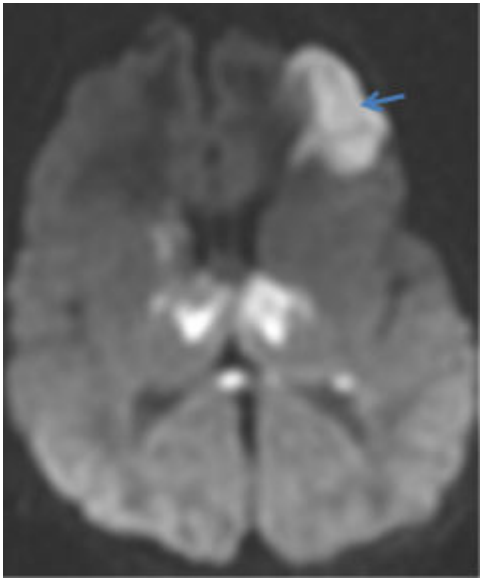


Figure 3: Diffusion weighted MRI image shows restricted diffusion in bilateral thalami, bilateral posterior limb of internal capsule, head of the right caudate nucleus, splenium of the corpus callosum and left frontal lobe.

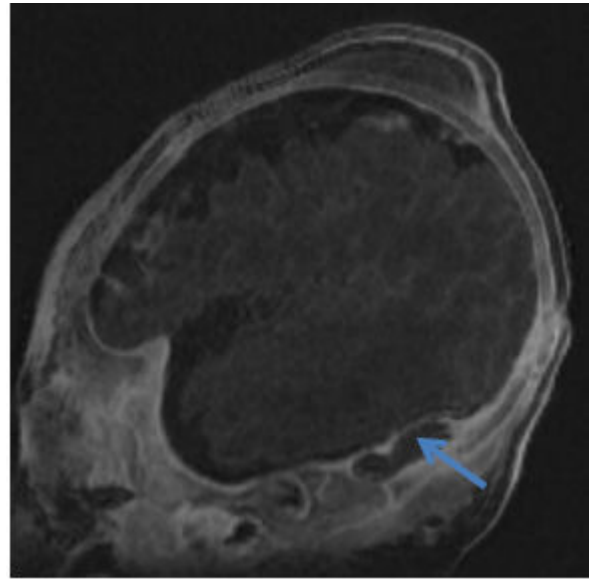


Figure 5: Post-contrast T1-weighted sagittal MRI image shows dural venous sinus thrombosis involving the left transverse sinus (arrow).

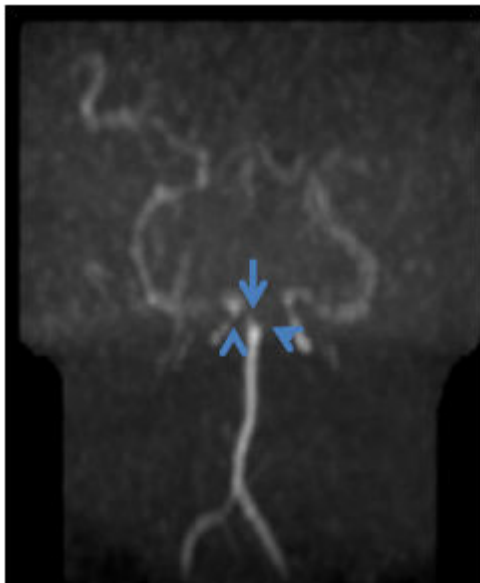


Figure 4: 3D rendered MRA image showed vasospasm of the terminal basilar artery (arrow) and bilateral P1 segment of the posterior cerebral arteries (arrowheads).

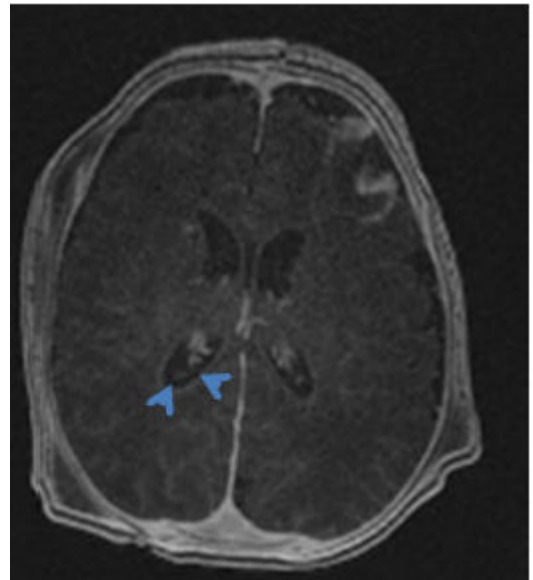


Figure 6: Post-contrast T1-weighted axial MRI image shows enhancement of ependymal lining (arrowheads) of bilateral lateral ventricles consistent with ventriculitis.

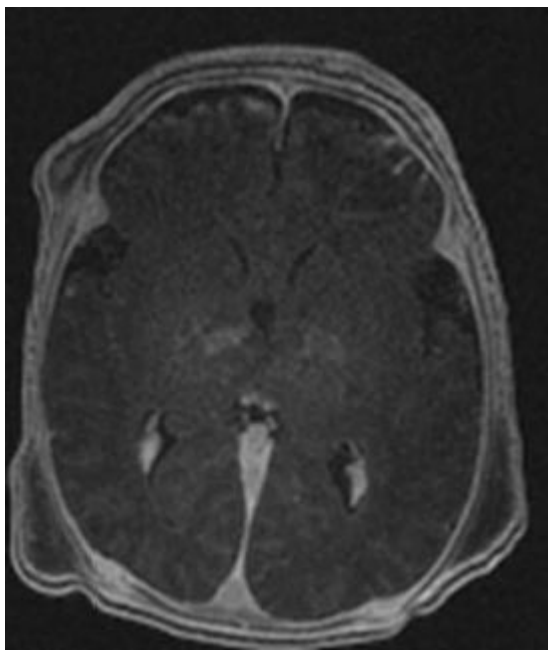


Figure 7: Post-contrast T1-weighted axial MRI image shows patchy enhancement in left frontal lobe, bilateral thalami and basal ganglia. Diffuse meningeal enhancement is noted bilaterally.

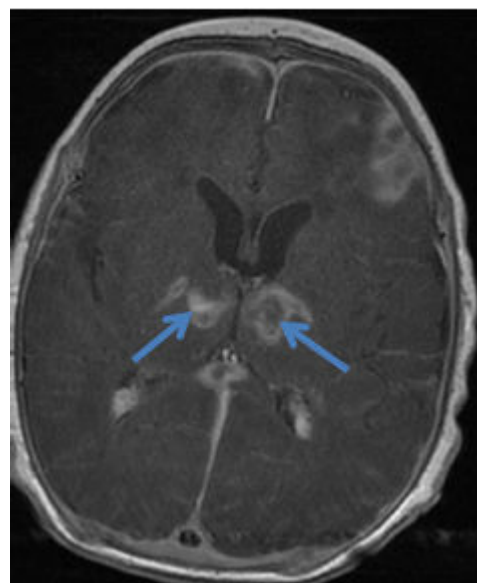


Figure 9: Precontrast T1-weighted axial MRI image shows multifocal curvilinear hyperintense signal consistent with cortical laminar necrosis at the site of prior ischemia in the brainstem, thalami and basal ganglia.

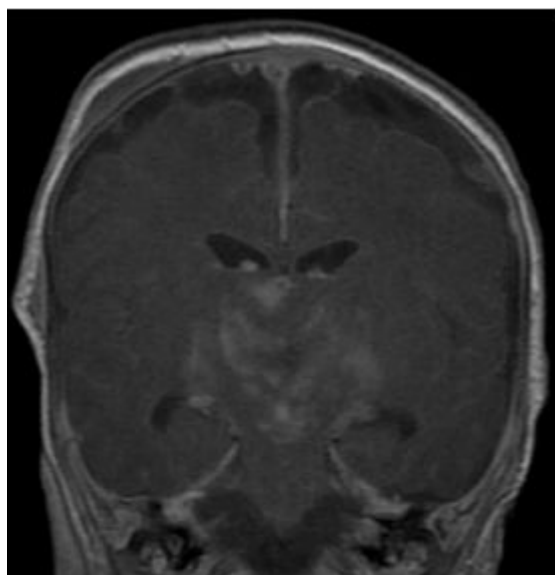


Figure 8: Post-contrast T1-weighted coronal MRI image shows patchy enhancement in bilateral thalami and basal ganglia. Diffuse meningeal enhancement is noted bilaterally.

Case 3

An 8-week old African American male born at 28 weeks gestation via normal spontaneous vaginal delivery presented to the ED with one day of swelling and redness of the right foot, with spreading throughout his leg. The pregnancy was complicated with unknown maternal GBS status, gonorrhoea/chlamydia positive, premature rupture of membranes for 17 days, and three doses of steroids. At birth, mother received clindamycin and gentamicin for preterm premature rupture of membranes, magnesium for neuroprotection, and vancomycin for GBS prophylaxis. During his seven-weeks in the NICU, he initially received Infasurf but then only required nasal cannula oxygen supplementation after that. He suffered a grade 1 intraventricular haemorrhage and did not have any additional complications. On physical exam, he was afebrile, with a BP 82/66 mm of Hg, pulse 147/min, respiratory rate 32/min, and SpO₂ by pulse oximetry of 99%. There were palpable peripheral distal pulses present bilaterally. Right hip/leg/foot edema and non-localizing tenderness to the right foot were present. A macular 0.5 cm area of non-circumferential erythema on right ankle, knee, and hip was also present. The remainder of the physical exam was unremarkable.

Radiographs of the foot, leg, and pelvis demonstrated only soft tissue swelling. Ultrasound examination of the same area also showed diffuse soft tissue edema as well, without indication of an abscess or effusion. A CBC showed haemoglobin 6.8 g/dL and haematocrit 28.4%. A C-reactive protein was 33.2 mg/dL (Table 2). A blood culture obtained in the ED grew GBS in less than 24 hours. He was started on vancomycin empirically and switched to high dose ampicillin once the culture results were known. CSF analysis demonstrated RBC 887, WBC 11, glucose 55

mg/dL, protein 79 mg/dL, a differential was never obtained. The CSF culture as well as the repeat blood culture was sterile. There was clinical improvement of the leg and he remained afebrile throughout the hospitalization. Repeat radiograph (Figure 10) of the femur performed on day six showed periosteal reaction (arrowheads) along medial and lateral aspect of the shaft of the femur. Proximal metaphysis showed osteopenia (open arrow).

Table 2: Patient past medical history.

Patient past medical history			
	Case 1	Case 2	Case 3
Race	African American	African American	African American
Sex	Female	Male	Male
Gestational Age	39	31	28
Delivery Type	SVD	SVD	SVD
Maternal GBS	Positive	Unknown	Expired Testing
Maternal GBS Antibiotic Prophylaxis	3 doses of Ampicillin	Not treated	Vancomycin
			Ceftriaxone
			Gentamicin
ROM	13 hours	2 hours	17 days
Infant Age at Presentation	6 weeks old	8 weeks old	8 weeks old
Prior history Neonatal Fever	Yes	No	No

MRI on day seven revealed osteomyelitis at the proximal femoral metaphysis, sagittal short-tau inversion recovery (STIR) sequence (Figure 11) shows hyperintense STIR signal (arrow) at proximal femoral metaphysis and small amount of fluid (arrow) in the right hip joint. Axial (Figure 12) and coronal (Figure 13) T1-weighted fat-suppressed Figures of the right femur after injection of intravenous gadolinium based contrast agent revealed enhancement in the proximal femoral metaphysis (open arrow), enhancement along the femoral shaft (arrowheads) and enhancement along the synovium (arrow) at right hip joint, These findings are consistent with osteomyelitis of the right proximal femur with synovitis. Repeated radiographs and ultrasounds of the right hip showed no demonstrable abscess amenable to drainage. On day 14, he was discharged to complete 6 weeks of treatment with once daily ceftriaxone via a peripherally inserted central catheter for GBS bacteraemia and osteomyelitis.



Figure 10: Radiograph of the femur shows periosteal reaction (arrowheads) along medial and lateral aspect of the shaft of the femur. Proximal metaphysis shows osteopenia (open arrow).

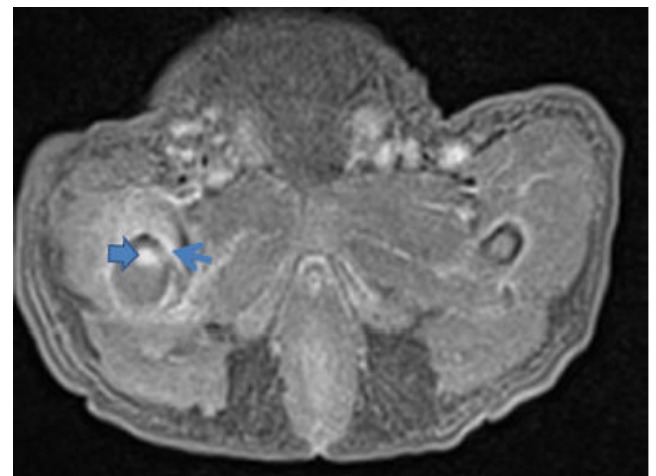


Figure 11: STIR MRI of the right femur in sagittal plane shows hyperintense signal (arrow) at proximal femoral metaphysis and small amount of fluid (arrow) in the right hip joint.

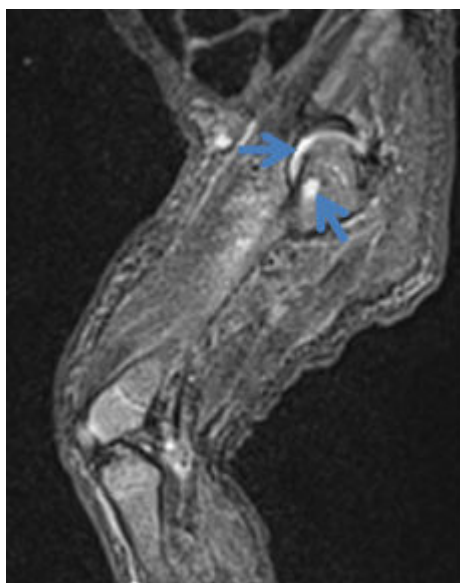


Figure 12: Post-contrast axial T1- weighted fat-suppressed MRI image shows enhancement in the proximal femoral metaphysis (open arrow), enhancement along the femoral shaft (arrowheads) and enhancement along the synovium (arrow) at right hip joint.

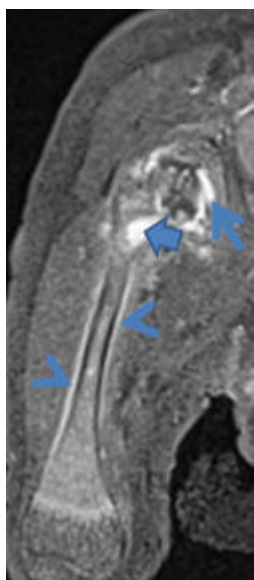


Figure 13: Post-contrast coronal T1- weighted fat-suppressed MRI image shows enhancement in the proximal femoral metaphysis (open arrow), enhancement along the femoral shaft (arrowheads) and enhancement along the synovium (arrow) at right hip joint.

Discussion

The three cases of late onset GBS diseases reported here illustrate the vast differences in presentation and severity of GBS sepsis. The first case shows the best-case scenario for a GBS

sepsis with a good outcome, while the third case shows an uncommon presentation of late onset GBS with osteomyelitis. Not only does osteomyelitis affect roughly only 0.2-1.6 out of 1,000 children annually, but Group B streptococcus is the but the third most prevalent bacteria found on culture in osteo-articular infections [6]. Our second case in particular shows a potential devastating outcome of late onset GBS disease.

GBS meningitis, a common complication of GBS sepsis, has a mortality rate described as high as 10% and permanent neurologic sequelae result in up to 25-35% of the meningitis survivors [7]. Research has shown that this seems to be partially due to hyper-virulence which has been associated with certain strains of GBS, including ones exhibiting ST-17 which is associated with causing meningitis, and HvgA, which seems to allow for greater migration across the intestinal barrier and the blood brain barrier [8]. Various new ideas of transmission and prevention are currently being investigated. There has been an identification of breast milk possibly being a risk factor for transmission of the disease [9]. While not perfect, tremendous advances have been made in the prevention of early onset GBS disease, with testing and prophylaxis, but the impact of this on late onset GBS disease if any has been very modest [10]. The ultimate prevention strategy for late onset GBS disease, and indeed early onset GBS disease, lies in the availability of an effective vaccine. While no GBS vaccine is currently available, attempts are being made to develop one. A GBS vaccine has been estimated to prevent over 85% of global group B streptococcus disease in infants younger than 3 months, affecting both early onset and LOD [11]. However, while the understanding of the transmission of late onset GBS is still being researched and the vaccine is currently in development, it is important for clinicians to be aware of the many different presentations of late onset GBS sepsis and the vastly different possible outcomes, dependent on proper identification and treatment. For the three cases reported here and despite the very different presentations, it is reassuring that two infants who were febrile would have been admitted by use of the Rochester Criteria for not being categorized as low risk infants, while the third case was admitted for concern of complications resulting from the infectious process and necessity of imaging. This also underscores the importance of good clinical evaluation.

Conclusion

As illustrated by these cases, late onset group B Streptococcal infection remains a serious disease that can present in many different ways and deserves aggressive management.

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