A 10 YEAR REVIEW OF GROUP B STREPTOCOCCAL INFECTION AMONG NEONATES ADMITTED TO HOSPITAL UNIVERSITI SAINS MALAYSIA

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ABBREVIATIONS

NICU	Neonatal Intensive Care Unit
Hospital USM	Hospital Universiti Sains Malaysia
GBS	Group B *Streptococcus*
CSF	Cerebrospinal fluids
EOD	Early onset disease
LOD	Late onset disease
HVS	High vaginal swab
IAP	Intrapartum antibiotic prophylaxis
PPROM	Preterm prelabour rupture of membranes
PROM	Prelabour rupture of membranes
PPHN	Persistent pulmonary hypertension of the newborn
AKI	Acute Kidney injury
CRP	C –Reactive Protein

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ABSTRAK (BAHASA MALAYSIA)

Kajian 10 Tahun Jangkitan Streptokokal Kumpulan B Dalam Kalangan Bayi Yang Dimasukkan Ke Hospital Universiti Sains Malaysia

Latar Belakang: Streptokokal Kumpulan B (GBS) adalah penyebab jangkitan yang penting yang menyebabkan mortaliti dan morbiditi yang signifikan di kalangan bayi. Jangkitan GBS adalah biasanya melalui jangkitan langsung melalui proses kelahiran vagina pada ibu yang di koloni kuman GBS. Antibiotik pencegahan semasa kelahiran yang berisiko menjadi intervensi utama dalam mengurangkan transmisi GBS kepada bayi. Kajian ini bertujuan untuk melihat jumlah dan ciri-ciri klinikal GBS pada bayi yang dimasukan ke Hospital USM.

Objektif: Mengkaji jangkitan awal dan lewat GBS dan faktor-faktor berkaitan bagi bayi yang dijangkiti GBS yang dimasukan ke unit rawatan rapi bayi di Hospital USM.

Metodologi: Satu kajian keratan rentas dan retrospektif terhadap rekod bayi-bayi yang dijangkiti Streptokokal Kumpulan B di antara Januari 2008 dan Disember 2017. Jangkitan awal GBS (EOD) didefinasikan sebagai jangkitan yang berlaku pada umur bayi dibawah 7 hari manakala jangkitan lewat GBS (LOD) berlaku pada umur bayi lebih dari 7 hari. Kes-kes positif dikenal pasti melalui makmal mikrobiologi Hospital USM mengunakan sistem WHONET. Rekod-rekod bayi dikesan mengunakan nama dan

nombor pendaftaran. Data-data berkaitan jumlah bayi EOD dan LOD, dan data klinikal bayi diambil daripada rekod dan di analisis melalui statistik deskriptif. Ujian "Chi-square" dan "Fisher exact" digunakan untuk menentukan perbezaan signifikan antara presentasi klinikal, keputusan darah dan jangka masa kemasukan ke wad bagi kumpulan bayi EOD dan LOD dijangkiti GBS. Nilai $p < 0.05$ di anggap sebagai nilai yang signifikan bagi kajian ini. Analisis statistik logistik regresi pelbagai digunakan untuk menentukan kaitan diantara faktor-faktor klinikal ibu dan bayi terhadap GBS di peringkat awal (EOD).

Keputusan: Sebanyak 123 rekod bayi di semak dan maklumat bayi diperoleh. Hasil kajian menunjukan sebanyak 111 (90.2%) kes jangkitan awal GBS dan 12 (9.8%) kes jangkitan lewat GBS. Umur bayi yang di masukkan adalah dalam lingkungan 1 hari sehingga 26 hari dengan purata umur adalah 2.76 hari. Majoriti kes bayi dijangkiti GBS disahkan melalui ujian air kencing menggunakan "GBS latex agglutination test " dengan jumlah 68(55.3%) bayi di ikuti kultur darah iaitu 24 (19.5%) bayi. Sejumlah besar bayi adalah lelaki iaitu 80 (65%) kes. Bilangan jumlah bangsa Melayu adalah 121 (98.4%) di dalam kajian ini. Berat majoriti bayi adalah di lingkungan 2.5kg sehingga 3.99 kg dengan jumlah 89 (72.4%) bayi dan gestasi bayi yang paling banyak adalah di antara 37 hingga 39 minggu. Majoriti bayi dilahirkan di hospital dan melalui kelahiran vagina. Sejumlah 67 (54.5%) ibu berumur di antara 21 hingga 30 tahun dengan majoriti adalah merupakan kandungan ke 2 hingga ke 5. Kebanyakkan bayi adalah berasal dari daerah Kota Bharu iaitu 44.7% dan seterusnya dari daerah Besut iaitu 14.6% dan daerah Bachok iaitu 13.8% kes. Daripada rekod bayi, hanya 13(10.6%) ibu di periksa untuk GBS melalui swab vagina dan dari jumlah tersebut hanya 7(5.7%) ibu mengandung yang positif untuk GBS. Antibiotik semasa kelahiran (IAP) sebagai pencegahan GBS hanya diterima oleh 4 ibu sahaja daripada 7 ibu yang positive GBS. Di

dalam kumpulan bayi dengan jangkitan GBS awal, ciri-ciri klinikal yang paling biasa berlaku ialah sepsis, di ikuti oleh jangkitan kuman paru-paru pada 31(27.9%) bayi dan kuning pada 21(18.9%) bayi. Walaubagaimanapun, adalah didapati pada kumpulan bayi dengan jangkitan lewat GBS , ciri-ciri klinikal paling biasa adalah kuning pada 5(41.7%) bayi dikuti oleh sepsis pada 4(33.3%) bayi dan demam pada 3 (25.0%) bayi. Sejumlah 61 (49.6%) bayi memerlukan bantuan pernafasan dan dari jumlah tersebut majoriti bayi memerlukan oksigen melalui prong nasal oksigen atau "headbox" oksigen. Parameter darah yang tidak normal hanya berlaku di jangkitan GBS awal dimana sel darah putih tinggi adalah ketidaknormalan yang paling kerap berlaku dengan jumlah 24 (21.6%) bayi. CRP hanya positif di dalam sejumlah kecil pesakit dengan jumlah keseluruhan 23 (18.7%) orang bayi. Jangka masa kemasukan ke hospital adalah di antara 1 hari hingga 122 hari dengan purata keseluruhan adalah 14.15 hari. Hanya satu rekod kematian di analisa di mana bayi tersebut adalah pramatang 24 minggu dan meninggal pada umur 19 jam. Kultur darah bayi tersebut positif kuman GBS. Melalui analisa statistik logistic regresi pelbagai dengan faktor-faktor ibu dan bayi terhadap kumpulan bayi dengan jangkitan awal GBS, telah didapati peningkatan umur ibu memberi perlindungan atau mengurangkan risiko untuk mendapat jangkitan awal GBS dengan nilai p 0.046.

Konklusi: Majoriti bayi dengan jangkitan GBS adalah dalam kumpulan jangkitan awal GBS. Bayi dengan jangkitan kuman GBS kebanyakannya disahkan dijangkiti melalui ujian air kencing "GBS latex agglutinations test". Ciri-ciri klinikal yang dikenal pasti sebagai paling biasa terjadi kepada bayi dengan jangkitan GBS adalah sepsis, jangkitan kuman paru-paru, kuning dan demam. Hampir separuh bayi yang masuk dengan jangkitan kuman GBS memerlukan bantuan pernafasan dan kemasukan ke hosptal lebih

daripada 7 hari. Adalah dikenal pasti peningkatan umur ibu mengandung memberi perlindungan kepada bayi di dalam kumpulan bayi dengan jangkitan awal GBS.

ABSTRACT (ENGLISH)

A 10 Year Review of Group B Streptococcal Infection Among Neonates Admitted to Hospital Universiti Sains Malaysia

Background: Group B *Streptococcal* **(**GBS) is a well-known cause of infections which causes significant morbidity and mortality in neonate. Neonates are primarily infected through vertical infections from a GBS colonized mothers. Intrapartum antibiotic prophylaxis during labour in a mother with risk has become the primary intervention in reducing the rate of transmission to neonates. This study aims to look at the numbers and clinical characteristic of early and late onset GBS infections in neonates with GBS admitted to Hospital USM.

Objectives: To study the early and late onset GBS infections and its associated factors among neonates admitted to HUSM between January 2008 and December 2017.

Methodology: A cross-sectional and retrospective record review study of neonates with Group B Streptococcal infection was conducted between January 2008 and December 2017. Early onset disease (EOD) was defined as GBS infection occurred in neonates aged within 7 days of life whilst late onset disease (LOD) occurred after 7 days of life. The positive cases of GBS were identified from the microbiology laboratory Hospital USM WHONET system database. The data on the proportions of neonates with GBS

infection, EOD and LOD, and clinical characteristic and outcome were analysed through descriptive statistical analysis. The Chi-square and Fisher exact test were used to determine whether there were a significant difference of clinical presentations, laboratory parameters and duration of hospital stays in EOD and LOD. A p value less than 0.05 was considered significant in this study. Multiple logistic regression analysis was used to determine the association between maternal and neonatal factors toward early onset neonatal GBS.

Results: A total number of 123 complete medical records review and data were retrieved. The findings show a total number of 111 (90.2%) neonates with early onset GBS infection and 12 (9.8%) neonates with late onset GBS infection. The age of neonates admitted ranging from day 1 to day 26 of life with a mean of 2.76 days. A majority of GBS cases were confirmed through urine GBS latex agglutination test with a total number of 68(55.3%) neonates and followed by blood culture with 24 (19.5%) neonates. 80 (65%) neonates were male neonates. Malay makes up 121 (98.4%) of the studied neonates. The neonatal weight 2.5 to 3.99 kg makes up majority of the cases with 89 (72.4%) neonates and most neonatal gestation ranging from 37 to 39 weeks with 63 (51.2%) neonates. A majority of the neonates delivered in the hospital and through vaginal delivery. A total of 67 (54.5%) mothers were between the ages of 21 to 30 years old with majority maternal parity of gravida 2 to gravida 5. Most cases were from district of Kota Bharu with 44.7% neonates followed by Besut 14.6% neonates and Bachok 13.8% neonates. From the record retrieved, only a total of 13(10.6%) mother screened for GBS via HVS and from that 7(5.7%) mother were positive for GBS. Intrapartum antibiotic prophylaxis (IAP) was only received by 4 (57.1%) mothers during delivery in those with positive GBS HVS screening. The most common clinical presentation in the early onset of GBS infection were sepsis, in 50 (45.0%) neonates

followed by pneumonia in 31(27.9%) neonates and jaundice in 21(18.9%) neonates. However in late onset GBS infection, jaundice was the most common clinical presentation in 5(41.7%) neonates, followed by sepsis in 4(33.3%) neonates and fever in 3 (25.0%) neonates. A total of 61 (49.6%) neonates required some form of respiratory support with most of them needing oxygen support via nasal prong oxygen or headbox oxygen. Abnormalities of blood parameters only occur in the early onset of GBS neonatal infection group with leucocytosis was the most common laboratory abnormalities with a total of 24 (21.6%) neonates. CRP was only positive in a small number of cases with total of 23 (18.7%) neonates. The mean duration of hospital stay range between 1 day to 122 days with a mean of 14.15 days. Only 1 death was recorded whereby the baby was premature at 24 weeks with blood culture positive for GBS. Baby passed away at 19 hours of life. Through multiple logistic regression with various maternal and neonatal factors affecting the early onset group, it was noted that mothers with an increase of 1 year of age has a 0.89 the odds or 11% reduced risk or protection to have babies with early onset GBS.

Conclusion: The majority of neonatal GBS infections were in the early onset of GBS group. The confirmation of GBS infection was mainly from urine GBS latex agglutinations test. The most common clinical presentation for early and late onset GBS infection were sepsis, pneumonia, jaundice and fever. Nearly half of the neonates with GBS infection require some form of respiratory support and hospital admissions more than 7 days. Increasing maternal age has become a protective factor in the early onset of GBS infection.

CHAPTER 1: INTRODUCTION

1.1 Introduction to GBS

Group B *Streptococcus* (GBS) also known as *Streptococcus agalactiae* is a gram positive aerobic diplococci organism which produces a zone of beta haemolysis on blood agar. GBS is a well-known cause of infections which causes significant morbidity and mortality in neonates. Neonatal GBS infection was highlighted in early 1970s causing neonatal sepsis and meningitis with a mortality rate reaching up to 55% prior to intrapartum antibiotic prophylaxis (IAP) era[1, 2]. The mortality rate however reduces to 5% as after the introduction of IAP [3]. The clinical presentations can be a spectrum from asymptomatic neonate to a neonate with full-blown GBS septicaemia. The source of infections is mainly vertical infections from mother to baby during delivery in which intrapartum prophylaxis plays major role in preventing and reducing the risk of GBS infections in neonates.

1.2 Epidemiology of Neonatal GBS Infection

Based on the global epidemiological studies done by K. Le Doare et al. in 2013, it showed that by early 1980s, GBS become the commonest cause of neonatal sepsis and meningitis in developed countries [4]. In light of these important findings, the medical community was made known on the recommendations and suggestions to further reduce

the risk of neonatal GBS infection by 1990s. This was a starting point between 1996 to 2001 when the American College of Obstetrician and Gynecologists (ACOG), the Centers for Disease Control (CDC) and the American Academy of Pediatrics (AAP) presented guidelines and recommendations for intrapartum antibiotic prophylaxis to prevent vertical transmission of GBS to the neonate.

The incidence of GBS infection may vary from one centre to another. Based on the Malaysia Neonatal Registry 2008, the overall incidence of confirmed bacterial infection was 10% (range of 3 -20%) and the primary organism were coagulase negative staphylococcus (CONS) followed by *Klebsiella* and Group B streptococcus (GBS) [5]. There was however no exact incidence of GBS infection provided in the registry.

Neonatal GBS infection was basically acquired vertically from GBS colonized mother during labour or delivery. In order to reduce the risk of transmission IAP was started in those with GBS evidenced in the mother either during the pregnancy or during the previous pregnancy (CDC 2010). Despite implementation of IAP all around the world, a Cochrane review in 2014 showed no reduction in the incidence of mortality but it reduced the rate of early onset disease of GBS infection [6]. The statement however comes with a caution of bias in view of the different in methodology of different studies. However, a recent meta-analysis done in Taiwan by Li et al. in early 2017 comprising 13 randomized clinical trials and 1 cohort study shows that IAP leads to reduction of GBS neonatal colonization and infection [7].

1.3 Clinical Presentation of GBS Infection

GBS infection presented as early onset disease (EOD) or late onset disease (LOD). The term of neonatal early onset disease (EOD) was used in infection occurring in neonates at day 7 of life or less and late onset disease (LOD) for those occurring

more than 7 days of life. The clinical presentations of GBS neonatal infection can be manifested till the age of 3 months old according McKenna et al [8]. It also stated that despite the high rate of vertical GBS (70%) only a minority of cases manifested the disease.

K. Le Doare et al (2013) and Pet Cools et al (2017) described that a majority of neonatal GBS infection presented in early onset group with the most common presentation are pneumonia and sepsis whilst those with late onset disease majority presented with meningitis [4, 9].

1.4 Risk Factors of GBS Infection

In the article by Mukhopadhyay et al (2012) describing the risk for EOD, the main factor identified was prematurity. Others were leaking liquor, maternal fever, any manipulation during labour including repeated vaginal examinations, invasive foetal monitoring and artificial rupture of membrane [10]. They also highlighted the presence of previous GBS positive pregnancy as one of the risks for EOD in which the reasons are the inability of host to mount the immune response and colonization with high virulence GBS.

1.5 Diagnosis of GBS

Apart from diagnosing GBS from culture positive specimen, urine GBS latex agglutination test was very helpful in determining the presence of GBS. The urine GBS latex agglutination test noted to have a sensitivity of 68.4% and specificity of 99.4% according to a study by Greenberg et al. In other reports, the sensitivity could be as low as 27 to 54% [11]. Despite the low sensitivity, GBS latex agglutination test remains a helpful modality in managing patients with suspected GBS infection.

CRP has become the important modalities in recent years of detecting infection and determining treatment duration in neonatal infection. CRP was an acute phase protein synthesized in the liver in response to inflammatory cytokines that triggered mainly by infections. It was very useful in indicating infections and guiding antibiotic therapy duration thus decrease antibiotic resistance rate and reduce duration of hospital stays. Benitz, W.E., et al states that in early onset sepsis a single CRP within 24 hours in onset of illness has a 93% sensitivity for "probable" sepsis whilst in late onset sepsis at 24-48 hours after the onset of infection has a sensitivity of 85% [12].It takes 6 to 12 hours, even up to 24 hours for CRP to rise following the onset of infection. Sensitivity of the test at presentation is only 40% [13].

1.6 Intrapartum Antibiotic Prophylaxis

Based on the global epidemiological study by K. Le Doare et al., since the year 2000 the estimated overall incidence is 0.53 to 0.67 in the European region and Americas respectively with 0.15 in Australasia [4]. It was noted that IAP was used more frequently in developed countries thus those that do not actively practice IAP noted to have 2.2 folds higher incidence of neonatal GBS infection. Looking around the Asean region, Al-Taiar A. et al. (2013) the observation of 4 neonatal care units in different countries noted that Malaysia have a higher GBS infection compared to China and Thailand with an incidence of 0.41 1000 live births[14].In another perspective, looking at Japan as a developed country in the Asean region, Matsubara et al. (2013) reported the incidence of less than 0.1 per 1000 live births [15]. Interestingly the incidence in Japan remains unchanged as despite the introduction of IAP, it was reported that there was a significant reduction in morbidity and mortality in both EOD and LOD GBS infection groups. The overall incidence of GBS ranged 0 – 3.06 per 1000 live births with the

reported EOD incidence of 0 –2.06 per 1000 live births [16].Although there was no exact figures of LOD found in Malaysia, the incidence of LOD were estimated at 0.1 in 1000 live births in a study done in Japan [17].

1.7 Complications of GBS Infection

The reported mortality associated with GBS infections varied between studies. According to a CDC the mortality reported, it was 0.55 per 100,000 populations. In a report from Japan the estimated mortality is 0.9–1.1 per 100 000 live births with the EOD death rate reported of 1.1 per 100 000 live births [15]. Besides the study conducted by Al-Taiar A. et al. (2013) on the Malaysia neonatal unit in Kuala Terengganu, there was no other major studies published through online publication on local neonatal GBS data. One article by Minhaj Azman A. et al. published in 1980 described the clinical characteristic of 6 neonates with GBS infections in Hospital Kuala Lumpur [18]. No local data available on Malaysian mothers' GBS colonization rate in relation to neonatal GBS infection and real incidence of neonatal GBS infection.

CHAPTER 2: OBJECTIVES

2.1 General Objectives

1. To study the early and late onset GBS infections and its associated factors among neonates admitted to HUSM between January 2008 and December 2017

2.2 Specific Objectives

1. To describe the proportions of early onset and late onset GBS infection among neonates in Hospital USM between January 2008 and December 2017.

2. To describe clinical characteristics and outcomes (the durations of hospital stay and mortality) among neonates with GBS infection in Hospital USM between January 2008 and December 2017.

3. To determine factors associated with early onset GBS infections in comparison to late onset GBS infection among neonates in Hospital USM between January 2008 and December 2017.

CHAPTER 3: METHODOLOGY

A cross sectional study and retrospective record review study were conducted in May 2018 on Group B Streptococcal infection among neonates admitted in neonatal unit Hospital USM between January 2008 and December 2017. The presence or evidence of GBS either in sterile samples (blood, urine and spinal fluid) and nonsterile samples (pus, endotracheal tube, swabs) and also positive urine GBS latex agglutination considered as GBS infection as neonates admitted to neonatal unit Hospital USM with signs and symptoms of infection are routinely screened for GBS.

The positive cases of GBS were identified from the microbiology laboratory Hospital USM WHONET system database. Using the names and registration number, patients' records were traced and the necessary data were collected. Subjects were excluded from the analysis if more than 30% of the data were incomplete.

Neonatal demographic data collected included age of presentation (days), gender, birth weight (kg), gestational weeks, place of delivery, the presence of foetal distress on CTG and delivery data (mode of delivery or any instrumentation). Maternal data collected were age, parity, presence of GBS on HVS screening, comorbidity of hypertension, diabetes mellitus, asthma, anaemia and obesity. Delivery data included IAP administration during delivery, fever, presence of chorioamnionitis and GBS UTI.

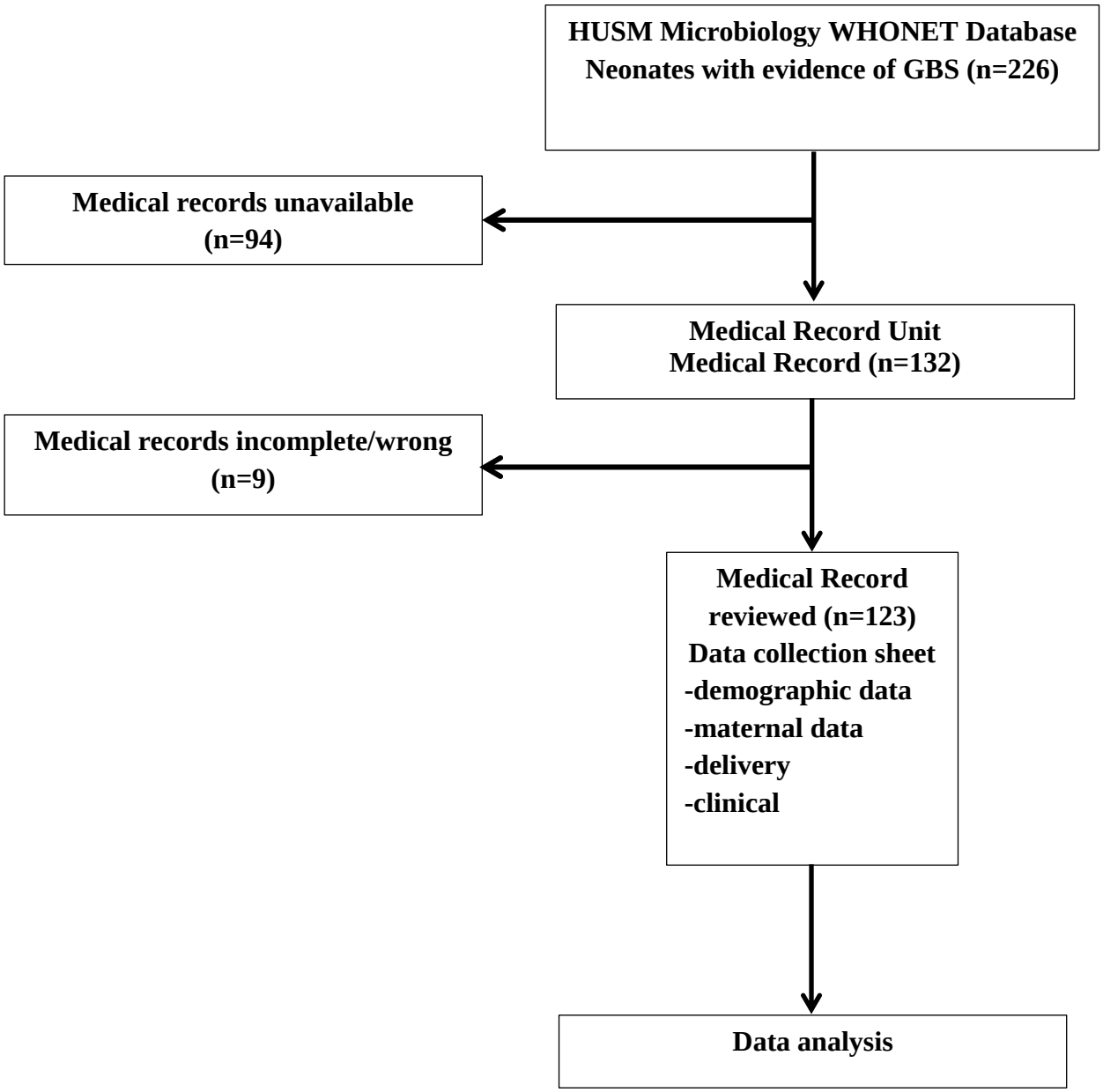
Post-delivery data collected were clinical features of neonates with GBS infection, duration of hospital stay and mortality (Refer appendix 8.3: data collection sheet).

From the data collected, cases were categorized into early onset disease (EOD) where GBS infection occurred in neonates aged within 7 days of life and late onset disease (LOD) where infection occurred after 7 days of life. The characteristics of neonates with EOD and LOD were analysed.

The data were entered and analysed using IBM SPSS version 24. Descriptive statistics were used to summarise the socio-demographic characteristics of neonates. Numerical data were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage).

Data on proportions of neonates with GBS infection, EOD and LOD, and clinical characteristic and outcome were analysed through descriptive statistical analysis. Chi-square and Fisher exact test were used to determine whether there is a significant difference of clinical presentations, laboratory parameters and duration of hospital stays in EOD and LOD. A p value less than 0.05 was considered significant. Multiple logistic regression analysis was used to determine the association between maternal and neonatal factors toward early onset neonatal GBS. The identified maternal and neonatal factors were run through simple logistic regression. Factors with significant values of $p < 0.25$ were then run through multiple logistic regression.

3.1 Study Flowchart



3.2 Sampling Method

Nonprobability convenient sampling was used in this study

3.3 Sample Size Estimation

Objective 1-2

No sample size calculations were needed

Objective 3

Using 2 proportions formula using PS software

Factors	α	(1-β)	*p0	p1	m	n	2n+10%	Ref
Neonatal fever	0.05	0.8	0.65	0.35	1	42	92	Hsiu et al, 2011
Pneumonia	0.05	0.8	0.1	0.3	1	62	136	Hsiu et al, 2011
Sepsis	0.05	0.8	0.68	0.38	1	42	92	Hsiu et al, 2011
UTI	0.05	0.8	0.48	0.78	1	39	86	K. Matsubara et al, 2013
Meningitis	0.05	0.8	0.52	0.22	1	39	86	K. Matsubara et al, 2013

3.4 Selection Criteria

Inclusion criteria: Neonatal GBS infection admitted to neonatal unit Hospital USM between January 2008 and December 2017.

Exclusion criteria: Incomplete medical record more than 30% of study variable (10 to 30% of incomplete variables will lead to bias in study outcome).

3.5 Operational Definitions

GBS infection	Positive findings of GBS either in blood, cerebrospinal fluid (CSF), urine, peritoneal or any other body secretions e.g. endotracheal tube (ETT) secretions and pus discharge. Serological investigations i.e. urine GBS antigen
Neonates	Baby age less than 28 days
Premature	Gestation of less than 37 completed weeks
Early onset disease/sepsis (EOD)	Presentation/ onset of symptoms less than 7 days of life
Late onset disease/sepsis (LOD)	Presentation/ onset of symptoms occur more than day 7 of life

GBS Pneumonia	Neonates presented with respiratory distress requiring respiratory support with positive GBS infection and abnormal chest roentgenogram (as determined by the managing clinician)
GBS Urinary Tract Infection (UTI)	Pure culture of GBS from urine sample obtained by bladder tap or sterile catheterization
GBS Meningitis	Positive GBS culture and/or positive latex particle agglutination test of a nontraumatic CSF; or positive gram-stained smear of CSF and/or significant pleocytosis in a nontraumatic CSF in the course of GBS infection with pathologic findings consistent with acute meningeal inflammation.
Maternal chorioamnionitis	Maternal fever, uterine tenderness, foul smelling vaginal discharge or amniotic fluid, maternal leucocytosis, maternal and or foetal tachycardia
High vaginal swab (HVS)	Vaginal swabs taken for microscopy and culture of pathogens
Intrapartum antibiotic prophylaxis (IAP)	Antibiotics given during labour to prevent or reduce the harm caused by group B streptococcal infection

Preterm prelabour rupture of membranes (PPROM)	Rupture of membranes that occur before labour starts in women who go on to give birth at less than 37 completed weeks of gestation
Prelabour rupture of membranes (PROM)	Rupture of membranes that occur before labour starts in women who go on to give birth at term gestation of more than 18 hours
Fever	Core body temperature greater than 38°C in infants younger than 28 days of life
Shock	Cardiovascular dysfunction requiring fluid resuscitation or inotropic support
Persistent pulmonary hypertension of the newborn (PPHN)	Pulmonary hypertension that causes hypoxemia with recorded saturation differences of greater than 5% to 10% or PaO2 differences of 10 to 20 mm Hg between right upper limb and lower limbs despite application of 100% oxygen in conjunction with mechanical ventilation and right-to-left or bidirectional shunt from the ductus arteriosus and/or foramen ovale revealed by an echocardiogram.
Acute kidney injury (AKI)	Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatitis	Alanine transaminase 2 times upper limit of normal for age7 or 50% increase over patient's baseline
Hyperbilirubinemia	Jaundice at which total serum bilirubin requiring intensive phototherapy or exchange transfusion as determine by Malaysia CPG guideline for neonatal jaundice
Urine GBS antigen test	Urinary latex test for detection of antigens from group B Streptococcus (GBS)

3.6 Problem Statement and Study Rationale

GBS is a common organism causing neonatal sepsis. Despite the introduction of IAP, GBS remain a significant cause of infection in newborns requiring admission to NICU and those who had complicated GBS infection required prolonged hospital stay and may end up with significant morbidities or mortalities. However, there is no such local data to support such statement. The presentations could vary from asymptomatic neonate to a full-blown sepsis with subsequent significant burden to NICU.

The results of this study can be compared with similar studies which were done in other centres in this country or other countries. The clinical characteristics of GBS infection can give a valuable insight on the spectrum of GBS infection presented to our neonatal unit. This study is helpful in further managing the neonates with GBS infection admitted to our neonatal unit in Hospital USM.

3.7 Research Questions

1. What are the numbers of GBS positive among neonates in Hospital USM?
2. What are the proportions of early and late GBS in Hospital USM?
3. What are the factors associated with early onset GBS in Hospital USM?

3.8 Ethical Approval

This study received ethical approval from the Research and Ethical committee, school of Medical Sciences, Universiti Sains Malaysia on 17th May 2018

USM/JEPeM/18030189

3.9 Research Tool

Proforma checklist (data collection sheet) was used in collecting data from medical record

CHAPTER 4: RESULTS

4.1 Numbers of Neonate with positive Group B Streptococcus

They were 226 babies with positive GBS admitted to our neonatal unit Hospital USM (Nilam 1, Nilam 2 and 1Timur Belakang) from January 2008 until December 2017. All 226 babies were analysed for distributions by year (Figure 1) and type of positive samples (Figure 2).

Only 123 medical records were able to be analysed for clinical characteristics and outcome. The rest of 103 medical records had more than 30% missing data hence excluded from further analysis.

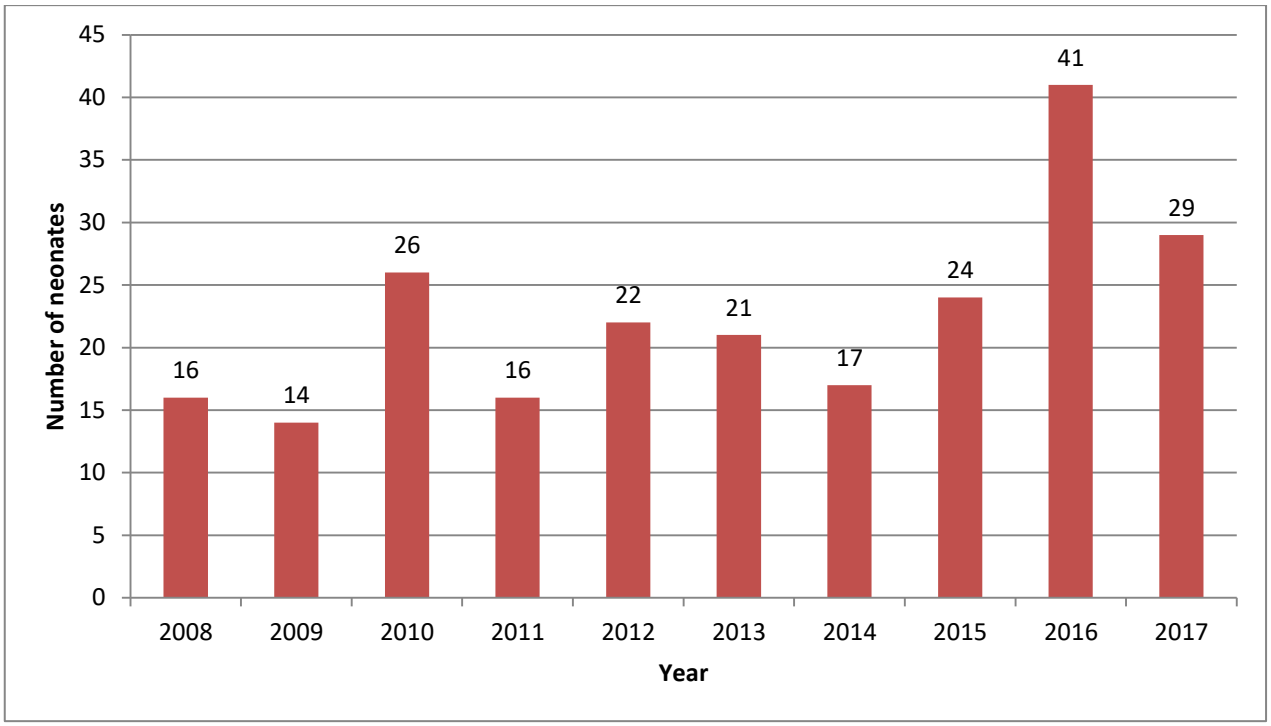


Figure 1: Neonatal GBS distribution by year from January 2008 till December 2017

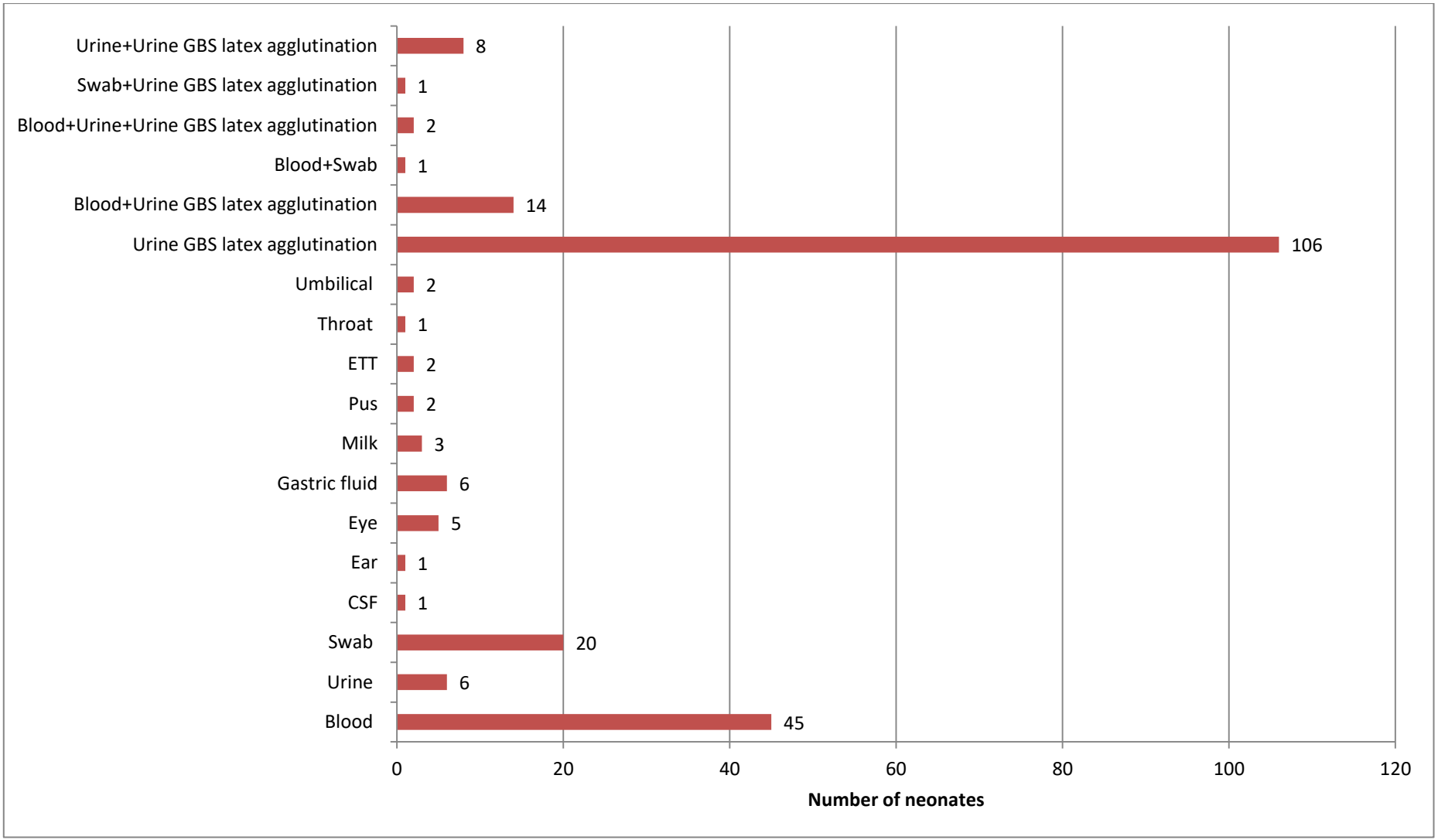


Figure 2: Neonatal GBS isolation through various cultures samples and Urine GBS Latex Agglutination Test

Figure 2 shows that majority of GBS detection is via urine GBS latex agglutination with 106 samples from 226 babies. A total of 26 babies having 2 and more positive culture of GBS from various samples.

4.2 Proportions of Early Onset and Late Onset GBS infection

For the subsequent result, data were analysed from 123 medical records that fulfilled the criteria.

Table 1: The numbers of neonate with positive GBS according to days of presentation

Onset of presentation (days)	Frequency	Percentage (%)
Early onset GBS	111	90.2
Late onset GBS	12	9.8
Total	123	100.0

Early onset GBS < 7 days
Late onset GBS > 7 days

Early onset GBS constitutes the majority of cases (90.2%) admitted to our neonatal unit as shown in Table 1. The age of neonates admitted ranging from day 1 to day 26 of life with mean age of 2.76 days as depicted in the histogram in Figure 3.

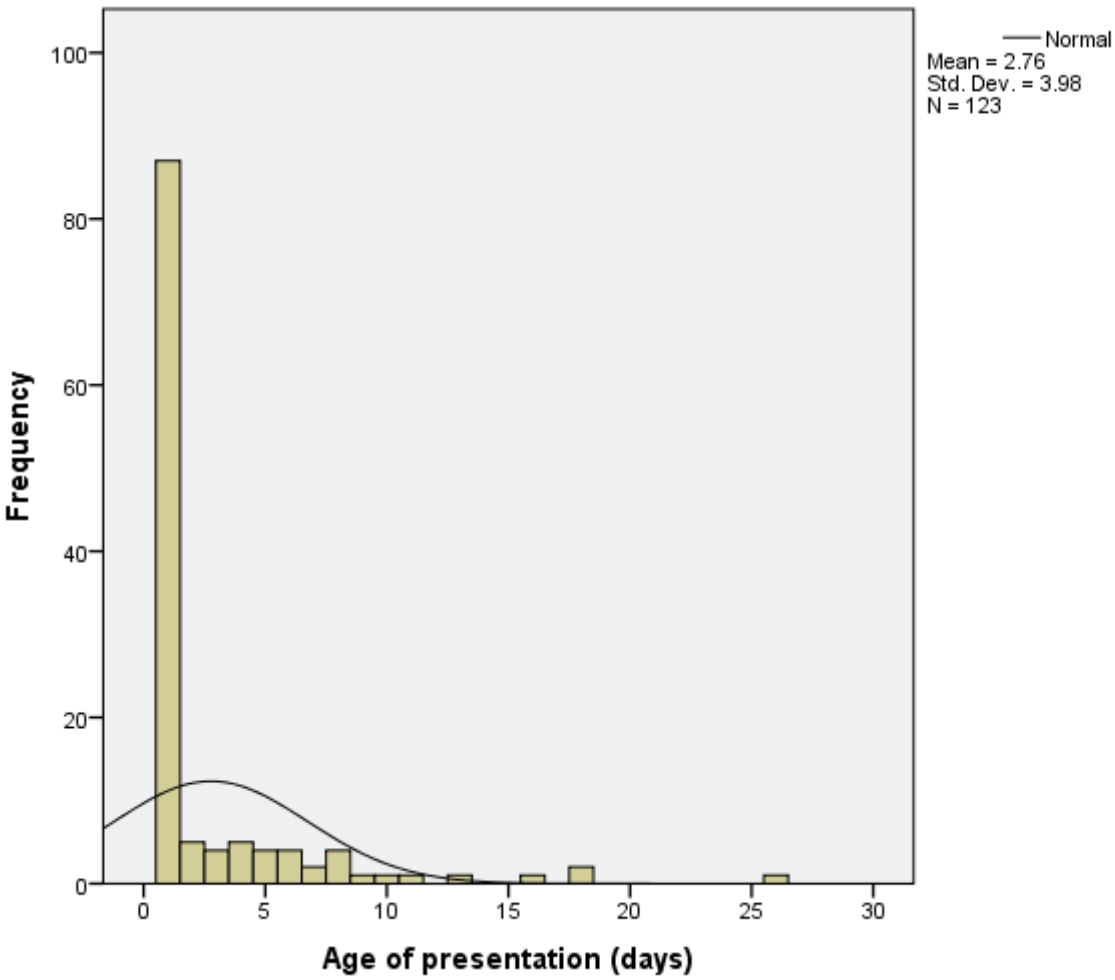


Figure 3: Histogram age of presentation distribution of neonates with GBS

Table 2 below shows the majority of GBS cases were confirmed through urine GBS antigen test with 55.3% followed by positive GBS in blood culture and umbilical swab culture.

Table 2: The confirmation of GBS infection in neonates admitted to Hospital USM

Confirmation of GBS infection	Frequency	Percentage (%)
Urine GBS antigen	68	55.3
Blood culture	24	19.5
Umbilicus swab culture	13	10.6
Urine culture	5	4.1
Skin swab culture	4	3.3
Eye swab	2	1.6
Gastric fluid culture	2	1.6
Milk (EBM) culture	2	1.6
Ear swab culture	1	0.8
CSF GBS latex agglutination	1	0.8
Peritoneal swab culture	1	0.8
Total	**123**	**100.0**

EBM culture =express breast milk culture
CSF=cerebrospinal fluid

4.3 Demographic Data of Neonates with GBS Infection

The demographic characteristic of neonates admitted with GBS infections were shown in Table 3. Majority of cases were male (65%). Malay ethnic made up 98.4% of the studied neonates. 25.2% of babies born at gestational age less than 36 weeks with low birth weight babies of 25%.

Majority were born between 37 to 39 period of amenorrhea (51.2%) with majority birth weight range 2.5 to 3.99 kg (72.4%). Majority of the neonates was delivered in the hospital and through vaginal delivery. In terms of maternal data, 54.5% between the age of 21 to 30 years old with majority maternal parity of G2 to G5.

Table 3: Demographic characteristic of neonates with GBS infection admitted to Hospital USM.

Demographic	Frequency	Percentage (%)
Gender		
Male	80	65.0
Female	43	35.0
Race		
Malay	121	98.4
Indian	1	0.8
Siamese	1	0.8
Birth weight in kilogram (mean 2.83)		
<1.00	3	2.4
1.00 - 1.49	7	5.7
1.50 - 1.99	6	4.9
2.0 - 2.49	14	11.4
2.5– 3.99	89	72.4
> 4.00	4	3.3
Gestational age in weeks (mean 37)		
< 28	3	2.4
28 - 32	9	7.3
33 – 36	19	15.4
37 - 39	63	51.2
>40	29	23.6
Delivery		
Place of delivery		
Hospital	119	96.7
Clinic	4	3.3
Mode of delivery		
Vaginal	93	75.6
Caesarean	30	24.4

Maternal Data		
Maternal age group (year) (mean 29.8)		
≤ 20	2	1.6
21 -30	67	54.5
31 -40	48	39.0
≥ 41	6	4.9
Maternal parity		
G1	49	39.8
G2 –G5	63	51.2
≥ G6	11	8.9
Comorbid		
Diabetes	25	20.3
HPT/PIH	9	7.3
Asthma	4	8.3
Anemia	18	14.6
Obesity	5	4.1
Risk factors		
Fever	10	8.1
Chorioamnionitis	5	4.1
UTI	9	7.3
PPROM/PROM	26	21.1

HPT=hypertension, PIH=pregnancy induced hypertension
UTI=urinary tract infection
PPROM=preterm prelabour rupture of membrane, PROM=prelabour rupture of membrane

In terms of origin of neonates based on the district of Kelantan and other places, majority of cases 44.7% were from Kota Bharu followed by Besut 14.6% and Bachok 13.8% as depicted in Table 4. There were 4 (3.3%) cases in which they were not originated from Kelantan.

Table 4: Distribution of GBS positive cases based on district

District	Frequency	Percentage (%)
Kota Bharu	55	44.7
Besut	18	14.6
Bachok	17	13.8
Pasir Puteh	15	12.2
Tanah Merah	4	3.3
Pasir Mas	3	2.4
Machang	3	2.4
Tumpat	2	1.6
Kuala Krai	1	.8
Gua Musang	1	.8
Others	4	3.3
Total	123	100.0

From the record retrieved, a total of 13 (10.6%) mother had indication for GBS screening via HVS and from that 7 were positive for GBS. Intrapartum antibiotic prophylaxis only received by 4 patients (57.1%) in those with positive GBS HVS screening. Further details were in Table 5.

Table 5: Maternal antenatal HVS screening for GBS

Results	Frequency	Percentage (%)
Done	13	10.6
Positive for GBS	7	5.7
Negative for GBS	6	4.9
Not done/Unknown	110	89.4
Total	123	100.0