



GUIDELINES AND AUDIT  
IMPLEMENTATION NETWORK

**Prevention of Early Onset Group  
B Streptococcal Disease –  
Northern Ireland Audit Report  
2013**

**FINAL REPORT**

**March 2013**

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## **Foreword**

This Audit was commissioned by the Chief Medical Officer following publicity about Group B Streptococcal (GBS) prevention in pregnancy and neonatal infection. It has been my privilege to chair the GAIN Working Group who were instructed to ascertain adherence to the 2003 Royal College of Obstetricians and Gynaecologists (RCOG) Guideline, establish the burden of this disease affecting newborns and stillborns and investigate differing approaches to prevention of the disease by health professionals in Northern Ireland. The members of the Working Group have given an enormous time commitment to this work for which I am most grateful. The keen involvement of medical, nursing, midwifery, administrative and information technology staff from all Health and Social Care Trusts and the Public Health Agency has been most impressive. I thank them most sincerely.

The purpose of the Report is to obtain a better understanding of the circumstances and the numbers of GBS infection in Northern Ireland and make recommendations. A draft summary of the audit findings was submitted to the UK National Screening Committee (NSC) to inform their review of screening for GBS in pregnancy which was issued for public consultation in July 2012. In December 2012 the NSC recommended no change to the policy. The present approach to prevention is risk based as recommended by the RCOG in 2003 and further endorsed with changes in 2012.

Recommendations focus on further raising of awareness of GBS disease amongst health professionals and pregnant women, better data collection processes, development of care pathways for mother and baby and an enhanced pathology service to provide improved diagnosis of infection. Finally, this most valuable process of examining our practice in Northern Ireland was greatly assisted by the families of infants affected by the disease. The questions asked and the stories told were potent drivers to seek answers.

**Robin G. Ashe MAO, FRCOG, DCH**  
**Consultant Obstetrician and Gynaecologist**

## **Executive Summary**

During the summer of 2011 in Northern Ireland there was considerable public interest in Group B Streptococcal Disease (GBS) prevention in pregnancy. Calls were made for a screening programme in pregnancy, as is the case in several countries and questions were asked about the number of babies who developed Early Onset GBS (EOGBS) or were stillborn as a result of GBS.

In September 2011 the Chief Medical Officer requested the Guidelines and Audit Implementation Network (GAIN) to undertake an audit of GBS in Northern Ireland to examine aspects of the disease from both the obstetric and neonatal perspective. The following four areas of practice were assessed:

- Adherence during 2009 - 2010 to the Royal College of Obstetrics and Gynaecology (RCOG) 2003 Green-top guideline on the Prevention of GBS disease in infants.
- Laboratory confirmed GBS in pregnant women and their outcomes from 2009 – 2010 in a single maternity unit in Northern Ireland which had an opportunistic testing programme for prevention of the disease.
- Number of infant infections, their outcomes and the obstetric history of the women from 2008 - 2010 inclusive.
- Number of stillbirths (no sign of life at delivery after 24 weeks gestation) where GBS was identified from 2009 - 2010 inclusive.

Although no centralised database existed, it was agreed that GAIN should examine information that may be available on anaphylaxis in pregnancy.

The purpose of the Audit was to obtain a better understanding of the circumstances and the numbers of GBS infection in Northern Ireland and make recommendations.

## **Key Findings**

### **Adherence to the 2003 Royal College of Obstetrics and Gynaecology (RCOG) Green-top Guideline on the Prevention of GBS Disease in infants from 2009 – 2010 inclusive**

The main audit standards were derived from the RCOG Green-top Guideline 2003. These were adopted by maternity units with minor variations. To assess the degree of adherence to these guidelines the audit focused on three risk factors for GBS disease.

A Northern Ireland wide population sample based on these three risk factors was assessed:

1. Pre-term labour at <37 weeks.
2. Prolonged rupture of membranes at >24 hours (RCOG risk factor is >18 hours; this information is not available using the Northern Ireland Maternity System - NIMATS).
3. Pyrexia > 38 degrees centigrade in labour.

All Trusts in Northern Ireland have a guideline for the prevention of GBS neonatal disease adapted from the RCOG 2003 Guideline. The recommendations of the latter on the use of intrapartum antibiotics to prevent neonatal GBS are non-directional. Additionally, differences exist between this Guideline and NICE guideline CG55 (*Intrapartum care: management and delivery of care to women in labour*) which add to the difficulties of decision making for the clinician in the case of a

complication of pregnancy. These have been resolved in the updated RCOG Green-top Guideline published in July 2012.

In women with one or more risk factor of GBS disease, at all gestations, antibiotics were administered in 42% of the sample population of 574. Further stratification of risks into gestational age and whether one or more risk factors were present at the onset of labour reveals a trend towards more antibiotic administration with an increase in risk. However, at best, observance of the guideline is estimated at 50%–70% for two or more risk factors, where numbers are sufficient to draw conclusions. This variable adherence by clinicians may reflect the non-directional guidance of the RCOG Guideline and concerns about maternal and infant risk of antibiotic administration in labour or missed opportunities for prophylaxis.

From the sample of 574 high risk women, two infants were delivered who had early onset neonatal GBS disease. Neither of the infants' mothers received intrapartum antibiotic prophylaxis. Both babies are alive and well.

The incidence of neonatal GBS disease in this high risk sample of pregnant women is 3.59/1000 live births or approximately 1 in every 280 women with risk factors.

### **Evaluation of an opportunistic GBS Testing Programme in one maternity unit 2009-2010**

This is a preliminary analysis of the contribution of an opportunistic testing programme for the prevention of GBS disease in the neonate during 2009 and 2010 undertaken within one maternity unit in Northern Ireland. The thrust of the prophylaxis guideline was focused on the administration of antibiotics to women with GBS positive vaginal culture with additional risk factors and their babies if they were skin culture positive. The focus was primarily on identifying risk factors that would indicate to paediatricians that a baby was more likely to have GBS than to identify risk factors which would indicate the mother should be offered IAP in labour. Despite such measures the incidence of disease within the Unit was 0.54 /1000 live births during these two years. This is similar to the published incidence of EOGBS for Northern Ireland in 2010 of 0.68/1000 live births and the incidence within this audit of 0.57/1000 live births. The outcome of this opportunistic testing for the prevention of neonatal GBS disease did not yield the expected reduction in incidence.

Much information is unavailable within this preliminary analysis to allow a more thorough evaluation of this opportunistic testing program. The authors recommend a broadening of this work, if feasible, to be published as a supplementary report.

### **Number of infant infections: their outcomes and the obstetric history of the women from 2008 - 2010 inclusive**

Neonatal infection was defined as a positive blood or cerebrospinal fluid (CSF) culture. EOGBS disease was defined as GBS infection within the first 7 days of life. A list of infants with positive blood or CSF cultures up to age 90 days was retrieved from laboratories in all 5 Trusts and the Public Health Agency for the calendar years of 2008 -2010.

The burden of EOGBS disease in the neonatal population of Northern Ireland in 2008 - 2010, is approximately 1 in 1750 live births. This incidence, 0.57/1000 live births, is marginally higher than other regions of UK as reported for 2010 (0.41/1000 live births) for England, Wales and Northern Ireland by the Health Protection Agency but less than the incidence for Northern Ireland in the British Paediatric Surveillance Unit (BPSU) survey of 2001, 0.73/1000 live births. This reduction in incidence may represent improvements in perinatal care following the publication of the RCOG Guideline 2003. The mortality and morbidity rates of 11.6% and 8.7% however, remain similar to the 10.6% and 7.9% mortality and morbidity rates reported by the BPSU survey group.

Almost 3/4 (32/43) of cases of EOGBS in this audit were born at term, defined as  $\geq 37^{+0}$  weeks gestation. In 56% (24/43) of women there was a recognised risk factor present during the pregnancy. Of those with a single risk factor 30.8% (4/13) received intrapartum antibiotic prophylaxis (IAP) for the prevention of EOGBS. In the 7 women with 2 risk factors, all 3 who delivered at term (42.9%), received IAP. None of the 4 women who delivered prematurely received intrapartum intravenous antibiotics. This may reflect the controversy regarding the use of antibiotics in preterm labour following revelations of adverse long term effects by the Oracle Trial team. In the 4 women with 3 risk factors, all were given antibiotics.

Five infants died with GBS infection. Two infants died for reasons other than EOGBS, one from complications of prematurity and the other due to an underlying lethal genetic condition. In neither case was intrapartum antibiotics used. The other 3 infants died directly of their sepsis despite intrapartum antibiotics being given to 2 of the 3 women. The mortality rate is in keeping with other studies in this area and is unchanged despite a falling incidence.

### **Number of stillbirths (no sign of life at delivery after 24 weeks gestation) where GBS was identified from 2009 – 2010 inclusive**

Five stillbirths during the calendar years of 2009 and 2010 were assessed as being due to Group B Streptococcal disease. The parameters used to conclude that GBS infection was the cause of death were a combination of fetal/placental histology, microbiological culture and clinical opinion. All presented at  $>35$  weeks gestation and all had acute chorioamnionitis on placental histology. One mother had a positive GBS vaginal swab result. As all had intrauterine deaths before labour without risk factors (other than one case with positive vaginal swab culture for GBS), antibiotic prophylaxis was not possible.

Not all stillborn babies or placentae undergo pathological examination. Within Northern Ireland 55% of stillbirths ( $\geq 24$  weeks) undergo this investigation as compared with 45% for England, Wales, N. Ireland and Crown Dependencies. 78% of placentae from stillborn infants are assessed within the England, Wales, N. Ireland and Crown Dependencies. In Northern Ireland, no regional placental pathology reporting service exists, although the Regional Paediatric Pathology Service recommends that the placentas of all babies who miscarry, are stillborn or who die in the neonatal period are referred to the service for specialist examination. This limited pathological assessment of stillbirths and placentas contributes to a possible underestimate of GBS disease.

The contribution of infection to the cause of stillbirths is 5.1% within the UK and 7.7% within Northern Ireland.

## **Anaphylaxis**

Five cases of severe antibiotic allergy have been diagnosed in pregnant women or immediately following delivery from January 2011 until October 2012 in Northern Ireland. All 5 mothers and their babies survived.

A sixth case which resulted in a maternal and infant death has also occurred in the recent past (2007) and was reported in the Confidential Enquiry into Maternal & Child Health (CEMACH) report 2006-2008.

The UK Obstetric Surveillance System (UKOSS) Annual Report 2012 has highlighted the increase in antibiotic prophylactic regimens in pregnancy (GBS and Caesarean Section) in addition to recent guideline changes on antibiotic timing. The limited data on incidence of anaphylaxis within the UK is recognised. Their study plan is to collect *'information about the incidence, management and outcomes of anaphylaxis in pregnancy in the UK'*. This study has been approved by the UKOSS Steering Committee to start in 2012/2013. The latter is timely.

The risk of anaphylactic reaction to antibiotics needs to be weighed against the potential benefits of intrapartum antibiotic prophylaxis in reducing early onset neonatal GBS.

## Recommendations

- Continue to raise the awareness of pregnant women and health professionals about GBS disease.
- Clinicians should be aware of the possible neonatal and maternal risks of antibiotic prophylaxis.
- Maternity Information Systems require revision. The information collected needs to be relevant to professional practice and able to support monitoring and audit of practice against clinical standards. This will assist in the future evaluation of outcomes of care.
- There is a need to improve the completeness and quality of data input to maternity information systems.
- A comprehensive retrospective evaluation of GBS testing, within a single maternity unit, for the prevention of GBS disease of the neonate should be undertaken, if feasible.
- An agreed pathway of care for the prevention of EOGBS infection in neonates.
- An agreed pathway of care for infants with suspected early onset sepsis e.g. the adoption of the recently published NICE guidelines on “Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection.”
- Maternal and neonatal case notes of all GBS culture positive neonates should be audited.
- An enhanced Regional Placental Pathology Service should be considered.
- Specific measures to enhance the identification of infection as a cause of Stillbirth:
  - Expedite the transport of infants for Post Mortem to the Regional Paediatric Pathology Centre.
  - Emphasis on technique of bacteriological culture of the infant and placenta at delivery.
  - Improvement of the uptake of autopsy examinations.
- All suspected anaphylactic reactions in pregnancy should be referred to the Regional Immunology Service for investigation.



## Introduction

### Group B Streptococcus

GBS is a bacterium which colonises the bowel, vagina and urethra in women; men and children of all ages also carry GBS. In women who are pregnant, the prevalence of colonisation in the vagina (termed GBS positive) varies from 6.5% - 36% in Europe <sup>(1)</sup>. Around the time of labour and the birth, many babies come into contact with GBS and are colonised by the bacteria. It usually causes no harm. Most pregnant women who carry GBS bacteria have healthy babies. However, rarely, GBS infection in newborn babies can cause serious complications and can be life threatening with tragic family consequences.

### Why is it important?

GBS is the most common cause of mortality and morbidity due to neonatal infection. The incidence of infection is approximately 1:2000 live births.

GBS disease in the neonate may be early onset (within first 7 days) or late onset ( $\geq 7$  days and up to three months of age) and manifests as respiratory disease, sepsis or meningitis. The majority of early onset disease presents within 24 hours of delivery.

### Prevention of GBS disease

Prevention of early onset GBS is a complex area. The Royal College of Obstetricians and Gynaecologists (RCOG) published a Green-top guideline in 2003 entitled 'Prevention of Early Onset Neonatal Group B Streptococcal Disease' <sup>(2)</sup>. The guideline advises healthcare professionals on the clinical assessment of individual women and the indications for considering antibiotics during labour. This approach centres on the identification of risk factors which include:

- High temperature during labour
- Pre-term labour (prior to 37 completed weeks of pregnancy), and
- The woman not having given birth 18 hours after her waters have broken.
- The guideline also recommends that healthcare professionals should offer antibiotics if the woman had a previous baby with GBS infection.

It advises that antibiotics should also be considered if:

- GBS has been found asymptotically in the urine during pregnancy, or
- GBS is detected incidentally following a clinical presentation.

Over 60% of cases of early onset GBS infection are associated with these identifiable risk factors and it is thought that the majority of severely affected cases could be prevented by targeting this group. Antibiotics given during labour will not prevent all deaths. Unfortunately, even when treated appropriately some babies will still die of early onset disease, particularly when the disease is well established prior to birth.

An updated version of the 2003 RCOG guideline was published in 2012. The differences between the 2003 and 2012 guideline are detailed in italics in the box. The main changes within the 2012 Guideline are use of the term 'offered' rather than 'discussed' or 'considered' and the withdrawal of the recommendation for IAP in preterm labour (<37 weeks) or prelabour prolonged rupture of membranes (>18 hours) in term pregnancy, unless known to be colonised with GBS.

## RCOG Guideline differences between 2003 – 2012

### Indications for *discussing/considering or offering* GBS-specific IAP 2003 <sup>(2)</sup>

- Previous baby with invasive GBS infection.
- GBS bacteriuria in the current pregnancy.
- Vaginal swab positive for GBS in current pregnancy.
- Pyrexia (>38°C) in labour (give broad-spectrum antibiotics to include GBS cover).
- Chorioamnionitis (give broad-spectrum antibiotics to include GBS cover).
- *Pre-term labour <37 weeks gestation.*
- *Prolonged rupture of membranes > 18 hours.*

### Indications for *offering* GBS-specific IAP 2012 <sup>(3)</sup>

- Previous baby with invasive GBS infection.
- GBS bacteriuria in the current pregnancy.
- Vaginal swab positive for GBS in current pregnancy.
- Pyrexia (>38°C) in labour (give broad-spectrum antibiotics to include GBS cover).
- Chorioamnionitis (give broad-spectrum antibiotics to include GBS cover).

## Antenatal Screening for GBS

The UK National Screening Committee (NSC) reviewed the evidence on screening for GBS in Pregnancy in 2003 and 2008 and advised that it should not be offered routinely to all pregnant women. An update review of the policy was issued for public consultation in July 2012. The outcome of this review in December 2012 is that the policy advice should not change.

The National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines No 62 – Antenatal Care <sup>(4)</sup> advises that pregnant women should not be offered routine antenatal screening for GBS. The Royal College of Obstetricians & Gynaecologists (RCOG) have also recommended that screening should not be offered.

A number of countries including the US, Canada, Australia, Italy and Spain offer screening for GBS to all women in late pregnancy, usually 35-37 weeks gestation using vaginal and/or rectal swabs to assess presence or absence of colonisation with GBS and the administration of antibiotics in labour to GBS positive women. Variations in practice do exist whereby some services recommend intravenous antibiotics in labour with a positive swab test and no other risk factor (US) <sup>(5)</sup> and some require an additional risk factor before an intravenous antibiotic is considered (Canada) <sup>(6)</sup>.

## Reasons for the Audit

During the summer of 2011 there was considerable public interest in GBS in pregnancy including calls for a screening programme and questions on the number of babies who developed early onset GBS or were stillborn as a result of GBS. In September 2011 the Chief Medical Officer requested the Guidelines and Audit Implementation Network (GAIN) to undertake an audit of GBS in Northern Ireland. He asked that the audit focus on GBS from both an obstetric and neonatal perspective and include:

- Adherence to the RCOG guideline.
- Evaluation of an opportunistic GBS Testing Programme in one maternity unit.
- Number of neonatal infections; their outcomes and the obstetric history of the mother.
- Number of still births where GBS was identified and the obstetric history of the mother.

### **Audit Working Group**

An audit working group which had representation from DHSSPS, GAIN, HSC Trusts and the Public Health Agency was established to oversee the audit. Membership of the group included consultants from obstetrics, neonatology, paediatric pathology, microbiology and public health as well as midwives and audit staff (Appendix 1).

From November 2011 until June 2012 the group met on six occasions and used email for correspondence where possible.

### **Audit Standards**

1. This audit was conducted against the RCOG 2003 Green-top guideline, 'Prevention of Early Onset Neonatal Group B Streptococcal Disease'. Green-top guidelines are evidence-based documents, providing specific practice recommendations on focused areas of clinical practice.
2. An evaluation of the opportunistic GBS testing programme previously in place at a single unit in Northern Ireland was conducted against the then hospital policy on antenatal GBS testing.

A risk based approach is recommended by the RCOG and is presently used within the UK and Ireland <sup>(2)</sup>. In this approach, intravenous antibiotics should be considered for those with risk factors for GBS infection. The indication for intravenous antibiotics increases if more than one risk factor is present.

It is recognised that prophylaxis with intravenous antibiotics in labour reduces the incidence of early onset GBS disease in the neonate <sup>(2)</sup>.

### **Audit Design**

To achieve the objectives of the audit three work streams were identified:

1. **Antenatal Care work stream:** this was in two parts (i) an audit of adherence to the RCOG guidance in 2009-2010 and (ii) an evaluation of the opportunistic GBS testing programme which was in place in a single maternity unit in 2009-2010 but ceased in February 2011.
2. **Neonatal work stream:** this consisted of identification of all babies with early onset GBS infection during 2008 - 2010, their outcomes and a look back at the maternal clinical notes for any risk factors for GBS and their management.
3. **Pathology work stream:** this entailed gathering data on post-mortems of GBS related still births from 2009 – 2010 and a look back at the maternal clinical notes for any risk factors for GBS and their management.

The Committee were of the opinion that the report should contain information on rare deleterious effects of antibiotic prophylaxis to inform health professionals and pregnant women of risks. For this reason a case series of women with severe allergic responses to antibiotics is included.

Clinical leads were allocated to the main areas of the audit.

### **Audit Questionnaire**

For each work stream a separate questionnaire was developed to assess the adherence to RCOG guidance. Additional questions were added to collect important contextual information and descriptive epidemiology. Proformas were piloted in early January 2012.

The audit including findings and recommendations is detailed for each work stream in the following Chapters.

## References

1. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No: CD007467. DOI: 10.1002/14651858.CD007467.pub2.
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4. National Institute for Health & Clinical Excellence (NICE). Antenatal Care. Clinical Guideline 62. London NICE; 2008.
5. Prevention of Perinatal Group B Streptococcal Disease. Revised Guideline from CDC. Nov. 19, 2010, Vol.59, No.RR-10.
6. SOGC. The prevention of early onset Neonatal Group B streptococcal Disease. *J Obstet Gynaecol Can* 2004; 26(9):826–32.

# **CHAPTER ONE**

## **Antenatal Care Work Stream**

### **Part One**

**Observance of the Risk Based RCOG Guideline (2003) in Northern Ireland**

## Introduction

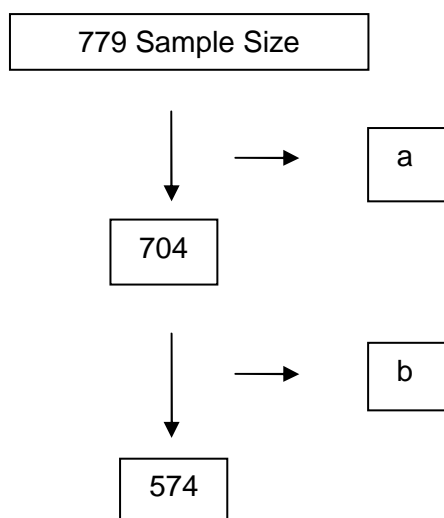
The aim of this work stream was to audit adherence to RCOG 2003 Green-top Guideline on Prevention of Early Onset Neonatal Group B Streptococcal Disease <sup>(1)</sup>.

The Guideline identifies a number of risk factors for EOGBS infection and advises that intravenous antibiotics during labour should be considered if they are present, also that the indication for antibiotics increases if more than one risk factor is present <sup>(1)</sup>. This risk based approach is used within the United Kingdom and Ireland. Whilst the guideline alludes to the problems in providing care to women at risk of neonatal GBS disease, there is debate around prevention: the risks of GBS neonatal disease must be balanced against the wishes of the mother and the risks of adverse reactions to antibiotics and the potential unknown risks to the infant.

## Methodology

1. Local guidelines on the prevention of GBS disease in the neonate were requested from all Maternity Units in Northern Ireland and assessed against the RCOG 2003 Guideline.
2. As not all risk factors for GBS are collected routinely on the Health and Social Care (HSC) information systems, it was agreed that the audit should focus on women who were recorded as having one or more of the following risk factors:
  - Pre-term labour (PTL) at <37 weeks' gestation
  - Prolonged rupture of the membranes (PROM) >24 hours (RCOG risk factor is PROM >18 hours: this information was not available using the Northern Ireland Maternity Information System - NIMATS)
  - Pyrexia >38°C.
3. Women with one or more of these risk factors who gave birth in 2009 and 2010 were identified from NIMATS or the Patient Administration System (PAS). A total of 5473 women were identified.
4. In order to safeguard against an unrepresentative sample, stratified random sampling was used to select cases for the audit. This method of sampling produces characteristics that are proportional to the overall population. Each Trust provided chart identification numbers of women with risk factors for GBS infection; these chart identification numbers were then divided into strata based on maternity units. A 15% random sample was selected from each unit. These sub-sets were then pooled to form a random sample.
5. The sample size was 779 cases however 574 cases were included in the audit. The following "Flowchart" outlines the achieved sample size:

## Flowchart: Algorithm of Project Sample Size (574)



- a. Some of the charts were unavailable as they were required for Antenatal Clinics and the time allocation for data collection was finite. On this account, the sample size was reduced by 75 from 779 to 704 cases.
  - b. During analysis, a further 92 cases, were found to have been mis-classified as 'pre-term'. These were subsequently identified as being "Term" (i.e. > 37wks with no risk factors). A further 38 cases, were found to have been mis-classified - they were in fact planned Caesarean sections, for which antibiotic prophylaxis is not recommended. As a result, these 130 cases were excluded from the sample size.
6. These 574 case notes were accessed by the individual Trusts (Table 1) and a case note review was undertaken to capture the required information using a data collection tool (Proforma 1, see Appendix 2).
  7. Data from the proformas were entered into Microsoft Excel and analysed.

**Table 1: Populations at risk and sample sizes in Health and Social Care Trusts**

HSC Trust	Population	Original Sample (with exclusions)	Final Sample for Report
BHSCT	1,512	211	177
NHSCT	1,192	162	91
SEHSCT	1,267	173	164
SHSCT	977	97	86
WHSCT	525	61	56
<b>Total</b>	<b>5,473</b>	<b>704</b>	<b>574</b>



## Results

### a) Assessment of GBS Guidelines in Maternity Units

Maternity Units in Northern Ireland broadly observe the RCOG Guideline for the prevention of early onset neonatal GBS <sup>(1)</sup>.

All maternity units forwarded their guidelines as requested. Differences in practice were identified. Variations from the RCOG Guideline <sup>(1)</sup> (excluding the single unit which undertook opportunistic testing in antenatal patients) were as follows:

1. Two units screened for GBS colonisation in women with pre-labour rupture of membranes (at term and pre-term).
2. Two units recommended antibiotic prophylaxis to women who had GBS detected on vaginal swab either in a previous pregnancy or during a previous gynaecological consultation.
3. One maternity unit did not give antibiotics to either the woman or the baby when there were no signs of infection in the woman, and in the absence of other risk factors, even if the membranes had been ruptured for more than 24 hours, in keeping with the NICE Guideline.
4. Patient Information: No unit had developed information leaflets on GBS. Seven Units provided "Group B Strep Support" Leaflets.

### b) Maternity Chart Evaluation

This has been reported as:

- i. Profile of women
- ii. Antibiotic Administration
- iii. Neonatal GBS infection from sample population

Five hundred and seventy four women at higher risk of GBS neonatal disease based on three risk factors (pre-term labour <37 weeks, pyrexia >38 degrees in labour and prolonged rupture of membranes >24 hours) were sampled from the five Trusts containing 10 maternity units in the calendar years 01 January 2009 to 31 December 2010.

#### i. Profile of Women

**Table 2: Trust where delivered**

Trust	No. of Women (n=574)
Belfast	177 (31%)
Northern	91 (16%)
South Eastern	164 (28%)
Southern	86 (15%)
Western	56 (10%)

**Table 3: Age of Women**

Age (Yrs)	No. of Women (n=574)
< 16	1 (0%)
16 -20	46 (8%)
21 -25	110 (19%)
26 - 30	169 (29%)
31 - 35	135 (24%)
36 – 40	79 (13%)
41 +	16 (3%)
Not Recorded	18 (3%)

**Table 4: Mode of Delivery**

Mode of Delivery	No. of Women (n=574)
Vaginal Delivery	385 (67% )
Emergency Caesarean Section	183 (32% )
Not Recorded	6 (1%)

**Table 5: Gestation**

Gestation (Weeks)	No. of Women (n=574)
Delivery @ Term 37+ with PROM/with Pyrexia/with PROM + Pyrexia	224 (39%)
PTL @ 34+0 – 36+6 only/PTL + PROM/PTL + Pyrexia/PTL + PROM + Pyrexia	242 (42%)
PTL @ < 34 only/PTL + PROM/PTL + Pyrexia/PTL + PROM + Pyrexia	106 (18%)
Not Recorded	2 (1%)*

\* Two cases did not have gestational age documented: one was a case of PTL <37 weeks, one had PROM >24 hours. The latter did not receive antibiotics. The former received intravenous penicillin in labour, which was administered < 2 hours before delivery.

## ii. Antibiotic Administration in Labour

The sample size was 572 as the 2 cases where the gestational age had not been recorded were omitted.

Tables 6-9 contain details of observation of the RCOG Guideline <sup>(1)</sup> in labour.

**Table 6: Administration of IV antibiotics in labour (for all risk factors at all gestations)**

One or More Risk Factors at all gestations	Number with Risk Factors	Received IV Antibiotic in Labour?	%	Received IV Antibiotic >2 hours before delivery
PTL < 37 wks, PROM >24 hours, Pyrexia > 38 degrees	572	239 / 572	42%	122/239 (51%)

**Table 7: Administration of IV antibiotics at Term with PROM, Pyrexia, or both**

Risk Factors Term	Number with Risk Factor	Received IV Antibiotic in Labour?	%	Received IV Antibiotic >2 hours before delivery
Term + PROM	182	98/182	54%	62/98 (63%)
Term + Pyrexia	35	25/35	71%	12/25 (48%)
Term + PROM + Pyrexia	7	5/7	71%	3/5 (60%)
<b>Total</b>	<b>224</b>	<b>128</b>	<b>57%</b>	<b>77/128 (60%)</b>

**Table 8: Administration of IV antibiotics to women between 34+0 to 36+6 weeks' gestation**

Risk Factors PTL (34+0 – 36+6 wks)	Number with Risk Factor	Received IV Antibiotic in Labour?	%	Received IV Antibiotic >2 hours before delivery
PTL Only (34+0 – 36+6 wks)	195	49/195	25%	15/49 (31%)
PTL + PROM (34+0 - 36+6 wks)	42	26/42	62%	19/26 (73%)
PTL + Pyrexia (34+0 - 36+6 wks)	4	2/4	50%	1/2 (50%)
PTL + PROM + Pyrexia (34+0 – 36+6)	1	1/1	100%	0/1 (0%)
<b>Total</b>	<b>242</b>	<b>78</b>	<b>32%</b>	<b>35/78 (45%)</b>

**Table 9: Administration of IV antibiotics to women less than 34 weeks' gestation**

Risk Factors PTL <34 wks	Number of Risk Factors	Received IV Antibiotic in Labour?	%	Received IV Antibiotic >2 hours before delivery
PTL Only (<34 weeks)	84	25/84	30%	7/25 (28%)
PTL + PROM (<34wks)	21	7/21	33%	2/7 (29%)
PTL + Pyrexia (<34wks)	1	1/1	100%	1/1 (100%)
PTL + PROM + Pyrexia (<34wks)	0	n/a	n/a	n/a
<b>Total</b>	<b>106</b>	<b>33</b>	<b>31%</b>	<b>10/33 (30%)</b>

For one or more risk factors at all gestations in the sample population, 42% of women had antibiotic administration in labour.

Results are presented by gestational age (Term, 34+0 to 36+6 weeks, < 34 weeks) to convey the opportunities available should a screening approach to prevention be a consideration. From the results, screening results would be available for Term pregnancies but probably not be available at 35-37 weeks gestation depending on the timing of the screening test; and would not be available at < 34 weeks gestation.

For the sample in Labour at Term (Table 7), IV antibiotics were administered to 54% of women with PROM and to 71% of women with pyrexia. Five of seven (71%) women who had combined PROM and Pyrexia received antibiotics in labour.

The largest number of deliveries in this high risk sample population occurred between 34+0 and 36+6 weeks (Table 8). For the single risk factor of PTL only, antibiotics were administered in 25% of women with an increase where more than one risk factor was present.

Numbers are small for PTL < 34 weeks (Table 9): 30% of women received antibiotics for the single risk factor of pre-term labour.

### Neonatal GBS infection from sample population

Table 10 details neonatal outcomes for this sample population. Two infants were delivered with early onset GBS disease according to the criterion of CSF and/or blood culture within 7 days of delivery. Neither of the mothers received intrapartum antibiotics.

**Table 10: Neonatal GBS infection from sample population (N = 2):**

High Risk Women (n=556)	Neonatal GBS Infection (n=2)	Women who Received IV Antibiotics in Labour	%	Outcome of Infants (n=2)
Incidence of Neonatal GBS Disease/1000 Live births in high risk women (excluding 18 still births, n=556)	3.59/1000 Live Births	0/2	0%	Alive

Infant 1 had a normal vaginal delivery at 41+2 weeks gestation (birth weight 4120g), with a single risk factor of Pyrexia >38°C in labour.

Infant 2 had a normal vaginal delivery at 40+6 weeks gestation (birth weight 3700g), with a single risk factor of PROM > 24hrs.

Both infants are alive and well.

The incidence of neonatal GBS disease for this high risk sample is 3.59/1000 live births.

## Discussion

### Assessment of GBS Guideline in Maternity Units

All Trusts in Northern Ireland have a guideline for the prevention of GBS neonatal disease. This is an important measure of quality of practice and an acknowledgement of the awareness of the maternity/paediatric team of GBS disease in the neonate.

Two maternity units tested for GBS colonisation in women with pre-labour rupture of membranes (at term and pre-term). This routine bacteriological testing antenatally is not an RCOG Guideline recommendation <sup>(1)</sup>. Two maternity units recommended antibiotic prophylaxis to women who had GBS detected on vaginal swab either in a previous pregnancy or during a previous gynaecological consultation. The RCOG Guideline state that “*there is no good evidence to support the administration of intrapartum antibiotic prophylaxis to women in whom GBS carriage was detected in a previous pregnancy*” <sup>(1)</sup>. These maternity units have adapted the RCOG Guideline. Consequently, more women receive antibiotics than is recommended by the RCOG Guidelines <sup>(1)</sup>.

One Maternity Unit identified a discrepancy in advice between the National Institute of Clinical Excellence (NICE) Intrapartum Guideline <sup>(2)</sup> and the 2003 RCOG Guideline. The NICE Guideline states:

*‘If there are no signs of infection in the woman, antibiotics should not be given to either the woman or the baby, even if the membranes have been ruptured for over 24 hours* <sup>(2)</sup>.

The NICE Guideline covers care of healthy women in labour from 37 – 42 weeks gestation.

The RCOG Guideline <sup>(1)</sup> advises:

*“Clinicians should discuss the use of intrapartum antibiotic prophylaxis in the presence of known risk factors...”*

The known risk factors include PROM >18hours. Thus, a difference exists in the timing (24 hours versus 18 hours) and recommendation for antibiotics: *should not be given* versus *should discuss the use*, between the NICE <sup>(2)</sup> and the RCOG <sup>(1)</sup> guidelines respectively.

Such differences in recommendations from nationally accepted Guidelines add to the difficulties of decision making for the clinician in the case of a complication of pregnancy. This issue has now been resolved in the updated RCOG guideline published in July 2012 <sup>(3)</sup>.

Although not a remit for this review of practice, consideration has been given to Patient Information for GBS. During the audit period 2009 – 2010, seven maternity units provided information leaflets

from the “Group B Strep Support” Group <sup>(4)</sup>. The Chief Medical Officer and Acting Chief Nursing Officer issued a letter to health professionals in September 2011 advocating that pregnant women should be made aware of the risks of GBS in pregnancy as part of their routine antenatal care. <sup>(5)</sup> The *Pregnancy Book* <sup>(6)</sup> produced by the Public Health Agency (PHA) contains information on infections that may affect pregnancy, including GBS. This has been updated in the most recent edition published in March 2012 to clarify current Departmental policy on GBS. It is part of a wider section on infections that may affect pregnancy. In addition, the PHA has issued the RCOG patient information leaflet to Trusts and GPs requesting that professionals use it when discussing GBS with pregnant women. Information on GBS in pregnancy has also been placed on the PHA and NI Direct websites with links to other relevant websites. The Regional Maternity Hand Held Record is currently being updated and the information on infections in pregnancy has been expanded and includes information on GBS.

### **Antibiotic Administration in Labour**

The Maternity Information System in Northern Ireland (NIMATS) is limited in the type of information available to conduct such an Audit. The GBS Audit was restricted to the use of three risk factors from the RCOG Guideline <sup>(1)</sup> to the exclusion of other risks such as documentation of previous infant GBS disease and GBS colonisation. Information systems need to be user-friendly and more comprehensive in recording risk factors.

In view of the relatively high number of misclassifications on information systems, and in some cases basic information such as maternal age not having been recorded, there is a need to improve the completeness and quality of data input to maternity information systems.

In women with one or more risk factors, at all gestations, antibiotics were administered in 42% of the sample population. Further stratification by gestational age and whether one or more risk factors were present at the onset of labour reveals a trend towards more antibiotic administration with an increase in risk. This trend is evident in term and both pre-term birth categories and is in line with the RCOG Guideline <sup>(1)</sup>, whereby:

*“The argument for (GBS) prophylaxis becomes stronger in the presence of two or more risk factors.”*

However, at best, observance of guidelines is estimated at 50% – 70% for two or more risk factors, where numbers are sufficient to draw conclusions. The design of this audit was to assess observance of the RCOG Guideline during 2009 - 2010, but does not allow an assessment as to the reasons for non-adherence.

Possibilities to be considered for the variable adherence to the Guideline would include presentation of the woman late in labour, antibiotic allergy and lack of consent for administration of antibiotics. Education of health professionals is also important: there may be a lack of awareness of the Guideline.

A further factor is concern about neonatal risk of maternal antibiotic administration. Women presenting pre-term with pre-labour rupture of membranes receive prophylactic oral antibiotic therapy (erythromycin) as recommended by the ORACLE Study <sup>(7)</sup>. This prophylaxis has neonatal benefits.

However, co-amoxiclav, a penicillin, cannot be routinely recommended because of an association with neonatal necrotizing enterocolitis. In the long-term study follow up of children at 7 years, the prescription of both antibiotics (co-amoxiclav and erythromycin) for spontaneous pre-term labour resulted in an increase of cerebral palsy but had no significant effect on children at 7 years whose mother had pre-term pre-labour rupture of membranes <sup>(8,9)</sup>.

The circumstances of the ORACLE study differ from GBS prophylaxis where, in the latter situation, antibiotics are administered for a much shorter duration. However, the possible risk to the neonate from maternal antibiotic administration is another factor to explain variable adherence to the Guideline and may account for the low figure of 25% and 30% for pre-term labour alone at 34+0 – 36+6 weeks and < 34 weeks respectively.

The only data available to allow comparison of practice within the UK and Ireland are from the written response of clinicians to the RCOG Audit in 2007 <sup>(10)</sup>. When asked whether or not they would recommend intravenous antibiotics in certain at risk circumstances similar to this audit, 50% of clinicians recommended antibiotics in preterm labour less than 35 weeks, 61% recommended antibiotics for prolonged rupture of membranes >18 hours and 87% recommended antibiotics for pyrexia >38<sup>0</sup> C in labour at term. Thus, despite Guidelines, clinicians are not unanimous in their prescribing habits.

The variable observance of the Guideline in clinical obstetric practice may also be accounted for by the non-directional language within the RCOG 2003 document. The recommendations are ambiguous (*“clinicians should discuss the use of antibiotic prophylaxis-----, intrapartum antibiotic prophylaxis should be considered -----”*) <sup>(1)</sup> which allows considerable variation in practice and is a difficult standard by which to conduct an Audit.

The RCOG Audit <sup>(10)</sup> recommended that when revising the RCOG Guideline <sup>(1)</sup>, ‘*care should be taken to ensure that recommendations are unambiguous and comprehensive*’.

Attention has been paid to this recommendation within the most recently published Guideline <sup>(3)</sup>. One of the main changes within the 2012 guideline is use of the more definitive term ‘antibiotics should be offered’ rather than ‘discussed’ or ‘considered’ when making decisions on administration of antibiotics for risk factors. This change gives clinicians more clear direction.

In the United Kingdom, a risk-based option is used to identify women who require IAP for the prevention of early onset GBS in neonates <sup>(1)</sup>. Antibiotic resistance is a known problem with increasing use of antibiotics. When using IAP for GBS prevention, if a mother is allergic to penicillin, clindamycin is administered. At present, the incidence of clindamycin resistance in the UK is low <sup>(10)</sup>. However, data from the US where IAP programmes are a decade ahead of the UK show an increasing problem with clindamycin and other antibiotic resistance with stronger and more toxic antibiotics now in use <sup>(12, 13)</sup>.

There are also other possible consequences of IAP. There are reports of clusters or increases in gram-negative infections among newborns in association with a decline in GBS infections in the context of increasing IAP use <sup>(14,15,16)</sup>. One large report of infants with very low birth weight documented a shift from gram-positive to gram-negative early-onset infections in the context of increased GBS prevention, with increases in Escherichia Coli infections (E.Coli) <sup>(17)</sup>. A further analysis of babies with E.coli sepsis in the first week of life compared with the birth cohort did not

reveal an increased risk of neonatal sepsis from E.coli associated with IAP <sup>(18)</sup>. This issue remains important and emphasises the need for ongoing neonatal infection surveillance. Chapter 5 contains a commentary on a case series of women with severe penicillin allergy in pregnancy - another possible deleterious effect of prophylaxis.

### **Neonatal GBS infection from sample population**

Two infants with EOGBS disease were delivered at Term. One had PROM >24 hours and one developed Pyrexia > 38<sup>0</sup>C in labour. Neither received antibiotic prophylaxis during labour. Both are well. The incidence of GBS disease in this high risk population, excluding stillbirths, is thus 3.59/1000 live births which is higher than the reported 0.57/1000 live births in the total maternity population of Northern Ireland (cf Chapter Three). This indicates a risk of GBS disease in approximately 1:280 for the high risk population as against approximately 1:1750 for the total population.

### **Key Messages**

- **All maternity units had a guideline for the prevention of GBS disease.**
- **Prophylactic antibiotic usage increased in labour with an increase in risk factors.**
- **Variable adherence to RCOG GBS Guideline, 50% – 70% at best. This may be a consequence of non-directional language within the text, concern about deleterious effects of antibiotic administration and lack of awareness of guideline detail by health service personnel.**

### **Recommendations**

- **Continue to raise the awareness of pregnant women and health professionals about GBS disease prevention.**
- **Clinicians should be aware of the possible neonatal and maternal risks of antibiotic prophylaxis.**
- **Maternity Information Systems require revision. The information collected needs to be relevant to professional practice and able to support monitoring and audit of practice against clinical standards. This will assist in the future evaluation of outcomes of care.**
- **There is a need to improve the completeness and quality of data input to maternity information systems.**



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# **CHAPTER TWO**

## **Antenatal Care Work Stream**

### **Part Two**

**Evaluation of an opportunistic GBS Testing Programme in one maternity unit 2009-2010**

## Introduction

Group B Streptococcus may be transmitted from mother to child through the lower genital tract during labour. Administration of IAP reduces the likelihood of transmission. The 2003 RCOG guideline recommends a *risk-based* strategy for delivering IAP rather than routine screening <sup>(1)</sup>. The risk factors that require IAP to be considered include: the incidental finding of GBS colonisation or bacteriuria in the current pregnancy; having a previous infant affected with GBS disease; intrapartum pyrexia; prolonged (>18 hours) prolonged rupture of membranes or pre-term labour.

In the US universal screening is recommended by the Centre for Disease Control (CDC) and has been in place since 2002 <sup>(2)</sup>. As a screening technique, the lower vagina and rectum are swabbed using either a single or dual-swab approach at 35-37 weeks gestation. IAP is then prescribed to all labouring women with a positive swab cultures for GBS; a previous infant with invasive GBS disease; GBS bacteriuria in the current pregnancy; or an unknown GBS status at the onset of labour with identifiable risk factors.

Surveillance of data, by the Active Bacterial Core Surveillance/Emerging Infections Program network, since the introduction of revised early onset disease prevention guidelines in 2002 in the US (screening at 35 – 37 weeks) show that EOGBS disease incidence decreased 27% (95% CI, 16%-37%), from 0.47 per 1000 live births in 1999-2001 to 0.34 per 1000 live births in 2003-2005 <sup>(3)</sup>. However, successive small increases in incidence occurred in 2004 and 2005. A further small increase in incidence occurred in 2006 to 0.40 per 1000 live births <sup>(4)</sup>. Before the introduction of any GBS prevention guidelines in the early 1990s, the incidence of EOGBS disease in the US was as high as 1.7 per 1000 live births.

In 1992, at a single maternity unit within Northern Ireland, obstetric and paediatric guidelines for the prevention of GBS disease were introduced at a time when no national guidelines for the prevention of GBS disease existed nor was data available to estimate the incidence of disease. The rationale for the introduction of preventative measures in this unit was on the basis that GBS infection was a common cause of neonatal sepsis in the UK and the introduction of prevention guidelines in the US in the early 1990s <sup>(5)</sup>.

The maternity unit guideline required:

- Vaginal swabs to be taken on all admissions after 24 weeks gestation (including those in labour) and to be cultured for GBS.
- Intrapartum – where the woman is GBS positive and risk factors are present treat mother with intravenous antibiotics and inform paediatrician. Infant requires antibiotic treatment.
- Intrapartum – where mother is GBS positive without risk factors, the paediatrician was to be informed.
- Intrapartum – where mother is GBS positive with risk factors and antibiotics have been given, inform paediatrician as infant automatically receives antibiotic treatment.
- Postpartum – where woman is GBS positive and no antibiotics given in labour, multiswabs (nose, umbilicus, rectum and, occasionally, gastric aspirate) from the baby to be sent to the laboratory for GBS culture. The infant was to be observed in hospital.
- If baby multiswabs are positive and baby well, treat with 5 day course of oral penicillin and monitor closely.
- If baby becomes unwell, perform appropriate investigations and consider intravenous antibiotics.

The purpose of this preventative strategy was investigation and prophylaxis for the neonate rather than the woman in labour, unless additional risk factors other than GBS positive culture were present. With the introduction of the RCOG Green-top in 2003, practice varied to allow:

- A consideration of the use of antibiotics in the woman with the presence of GBS positive culture as a single risk factor.

The focus of this chapter is laboratory confirmed GBS in pregnant women and their outcomes over two years (01 January 2009 – 31 December 2010). A sample of women positive for GBS on vaginal swab during pregnancy was assessed with regard to intrapartum and neonatal care. Time constraints for the audit and logistical difficulties in the collection of data have persuaded the authors to seek a more comprehensive assessment of the GBS testing process in this Unit as a further supplementary report. Herewith is a preliminary report to outline the adherence to this guideline within a unit that undertook opportunistic testing in pregnancy for GBS from 1992.

## Methodology

- The population was an existing dataset of n=827 women who had tested positive for GBS on vaginal swab (from 24 weeks) as a result of routine opportunistic testing in the calendar years 01 January 2009 to 31 December 2010. A 17% sample was randomly selected from this population of 827 and the sample size achieved was 139.
- A case note review of both mother and baby was undertaken retrospectively to capture the required information (Proforma 1, Appendix 2). Data were gathered on:
  - Use of antibiotics for women in labour.
  - All neonatal EOGBS infection in this population sample and
  - GBS positive skin colonisation of infant (termed 'culture positive neonate')

## Results

The number of deliveries from 01 January 2009 – 31 December 2010 was 5562. 827 women were GBS positive. The design of the audit did not seek to identify negative results of GBS culture. Thus the incidence of GBS positive culture in the population is unknown.

The following tables outline maternal history, antibiotic administration and neonatal outcome for the sample (N=139) of the population (N=827) of GBS positive women.

## Maternity and Neonatal Chart Evaluation

This has been reported as:

- i. Profile of women.
- ii. GBS Positive women and no risk factors – antibiotic administration and neonatal outcome.
- iii. GBS Positive women and risk factors – antibiotic administration and neonatal outcome.

Risk factors are as follows: preterm labour <37 weeks, pyrexia >38°C in labour, prolonged rupture of membranes > 18 hours, GBS bacteriuria or a previous infant with GBS disease.

**i. Profile of Women**

**Table 11: Age of Women**

Age (Yrs)	No. of Women (n=139)
< 16	-
16 -20	10 (7%)
21 -25	15(11%)
26 - 30	39(28%)
31 - 35	56(40%)
36 – 40	18(13%)
41 +	1(1%)

**Table 12: Mode of Delivery**

Mode of Delivery	No. of Women (n=139)
Vaginal Delivery	92 (66%)
Planned Caesarean Section	21 (15%)
Emergency Caesarean Section	26 (19%)

**Table 13: Gestation**

Gestation (Weeks)	No. of Women (n=139)
Delivery at Term	127 (91%)
PTL @ < 37 wks	12 (9%)

Tables 14 - 17 contain details of the use of antibiotics in labour and in the neonate for the maternity unit sample of culture GBS positive women with and without additional risk factors (N=22 and N=117 respectively).

**ii. GBS Positive women and no additional risk factors – antibiotic administration and neonatal outcome.**

For the sample of GBS culture positive women and no additional risk factors, a total of 15/117 (12.8%) were administered antibiotics in labour. Information is unavailable as to the number with a GBS positive result available at the time of labour.

**Table 14: Antibiotic administration for culture GBS positive women with no additional risk factors (N=117)**

Number with GBS Positive on Vaginal swab only and no additional risk factors at all gestations	Received IV Antibiotic In labour	Received IV Antibiotic >2 hours before delivery
N= 117	15 / 117 (12.8%)	8/15 (53.3%)

**Table 15: Culture positive neonates (positive skin swabs) and antibiotic administration from GBS positive women with no additional risk factors (N= 117)**

Culture positive Neonates	Neonatal Antibiotics	ICU Admission
N= 46	15/46 (32.6%)	1/46 (2%)

Thirty nine percent of neonates were culture positive of whom approximately 1/3 received antibiotics. No neonates had GBS infection. One neonate was admitted to ICU with poor feeding and tachypnoea after delivery at 41+3 weighing 3320g. This infant had positive nasopharyngeal, eye and umbilical swabs for GBS.

4/71 culture negative neonates received antibiotics one of whom was admitted to neonatal ICU with lethargy following emergency caesarean section at 39+1 week's gestation.

**iii. GBS Positive women and risk factors – antibiotic administration and neonatal outcome.**

Of the GBS culture positive women 22/139 had additional risk factors for GBS.

**Table 16: Antibiotic administration in Labour for culture GBS positive women with additional risk factors N=22**

One or More additional Risk Factors at all gestations (and culture GBS positive women) N = 22	Number with Risk Factors	Received IV Antibiotics in Labour	Received IV Antibiotics >2 hours before delivery
PTL < 37 wks, PROM >18 hours, Pyrexia >38 degrees, GBS bacteriuria, previous GBS disease	22/139 (15.8%)	10/22 (45.4%)	8/10 (80%)

For the sample of GBS culture positive women with additional risk factors at all gestations, a total of 10/22 (45.4%) were administered antibiotics in labour. An increase of risk factors resulted in an increase in antibiotic administration in labour. Ten women were at term and 12 were preterm at delivery.

**Table 17: Culture positive and negative skin swabs from neonates and antibiotic administration from GBS positive women with additional risk factors (n=22)**

Culture positive Neonates	Neonatal Antibiotics	ICU Admission
N= 9/22 (41%)	7/9 (77.7%)	2/9 (22.2%)

Culture negative Neonates	Neonatal Antibiotics	ICU Admission
N= 13/22 (59%)	6/13 (46.1%)	3/13 (23.1%)

No neonates in this sample had GBS infection. A considerable proportion of skin culture positive neonates (7/9, 77.7%) delivered from GBS positive women with risk factors received prophylactic antibiotic therapy.

Both culture positive neonates admitted to ICU were delivered preterm by emergency Caesarean section at 32 weeks and 30 weeks gestation. The women had intravenous antibiotics in labour. Both neonates were discharged well from the unit.

Three culture negative neonates were admitted to ICU. One delivered at term and two were preterm. The term neonate delivered normally and was admitted with tachypnoea. Mother was given IV penicillin in labour because of prolonged rupture of membranes. Intravenous antibiotics were administered to one of the women in preterm labour. All were discharged well from the neonatal intensive care unit.

### **Babies with GBS**

Within the total population of deliveries (5562) during 2009 – 2010, it is known from the Neonatal Infection audit that three infants had GBS disease none of which were part of this population sample of GBS positive women. All three were born at term and one of the three women was GBS positive on vaginal swabbing. This result was not known in advance of labour. One further infant had no maternal risk factors and one had prolonged rupture of membranes > 18 hours as a single risk factor. Neither had known GBS vaginal swab status. None of the three women received antibiotics in labour. All infants were diagnosed with GBS disease within 48 hours of birth and treated within the Neonatal Intensive Care Unit. The infants were well at discharge. Developmental follow up is normal for the three infants. The incidence of EOGBS Disease in this unit over the two calendar years from 2009 – 2010 was 0.54/1000 live births (3/5537).

### **Discussion**

This is a preliminary analysis of the contribution of opportunistic testing to the prevention of GBS disease in the neonate during 2009 and 2010. The thrust of the prevention guideline was focused on the administration of antibiotics to women with GBS positive vaginal culture and risk factors and the skin culture positive neonate. GBS positive women with risk factors received antibiotics in labour in approximately 45% (10/22) of cases. Antibiotics were administered to 77% (7/9) of neonates with positive skin cultures delivered by women with risk factors. Despite such measures the incidence of GBS disease within the Unit was 0.54/1000 live births during these two years which is only slightly less than the 2010 EOGBS rate of 0.68 / 1000 live births <sup>(6)</sup> in Northern Ireland in the Health Protection Agency Report and the incidence within this audit of 0.57/1000 live births.

Limited information is available, from this assessment of a sample of GBS culture positive women, on the value of testing. The outcome of this approach as applied in this unit does not yield the expected reduction in the incidence of disease. The audit tool used did not provide the information required to allow an analysis of the processes of care in women and their babies. This needs correction. Information unavailable that might prove valuable to allow a more thorough evaluation of opportunistic testing includes the gestation at which GBS vaginal swabs were taken, numbers of women with results available to the clinician in labour, outcomes of screen negative women, length of stay of culture positive and negative women and their infants, availability of neonatal swab



results after delivery, neonatal receipt of oral or intravenous antibiotics and a record of complications of prophylaxis.

A confounding factor within the opportunistic testing programme was the introduction of the 2003 Green-top Guideline from RCOG. The language used within the Guideline is non-directional and conveys an uncertain message about the use of prophylactic regimens.

Although no neonates within the random sample of 139 developed GBS disease, it is known from the Neonatal Infection audit that 3 infants had disease during 2009 – 2010. One infant was delivered to a woman who was GBS screen positive but the result was not known before labour. One further infant had no maternal risk factors and the final neonate had prolonged rupture of membranes > 18 hours as a single risk factor. Neither mother had known GBS vaginal swab status.

None of the three women received antibiotics in Labour. Of the three cases, one woman had a factor known intrapartum that predisposed their infant to GBS infection.

## Key Messages

- **Antibiotic use in labour increased from 12.8% for GBS positive women to 45% for GBS positive women with additional risk factors.**
- **Despite opportunistic testing and a multidisciplinary approach to prophylaxis incidence of neonatal infection was similar to the Northern Ireland rate for that period.**

## Recommendation

- **A comprehensive retrospective evaluation of testing, within a single maternity unit, for the prevention of GBS disease of the neonate should be undertaken, if feasible.**

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# **CHAPTER THREE**

## **Neonatal Work Stream**

### **GBS Neonatal Infection 2008 – 2010**

## Introduction

Neonatal infection in the UK population affects approximately 4.1 per 1000 live-births (LB) and 38 per 1000 neonatal admissions. Early onset sepsis (EOS) ( $\leq$  48 hours of age, EOS) is estimated at 0.9/1000LB and represents approximately 9/1000 neonatal admissions. The major organisms causing EOS are Group B streptococcus (GBS), E coli, non-pyogenic streptococcus species, Staphylococcus aureus, Enterococcus, Listeria monocytogenes, Enterobacteriaceae and Haemophilus influenza. However GBS is the single commonest cause of EOS, at approximately 40-50% of all causative organisms<sup>(1, 2, 3)</sup>.

In most studies GBS infections are defined as early-onset (EOGBS) if they occur within the first 7 days and late-onset (LOGBS) if they occur from day 7 to 90 days of age. This reflects the differing clinical presentations of the infection at different ages, with respiratory distress/septicaemia predominating in EOGBS and meningitis being much more prevalent in LOGBS.

A British Paediatric Surveillance Unit (BPSU) survey conducted in 2000-01 showed that the overall UK and Ireland incidence of EOGBS was 0.48/1000LB and that the incidence in Northern Ireland was 0.73/1000LB. It was associated with a mortality rate of 10.6% and a neurodevelopmental impairment rate of 7% in survivors<sup>(3)</sup>. Internationally, the incidence of EOGBS varies widely with rates of 0.39/1000LB in Spain, 0.75/1000LB in France, 0.34-0.37/1000LB in USA and 0.25/1000LB in Australia<sup>(4,5)</sup>. Data from the Health Protection Agency indicates an incidence of EOGBS bacteraemia in the UK (England, Wales and Northern Ireland) in 2010 as 0.41/1000LB and 0.68/1000LB in Northern Ireland. Such information is submitted voluntarily from laboratories to the Health Protection Agency and does not include clinical data.

## Methodology

Neonatal infection was defined as a positive blood or cerebrospinal fluid (CSF) culture. EOGBS was defined as GBS infection within the first 7 days of life. A list of infants, up to the age of 90 days with positive blood or CSF cultures was retrieved from laboratories in all 5 Trusts for 2008 - 2010. A cross-check of the cases which occurred in 2009 was also undertaken with the Neonatal Intensive Care Outcomes Research & Evaluation (NICORE) database: 2009 was the only year for which complete data is available from NICORE. Additionally, the Public Health Agency (PHA) provided a list of EOGBS cases that had been voluntarily reported to them by each Trust during 2008 - 2010, to further enable as complete a case cohort as possible.

Clinical data, relating to the birth, neonatal care and subsequent paediatric follow-up, contained in the charts of each affected infant was reviewed by 2 paediatric registrars and/or a consultant neonatologist.

The associated maternal charts of each affected infant were also reviewed for the following recognised GBS risk factors:

1. Rupture of membranes (ROM) >18 hrs
2. Preterm labour <37 wks
3. Fever in labour >38°C
4. Vaginal GBS carriage in current pregnancy (in the absence of universal screening, this is referred to as "incidental finding of vaginal GBS carriage")
5. GBS bacteriuria in the current pregnancy
6. A previous baby affected by GBS disease.

Additionally, for patients in one hospital only, where there was a policy of opportunistic testing for GBS in women attending at any time during pregnancy, there was a record noted of those who were “screen positive” for GBS on swabs obtained during labour.

The relevant data were collected onto a proforma (Proforma 2 Appendix 2). Data were then imputed onto Excel spreadsheets. The chart retrieval process was facilitated by audit personnel in each Trust.

## Results

The laboratory staff identified 59 infants who had positive blood or CSF cultures during 2008 - 2010. Two of these infants were born in hospitals in the Republic of Ireland and were therefore not included for analysis. Of the 57 infants with GBS infection who were born in Northern Ireland, 22 had LOGBS and 35 had EOGBS. An additional 8 cases of EOGBS were identified by the Public Health Agency (PHA), giving a total EOGBS cohort of 43 cases. All 43\* infants had positive blood cultures and 3 of them also had a positive CSF culture.

There were 75,856 live-births in Northern Ireland during 2008-10, which gives an EOGBS incidence for NI of 0.57/1000LB over the 3 year period.

It was noted that in 2 infants, the blood cultures also grew additional organisms, commonly called a “mixed growth”, which would suggest that the origin of the organisms was skin rather than bloodstream. This is a common finding in neonatal care and typical clinical practice would be to treat the infant for a period of time whilst observing for any signs of deterioration due to “true” bloodstream infection. In most studies of neonatal infection, “mixed growth” cultures would not be included but for the purposes of this audit, they have been included. If they are excluded, the EOGBS incidence for 2008-2010 would be calculated as 0.54/1000LB.

The gestational age of affected infants ranged from 23<sup>+4</sup> to 41<sup>+5</sup> weeks. The majority of infants, 74.4% (32/43) were born at term, defined as  $\geq 37^{+0}$  weeks. A more detailed breakdown of gestational age is presented in table 18. The birth weights of affected infants ranged from 659 to 4430g; a more detailed breakdown of the birth weights is presented in table 19 below.

**\*Footnote:** An additional infant affected by GBS was identified by post mortem examination. The extremely low birth weight infant was born to a mother, at a non-viable gestation and had a faint heart beat at delivery. Post mortem assessment revealed evidence of GBS infection. This case was not included in the overall incidence of EOGBS infection described above, due to the absence of bacteraemia or CSF culture, thus not meeting the audit criteria.

**Table 18: Gestational age of babies with EOGBS**

Gestational Age (weeks)	Number (%) (n=43)
≥37 <sup>+0</sup>	32 (74.4)
34 <sup>+0</sup> - 36 <sup>+6</sup>	3 (7.0)
<34 <sup>+0</sup>	8 (18.6)

**Table 19: Birth weight of babies with EOGBS**

Birth Weight (gms)	Number (%) (n=43)
>2500	35 (81.4)
1500 - 2500	1 (2.3)
<1500	7 (16.3)

Most infants were delivered vaginally, 26/43 (60.5%): 16/43 (37.2%) were delivered by emergency Caesarean Section and 1/43 (2.3%) by elective Caesarean Section.

The age at presentation ranged from <1 hour to 6 ½ days. Most infants, 81.4% (35/43), presented on the first day of life, the majority of whom, 88.6% (31/35), presented within the first 12 hours of life. Only four infants, 9.3% (4/43), presented after day 2 of life and three of them had positive CSF cultures (meningitis) in addition to positive blood cultures. Most infants, 81.4% (35/43), had some clinical signs of sepsis when blood cultures were undertaken (see discussion).

In 55.8% (24/43) of infants with EOGBS there was 1 or more maternal risk factor in labour. “Rupture of the membranes for >18 hours” and “preterm labour <37 weeks” were the commonest risk factors identified. A summary of the frequency of risk factors known in the intrapartum period is provided in table 20.

**Table 20: Frequency of known intrapartum risk factors in women. Some women had more than one risk factor**

Risk factor	No (%) of pts affected	Notes
No maternal risk factors	19 (44.2%)	
ROM >18 hrs	13 (30.2%)	
Preterm labour <37 wks	11 (25.5%)	
Fever in labour >38°C	8 (18.6%)	
Incidental finding of vaginal GBS carriage in current pregnancy	5 (11.6%)	
GBS bacteriuria current pregnancy	1 (2.3%)	
Other	1 (2.3%)	Source of maternal GBS in index pregnancy not known

In 30.2% (13/43) of cases, there was one maternal risk factor. In 5 women, the risk factor was “preterm labour” and in 4 women the risk factor was “rupture of membranes >18 hours in labour”. Only 1 woman had “fever in labour” and she received intrapartum antibiotics. In total, 4 women

received intrapartum antibiotics. The other 3 women were given antibiotics because of an “incidental finding of GBS” (1), preterm delivery by caesarean section for placental abruption (1) and “rupture of membranes >18 hours in labour” (1) along with evidence of fetal distress.

In 25.6% (11/43) of cases, there were two or more risk factors known in the antenatal or intrapartum period. Four women had 3 risk factors and all of them received intrapartum antibiotics. There were 7 women who had 2 risk factors: 3 of these women delivered infants at term gestation and all received intrapartum antibiotics. The other 4 women delivered prematurely: 1 received oral erythromycin, 2 did not have any antibiotics and 1 chart was unavailable to review. A summary of the frequency of risk factors known in the intrapartum period and use of intrapartum antibiotics is provided in table 21.

In the hospital where there was a policy of opportunistic testing for GBS for women attending at any time after 24 weeks gestation, five infants had EOGBS. Three infants were delivered to women who were GBS screen positive and two of these had a known result before labour. One further infant had no maternal risk factors and the final neonate had prolonged rupture of membranes > 18 hours as a single risk factor. Neither mother had known GBS vaginal swab status.

None of the five women received antibiotics in Labour.

**Table 21: Presence of known intrapartum risk factors and frequency of IV antibiotics to women in labour**

No of Risk factors	No of pts affected (n=43)	IV Antibiotics given (%) (n=11 for 1 or more risk factors)	Notes
0	19	1 (5%)	1 = Co-amoxiclav @ 41+ wks
1	13	4(31%)	1 = Co-amoxiclav @ 30 wks 1 = Co-amoxiclav @ 40 wks 1 = Clindamycin @ 40+ wks (Record of maternal vomiting secondary to Clindamycin) 1 = Benzyl Penicillin & Co-amoxiclav @ 41+ wks
2	7	3 (43%)	1 = Benzyl Penicillin @ 37+ wks 1 = Unknown intrapartum antibiotic @ 40 wks 1 = Benzyl Penicillin @ 40+ wks
3	4	4 (100%)	1 = Benzyl Penicillin @ 26+ wks 1 = Benzyl Penicillin @ 28+ wks 1 = Co-amoxiclav/Metronidazole @ 40+ wks 1 = Cefuroxime/Metronidazole @ 41+ wks

All infants received antibiotics, ranging from 1 - 21 days in duration. All 3 infants who had GBS meningitis received 21 days of antibiotics. The majority of infants, 93% (40/43) were admitted to a neonatal unit for their care for a range of 1 day to approximately 3 months. Three infants, however, received their antibiotics in post-natal wards and were not admitted to a neonatal unit at any time. None of these 3 infants had signs of sepsis when blood cultures were taken: blood cultures were taken from these asymptomatic infants because of the presence of maternal risk factors in the

current or previous pregnancies. In 1 of these 3 infants, the blood culture grew an additional organism suggesting that the source of both organisms was the infant skin rather than the blood stream. As stated above, this is a common finding in neonatal care and in keeping with typical clinical practice these infants were treated for a period of time whilst observing for signs of “true” infection. No deterioration occurred in any of these 3 infants.

Of the 43 infants who had EOGBS, 5 did not survive to discharge from hospital. Two infants died for reasons other than EOGBS. The other three infants died directly of their sepsis. One mother had 3 risk factors - vaginal GBS carriage, PROM and pyrexia, the other 2 each had one risk factor - preterm labour and PROM respectively (table 22). The direct mortality rate was 7.0% (3/43) with a total mortality rate of 11.6% (5/43). There was a proportionately higher mortality rate for infants born preterm (<37 weeks gestation), 18.2% (2/11), compared with those born at term, 9.4% (3/32).

**Table 22: Presence of risk factors and administration of IV antibiotics to women of the infants who died**

Infant	Age at presentation	No of Risk factors	Risk Factors	IV Antibiotics given
1	Day 1	2	1. Preterm labour 2. Vaginal GBS carriage	No
2	Day 1	1	Preterm labour	No
3	Day 1	0	-	No
4	Day 1	1	ROM >18hrs	Yes
5	Day 1	3	1. Vaginal GBS carriage 2. ROM >18hrs 3. Fever in labour >38°C	Yes

For the survivors, post-discharge follow-up information was available on 60.5% (23/38) infants. At their last paediatric review, 21 infants were noted to have normal neuro-developmental attainment. Two infants with birth weights <1000g had abnormal neurodevelopmental outcome secondary to complications of intraventricular haemorrhages which may occur in very ill preterm infants. It cannot be determined from this audit what component of these infants’ outcome is specific to the EOGBS infection. However these data give a neurodevelopmental impairment rate of 8.7% (2/23).

## Discussion

The burden of EOGBS disease in the neonatal population of Northern Ireland in 2008-10, is approximately 1 in 1750 live births. This incidence, 0.57/1000LB, is slightly higher than other regions of UK as reported in the 2010 HPA report but less than the incidence in the BPSU survey of 2001, 0.73/1000LB<sup>(3, 6)</sup>. As discussed above, this figure probably represents an overestimate of “true” disease and a rate of 0.54/1000LB is probably the more accurate picture of the incidence rate of EOGBS between 2008 and 2010. More importantly, however, the reduction in incidence, from 0.73/1000LB in the 2001 BPSU survey, may represent improvements in perinatal care



following the publication of the RCOG Guideline for the Prevention of Early Onset Neonatal Group B Streptococcal Disease in 2003 <sup>(7)</sup>. The mortality and morbidity rates of 11.6% and 8.7% however, remain similar to the 10.6% and 7.9% mortality and morbidity rates reported by the BPSU survey group <sup>(3)</sup>.

It was found that almost 3/4 of cases of EOGBS in this audit were born at term, defined as  $\geq 37^{+0}$  weeks gestation. Indeed, 67.4% (29/43) were born after  $38^{+0}$  weeks gestation. This is important to note because those women who deliver before  $38^{+0}$  weeks gestation, i.e. the remaining 32.6% (14/43), would have minimal opportunity to benefit if universal screening measures, involving recto-vaginal swabs at 35-37 weeks gestation, to prevent EOGBS were introduced. This population of women and infants would however benefit, were a vaccine against GBS to become available.

In 55.8% (24/43) of women there was a recognised risk factor present during the pregnancy. However it is recognised that most of the individual risk factors, such as preterm labour or rupture of membranes, are not specific to EOGBS. It should not therefore be a surprise that only 30.8% (4/13) of the women with a single risk factor received intrapartum antibiotics for the prevention of EOGBS. It is particularly difficult for clinicians when the only risk factor is preterm labour, as was the case in 5 of the 13 women (38.5%) with a single risk factor, as there is controversy regarding the use of antibiotics in preterm labour following revelations of adverse long term effects by the Oracle Trial team<sup>(9)</sup>. They found that the prescription of erythromycin or co-amoxiclav (both of these drugs are broad spectrum antibiotics) for women in spontaneous preterm labour with intact membranes was associated with an increase in the risk of cerebral palsy at age 7 years.

In the 7 women with 2 risk factors, all 3 who delivered at term 3/7, (42.9%), were given intrapartum antibiotics. This may reflect the controversy regarding the use of antibiotics in preterm labour following revelations of adverse long term effects by the Oracle Trial team <sup>(8)</sup>. None of the 4 women who delivered prematurely received IAP. One woman received oral erythromycin which would be in keeping with good perinatal practice. In one of the 2 other women for whom we have information, her delivery at an extremely low gestation was so rapid that there would not have been time to give IAP.

In the 4 women with 3 risk factors, all were given antibiotics. There was however, variation in the antibiotic regimens used and this probably reflects clinical concerns about maternal chorioamnionitis and infection which would require a broader spectrum of therapy than just Benzyl Penicillin or Clindamycin.

This audit noted a variable approach to the asymptomatic infant. 18.6% (8/43) of infants had no specific symptoms of sepsis when their blood cultures were taken. There were a number of different reasons why blood cultures were taken on asymptomatic infants. In 4 cases, blood cultures were done because of the identified risk factors in the mother rather than signs of infection in the baby per se. Two of these infants received their total hospital care in the post-natal wards and never required admission to a neonatal unit. One of these 4 infants had blood culture results which demonstrated a "mixed growth" suggesting that the source of the cultured organisms was skin rather than bloodstream. Repeat blood cultures (before antibiotics commenced) did not identify any organism and it is likely therefore that the infant did not have a "true" bloodstream infection. In case 5, the blood cultures were done as part of the routine admission procedures for a preterm infant. In case 6, the blood cultures were done because of foul smelling liquor and maternal pyrexia after delivery. This infant also stayed on the post natal ward throughout its treatment. In case 7, blood cultures were undertaken after investigations for a different condition revealed low platelets. This infant never showed signs of sepsis, despite the positive culture and

completed the course of antibiotics whilst at home. In the remaining asymptomatic infant, case 8, it was not clear to the investigator why blood cultures were done. In this infant the blood cultures were done on day 1 and produced a “mixed growth”: repeat cultures were negative. Again, it is likely that this infant did not have a “true” bloodstream infection.

As noted above, these scenarios are common findings in neonatal care, unlike that found in the care of older children or adults. They represent the low threshold that clinicians have in doing blood cultures in order to instigate prompt antibiotic treatment for newborn infants, because the signs of early sepsis can be subtle and non-specific and delay in treatment could cause serious harm. Common practice is therefore to investigate with blood cultures and treat with antibiotics pending the results of the cultures. Guidance on the use of antibiotics in suspected early onset neonatal sepsis has been published by NICE in August 2012 and this should lead to a greater degree of conformity of investigation and management by using the presence or absence of “red flags” in the assessment of whether to commence an infant on antibiotics or not <sup>(9)</sup>.

Five infants in this cohort did not survive to discharge from hospital. Two infants died for reasons other than EOGBS. One from complications of prematurity and the other due to an underlying lethal genetic condition. In neither case was intrapartum antibiotics used. The other 3 infants died directly of their sepsis: they were critically ill at birth or within a few hours and died within 2 days despite vigorous intensive care. Intrapartum antibiotics were given to 2 of the 3 women. The mortality rate is in keeping with other studies in this area and is unchanged despite a falling incidence rate.

The two infants with abnormal neurodevelopmental outcome were both born at very low gestation and extremely low birth weight. Their poorer outcomes when compared to term infants reflect the reduced ability of extremely preterm infants to overcome all illnesses including infection.

## **Summary**

The data presented in this chapter reveals that the incidence of EOGBS in Northern Ireland is lower in 2008-10 compared with 2001 but still slightly higher than other parts of the UK. Almost 3/4 of affected infants were delivered at term. In 55.8% of women there was a recognised risk factor present during the pregnancy. There was variability in intrapartum antibiotic practice probably related to the possibility of maternal conditions such as chorioamnionitis, premature delivery or rapid delivery and the uncertainties that clinical staff face when interpreting the 2003 RCOG Guideline. Over 80% of affected infants presented on day one of life and 93% were admitted to a neonatal unit. There was variability in the assessment and management of asymptomatic infants in whom there were maternal risk factors. This may change following recent publication of new NICE guidelines on the use of antibiotics for early onset neonatal sepsis. The mortality and morbidity rates of EOGBS are 11.6% and 8.7% respectively and remain similar to the rates seen in 2001, reported by the BPSU.

## Key Messages

- **The incidence of GBS disease in Northern Ireland is 1 in 1750 live births from 2008 – 2010. This is marginally higher than the UK as a whole.**
- **55.8% of women with GBS infected infants had risk factors for GBS in labour.**
- **Antibiotic prophylaxis in labour increased with rising maternal risk of GBS.**
- **Antibiotic prophylaxis does not prevent all cases of EOGBS infection or loss of life.**
- **Variation in management of the asymptomatic infant. This may be resolved with recently published NICE Guideline on use of antibiotic for early onset sepsis.**

## Recommendations

- **An agreed pathway of care for the prevention of EOGBS infection in neonates.**
- **An agreed pathway of care for infants with suspected early onset sepsis e.g. the adoption of the recently published NICE guideline on “Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection.”**
- **Maternal and neonatal case notes of all GBS culture positive neonates should be audited.**

## References

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# **Chapter Four**

## **Pathology Work Stream**

### **Prevention of Perinatal Group B Streptococcal Disease in Northern Ireland: GBS Stillbirths 2009 – 2010**

## **Introduction**

To provide comprehensive information on the burden of GBS disease in Northern Ireland a retrospective assessment of the antenatal and intrapartum stillbirths referred for autopsy to the Regional Paediatric Pathology Service was undertaken during the calendar years 2009 and 2010 in order to establish the number due to GBS infection. It is important to note that not all stillbirths undergo post mortem examination - within Northern Ireland 55% <sup>(1)</sup> of stillbirths (>24 weeks) undergo this investigation as compared with 44% across England, Wales, Northern Ireland and Crown Dependencies <sup>(2)</sup>.

The number of stillbirths due to GBS infection recorded by the General Registry Office may differ from that found by the audit as not all stillbirths will have a post mortem. Also detailed clinical information may not be available for some time after the stillbirth is registered.

The following sections give some information on the role of the autopsy in determining the cause of death and the other findings that have to be taken into consideration.

## **The role of the autopsy in determining the cause of death**

A post-mortem (autopsy) examination may provide information about why a baby has died <sup>(3)</sup>. The following indicates how a post mortem contributes to such information:

- May confirm an existing clinical diagnosis
- May identify conditions that might not have been diagnosed clinically
- May exclude possible factors such as malformation, infection, or growth restriction
- In stillborn infants may give an approximation of the time of death
- It may resolve specific questions about the care of the pregnant woman
- May help with grieving by addressing family concerns
- It may indicate the need for genetic counselling
- May contribute to the audit of antenatal and post natal diagnostic procedures
- May help identify complications of care and treatment <sup>(4)</sup>

All post mortem examinations on fetuses and babies in Northern Ireland are carried out by specialists in perinatal pathology in the Northern Ireland Regional Paediatric Pathology Service which is based at the Royal Victoria Hospital, Belfast. There is dedicated mortuary space and specialist equipment at this site for paediatric cases.

When maternal/parental consent has been obtained for an autopsy, the baby's body is transferred from other HSC Trusts to the Regional Centre for examination.

## **Infection as the Cause of Stillbirth**

There are several systems used to classify the cause of a stillbirth, and some of these have led to a high rate of 'unexplained' cases Wigglesworth's pathophysiological classification, the fetal and neonatal classification, the revised Aberdeen obstetric classification <sup>(5)</sup> The Centre for Maternal and Child enquiries (CMACE) introduced a classification system from 2008 aiming to identify the condition that initiates the series of events that lead to a death. This has always been considered more important than identifying the immediate cause of death as it would allow early interventions to improve outcome. This classification system takes into consideration maternal and fetal factors in addition to placental histology <sup>(6)</sup>.

Autopsy diagnosis is generally considered the 'gold standard' by which to assess infection as a cause of death in the CEMACH classification. In the most recent Perinatal Mortality Report infection accounted for 5.1% of the total stillbirths in England, Wales and Northern Ireland <sup>(2)</sup>. The suggestion from this report is that more precision about the cause of death from an improved perinatal mortality classification system would increase the value of these reports to clinicians, epidemiologists and those responsible for planning services.

The ultimate aim is for better information to inform interventions that may reduce perinatal mortality. With this in mind, full post-mortems or modified post-mortems (a limited examination) need to be encouraged.

### **Pathology Aspects of Intra-amniotic Infection - Acute Chorioamnionitis**

Infections may reach the placenta and the fetus in several ways <sup>(7)</sup>:

- By ascending through the endocervical canal
- By spreading via maternal blood (haematogenous route)
- By direct introduction into the uterus, for example during amniocentesis, cord blood sampling or chorionic villus sampling
- By direct extension from infection in the endometrium

The vast majority of infections in the uterine cavity occur by the first two methods.

Acute chorioamnionitis is the stereotypical pattern of inflammatory changes seen in response to microorganisms in the amniotic fluid: it is indicative of an ascending bacterial infection in the amniotic cavity. Ascending infection can occur in the presence of intact fetal membranes, and the loss of membrane integrity resulting from inflammation due to bacterial infection predisposes to membrane rupture <sup>(8)</sup>.

Initially, the inflammatory response to the bacteria that enter the amniotic cavity is maternal in origin, followed by a fetal response with acute inflammatory cells migrating out of the fetal vessels in the umbilical cord (acute funisitis) and the chorionic plate: this can take some time to develop, with some commentators suggesting days rather than hours.

There are two components to the inflammatory response in the placenta: maternal and fetal.

### **Maternal Inflammatory Response**

This refers to diffuse infiltration of the chorionic plate and the membranes by maternal neutrophils (acute inflammatory cells from the maternal circulation) from the maternal blood in the intervillous space and the venules in the decidua (the lining of the uterus). The definition of acute chorioamnionitis is the presence of acute inflammatory cells in the fetal membranes of the placenta.

The pattern of placental inflammation can indicate to some extent the aetiology and the timing of onset of the infection.

There is a grading system for acute chorioamnionitis, based on the extent of the spread of acute inflammatory cells (initially the cells are found in the subchorionic space, then infiltrate into the

chorion, and then the amnion) but this grading system does not reliably correlate with fetal outcome.

GBS is associated with both preterm infant and term infant infections. It is recognised that intra-amniotic infection with GBS may occur without significant histological acute chorioamnionitis being identified. This may be due to host factors and bacterial toxin production <sup>(9)</sup>.

Other causative organisms can include normal endogenous flora, the abnormal flora associated with bacterial vaginosis, and organisms colonising the vagina from gastrointestinal sites.

### **Fetal Inflammatory Response**

Neutrophils from the fetal circulation migrate through the walls of the large fetal vessels in the chorionic plate and the umbilical cord. The neutrophils are most dense in those areas that face the amniotic cavity. Upon leaving the walls of the blood vessels the neutrophils migrate across the connective tissue of the umbilical cord.

The umbilical cord does not receive any circulation from the mother, and its blood flow is purely fetal. Any inflammatory reaction seen in the cord is therefore direct evidence of a fetal response to an antenatally acquired infection: the baby is responding to an infection which it has acquired or been exposed to whilst still in utero. Chorionic plate vasculitis and umbilical cord arteritis or cord phlebitis are therefore direct proof that the baby was responding to an infection before birth. The length of time taken to develop a fetal inflammatory response is at least several hours, and some authors suggest it may be longer <sup>(10)</sup>.

Histological chorioamnionitis is the 'gold standard' for the diagnosis of amniotic fluid infection. Clinical chorioamnionitis, based on maternal symptoms including fever, maternal leukocytosis, foul smelling discharge or tachycardia, does not manifest in up to 75% of women with histological acute chorioamnionitis. Other investigations such as assays for cytokines in amniotic fluid, or culture and Gram stain of the fluid, provide better correlation than clinical evaluation.

It is recognised that there is little correlation between the severity of inflammation of the placenta and the clinical condition of the baby at birth. For example, there may be severe inflammation in the placenta but the baby is relatively well at delivery: conversely, babies who are seriously ill at delivery may have minimal inflammation in the placenta <sup>(11)</sup>.

There is one feature that **does** correlate strongly with the clinical outcome and that is the presence of umbilical cord involvement. Umbilical arteritis is associated with an increased risk of neurological impairment in the baby and with increased fetal sepsis <sup>(12)</sup>.

During intrauterine life, the fetus normally swallows and breathes in amniotic fluid, and so exposure to any bacterial organisms can occur and result in a fetal response to infection. At autopsy, samples of fetal tissues are processed for histological examination. It is possible to identify congenital pneumonia (intrauterine pneumonia) from around 18 week's gestation. Neutrophil polymorphs can be seen in the stomach or small intestinal tract on histological examination, providing direct evidence that the fetus swallowed infected amniotic fluid.



## **Investigation of Infection at the time of Autopsy**

Taking swabs for microbiological culture from a miscarried or stillborn baby is the responsibility of the pathologist. The sites most commonly assessed are heart, lung and stomach. The surface skin of the baby is not generally sampled as this may become contaminated when the baby is handled. The heart blood, lung and stomach should be sterile sites in utero.

Babies 'practice' breathing and swallowing during intrauterine life and inhale and swallow amniotic fluid. If the amniotic fluid that the baby has aspirated or swallowed is infected, then a positive culture from the lung or stomach swab indicates infection.

From around 16-18 weeks gestation, a fetus is capable of an immune response to infectious organisms, and the presence of congenital pneumonia is regarded as proof of intra-amniotic infection with a fetal response. If pus cells (neutrophil polymorphs) are seen in the stomach or small bowel on histological examination, this is proof that the baby has swallowed infected amniotic fluid. Pus cells in the main airways indicate that the baby has aspirated infected fluid. These features are only seen in ascending bacterial infection, not in bacterial infection spread via a haematogenous route.

A positive culture from a swab taken from the fetal heart blood indicates fetal bacteraemia or septicaemia i.e. haematogenous infection in the baby.

The swabs are taken as soon as the body cavity is opened: the sterile swabs used are provided by the microbiology department and are identical to those used in clinical practice. The technique used is as aseptic as possible using a sterile scalpel blade and biopsy forceps cleaned with bactericidal disposable cloths.

Taking swabs for culture is regarded as good practice and is generally a routine examination. However, swabs may not be taken in certain circumstances, for example:

- Limited autopsy examination: the parents may only give consent for an external examination, or limited to a body system or body cavity. If this is the case, swabs may not be possible. Occasionally, in a limited external autopsy, an oropharyngeal swab may be taken.
- Where there has been tissue deterioration which may affect results
- Babies in whom there has been a prolonged delay between delivery and autopsy.
- Very early pregnancy losses i.e. 12-14 weeks gestation
- Early losses where the fetal tissues may have been placed in formalin

If clinically appropriate, placental swabs may be obtained after delivery. This is usually performed by delivery suite personnel or by the pathologist at the time of the autopsy examination. The swabs are taken from the chorionic plate (the fetal surface of the placenta) using an aseptic technique by swabbing the chorioamniotic membrane interface i.e. lifting the amniotic membrane and swabbing beneath this. Swabbing the surface of the chorionic plate is not sufficient as conventional swab cultures from the surface of the placenta may be contaminated by vaginal flora. If the amnion membrane has been disrupted during delivery, the swab may be taken from the subchorionic fibrin

layer. It is not possible to obtain microbial cultures from placental tissue that has been formalin fixed. Ideally, a placental swab should be taken as soon as possible after delivery because storage of the placenta in refrigerated conditions may give results of questionable value.

## Investigating the Number of Stillbirths related to GBS

### Methodology

All autopsy reports from the calendar years 2009 and 2010 were accessed from the departmental database.

All cases of stillbirth (>24 weeks gestation) where the following criteria were met were recorded:

- Histopathological evidence of inflammation in the placenta or the fetal tissues e.g. congenital/intrauterine pneumonia, pus cells in the stomach or small intestine with or without a positive culture
- A positive culture of any organism from the baby (usually from heart, lung or gastric swabs): The organism identified was recorded.

Each case where histological inflammation had been seen, or a positive culture had been identified by the initial pathologist was then reviewed by an independent consultant obstetrician and paediatric pathologist. The clinical history was assessed and a consensus agreement was reached as to whether the death was due to infection by GBS alone, or whether other factors needed to be considered.

### Examples (these examples do not represent actual cases, but are representations of the decision making process):

#### **Case Study 1**

The mother is a healthy 25 years para 1. The pregnancy had been uneventful until she presented with loss of fetal movements at 39 weeks gestation. On admission to hospital she had low grade pyrexia. At delivery, the liquor was meconium stained, as was the baby. Autopsy examination revealed a normally formed stillborn baby of body weight and measurements on the 50<sup>th</sup> centile. Histological examination of the placenta showed acute chorioamnionitis with acute funisitis of the cord indicating a fetal response to intra-amniotic infection, and intrauterine pneumonia was seen in the baby's lungs. A gastric swab was taken from the baby and group B streptococcus was cultured from this. An axillary skin swab had been taken from the baby at the time of delivery and GBS was again cultured.

**Outcome: GBS was considered to be the cause of the stillbirth**

#### **Case Study 2**

The mother is a healthy 31 year old primigravida: this was a spontaneous dichorionic twin pregnancy. She presented in established labour at 32 weeks gestation. On auscultation, only a single fetal heart was heard and intrauterine death of one twin was confirmed. She delivered by Caesarean section. On examination, the stillborn twin had multiple abnormalities and was macerated indicating that he had died at least 4 days prior to delivery. The placenta was dichorionic with two separate discs. The disc of the live born twin showed early acute inflammation. No inflammation was seen in the placenta of the second born (stillborn) twin but coliforms were cultured from a stomach swab.

**Outcome: Infection was considered to be unlikely to have been relevant to the death of the baby.**

In general, the following principles were followed:

- In the presence of histological inflammation of the placenta and evidence of a fetal response (chorionic plate vasculitis, umbilical cord funisitis or congenital pneumonia), infection was considered to be the cause of death whether or not an organism was identified.
- If there was histological inflammation indicating a maternal response to infection, but no evidence of a fetal response, infection may have become established before or after fetal death and it was therefore not possible to determine whether infection was the likely cause of stillbirth.
- If a positive culture was obtained, but no histological inflammation was identified either in the placenta or the fetal organs, infection was considered as unlikely to have been the cause of the stillbirth. The organism was more likely to have been a contaminant.
- If a mixture of organisms was obtained, and no histological inflammation was identified, this was generally considered to be contamination rather than infection.

## Results

**Table 23: Total autopsies 2009 and 2010 – Miscarriages >12 weeks, Stillbirths and neonatal deaths associated with infection**

	2009	2010
Number of autopsies	243	249
Number of cases where infection was considered possible as the cause of death	80	73
Number which were neonatal deaths	9	7
Number which were pre labour stillbirths	21	18
Number which were intrapartum stillbirths	3	3
Number which were miscarriages (12-23 weeks)	47	45

Table 23 includes miscarriages of 12 weeks gestation or more, stillbirths and neonatal deaths where there was histological inflammation or positive cultures suggesting that infection needed to be considered as a possible cause of death.

Twenty four stillbirths in 2009 and 21 stillbirths in 2010 were identified where there was the possibility that infection was a factor in the death of the baby.

A wide range of infective organisms were identified in these cases where infection was considered possible as the cause of death. They included a number of different bacteria such as coliforms, enterococcus, E.Coli, clostridium and Group B Streptococcus, also viral and fungal organisms. The positive culture of an organism does not always mean that the death was definitely due to that infection. When the stillbirths, where an organism was identified, were reviewed fewer cases than the 24 and 21 in 2009 and 2010 respectively were considered as being definitely due to infection. Some were babies with multiple abnormalities who died with rather than due to infection. Others were compromised babies with placental dysfunction where the infection was a co-factor, but not

the only factor in the death. In the remainder infection was the definitive cause of death. The number of stillbirths falling into each of these categories is given in table 24.

**Table 24: Stillbirths associated with infection**

	2009	2010
Definite Cause	13	10
Co-factor	3	6
Not related	8	5

### Results following review of the Clinical History

**Note:** to preserve patient confidentiality, limited clinical information is included and identifiers have been removed.

Following review of the clinical histories by a paediatric pathologist and consultant obstetrician, GBS infection was assigned as the primary cause of death in 3 stillbirths in 2009 and 2 stillbirths in 2010. Four stillborn infants were delivered at 37 – 42 weeks and one delivered at 35 – 37 weeks gestation. A single risk factor of GBS on vaginal swab was present in the patient with a pre-term delivery. None were intrapartum stillbirths and antibiotics were not administered.

### Discussion

Collecting information retrospectively for an audit in any field of practice is inexact. Not all stillborn babies undergo autopsy and not all placentas are examined. Within Northern Ireland 55% <sup>(1)</sup> of stillbirths (>24 weeks) undergo this investigation as compared with 44% across England, Wales, N. Ireland and Crown Dependencies. 78% of placentas from stillborn infants are assessed within the England, Wales, Northern Ireland and Crown Dependencies <sup>(1)</sup>. In Northern Ireland, no regional placental pathology reporting service exists, although the Regional Paediatric Pathology Service recommends that the placentas of all babies who miscarry, are stillborn or who die in the neonatal period are referred to the service for specialist examination. In 2009 and 2010, 95% of placentas from stillborn babies were referred to the Regional Paediatric Pathology service. However the proportion of placentas referred from babies who die in the neonatal period or miscarry is not known. This limited pathological assessment of stillbirths and placentas may contribute to a possible underestimation of GBS disease.

A further factor is a failure to culture organisms in suspected infection: a number of cases in each year under study occurred where there was histological evidence of inflammation in the placenta or the fetus, but no organisms were cultured despite swabs being taken.

This may be due to the time taken for a baby to be transferred to the Regional Centre in Belfast for examination. This can be variable as there is an understandable conflict between many parents' wish to spend time with their baby, and the benefits of carrying out the post mortem examination as soon as possible after death <sup>(3)</sup>. If there is to be a delay before transporting the baby to the Regional Centre, the post mortem may not yield as much information.

The remains may also be cooled for variable periods of time, which may impact on the success of culturing more fastidious organisms. Additionally, there were a smaller number of cases where the

pathologists did not take swabs from the baby at the time of the autopsy but histological inflammation was seen.

All of these factors may result in an underestimation of the burden of disease.

Infection as a cause of stillbirths is 5.1% within the UK<sup>(2)</sup> and 7.7% within Northern Ireland<sup>(1)</sup>.

## Summary

Five stillbirths during the calendar years of 2009 and 2010 were assessed as being due to Group B Streptococcal disease. The parameters used to conclude that GBS infection was the cause of death were a combination of fetal/placental histology, microbiological culture and clinical opinion. All stillbirths presented at >35 weeks gestation and all had acute chorioamnionitis on placental histology. One mother had a positive GBS vaginal swab result. As all had intrauterine deaths before labour without risk factors (other than one case with positive vaginal culture for GBS), antibiotic prophylaxis would not have been possible, and for the same reason antenatal screening for GBS carriage would not have prevented the deaths.

## Key Messages

- **55% stillborn infants undergo autopsy in Northern Ireland. Limited pathological assessment of stillbirths and placentas may contribute to a possible underestimation of GBS disease.**
- **Only one of 5 stillbirths had an identifiable risk factor.**

## Recommendations

1. **An enhanced Regional Placental Pathology Service should be considered.**
2. **Specific measures to enhance the identification of infection as a cause of Stillbirth:**
  - i. **Expedite the transport of infants for Post Mortem to the Regional Paediatric Pathology Service with emphasis on the appropriate transfer of placentas in a fresh i.e. unfixed state to enable placental swabs to be taken, if necessary.**
  - ii. **Emphasis on bacteriological culture of the placenta at delivery with awareness of the correct procedure for obtaining placental microbial cultures within the Delivery Suite.**
  - iii. **Improvement of the uptake of autopsy examinations.**

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# **Chapter 5**

## **Anaphylaxis - Case reports of severe allergy to Antibiotics in Pregnancy**

## Introduction

This chapter represents a case series of women referred to the Immunology Service for severe allergic responses to antibiotics and is not an audit of practice. This series does not allow calculation of prevalence or incidence as not all suspected or actual reactions to antibiotics during the time period have been included. The timing of the series is outside the audit period of 2008 – 2010. However, the authors were of the opinion that the report should contain information on rare deleterious effects of antibiotic prophylaxis to inform health professionals and pregnant women of risks.

## Diagnosing penicillin allergy

Adverse reactions to antibiotics are amongst the most commonly reported drug reactions in both community and hospital based healthcare. The majority of adverse reactions to drugs (approximately 90%) are said to be non immunologically mediated, leaving 10% immunologically mediated, a proportion of which would be immediate (Type 1 hypersensitivity) or truly “allergic”. Adverse reactions occur in up to 10% of patients who receive penicillin; furthermore, up to 10% of hospitalised patients report a previous reaction to penicillin, most incorrectly labelling this as an allergy<sup>(1, 2)</sup>.

The most common adverse reactions following penicillin administration include pain at the site of injection, rash, angioedema, nausea, vomiting and diarrhoea. These are usually mild and self-limiting. Severe reactions are more rare. Some of these are listed in table 25.

**Table 25: Moderate to severe reactions associated with penicillin usage.**

Allergic anaphylaxis
Seizures
Stevens-Johnson syndrome
Toxic Epidermal Necrolysis
Interstitial nephritis
Haemolytic anaemia
Deranged liver function

The incidence of anaphylaxis (the most severe life threatening allergic reaction) to penicillin is difficult to determine. This is mainly due to poor history taking at the time of reaction and lack of resources to diagnose or exclude allergy at a specialist clinic.

It would not take long, however, to overwhelm local allergy resources if up to ten percent of the population required investigation following adverse reactions to penicillin. In patients receiving penicillin, estimates for the true incidence of allergic anaphylaxis are between 0.01 -0.05 %<sup>(3)</sup>.



## **Testing for allergic anaphylaxis to penicillin**

Anaphylaxis is defined as a severe, life-threatening generalised or systemic hypersensitivity reaction. The diagnosis requires the presence of either breathing or circulatory difficulty <sup>(4)</sup> and is highly likely if all three of the following criteria are met <sup>(5)</sup>:

1. A life-threatening airway problem and/or breathing problem and/or circulatory problem
2. Sudden onset and rapid progression of symptoms
3. Skin and/or mucosal changes

The diagnosis of allergic anaphylaxis is best made using a combination of clinical history; laboratory testing, skin testing and direct provocative challenge (see Appendix 4).

## **Anaphylaxis in pregnancy**

Penicillin allergy during pregnancy resulting in anaphylaxis has been well reported previously <sup>(6)</sup>. The main indication for penicillin in these reports was prevention of group B streptococcal infection or to treat chorioamnionitis. The commonest presenting sign is severe hypotension often requiring epinephrine to be administered.

Whilst the outcome is generally favourable for the mother and baby, there are cases within these published reports of neonatal neurological damage and death following penicillin induced anaphylactic shock.

## **Case reports from within Northern Ireland 2011-2012**

Patients may be referred to the Regional Immunology Service at the Royal Victoria Hospital, Belfast, for investigation, as a result of a formal suspected drug reaction care pathway. As part of this process, an anaesthetist with a special interest in such allergy has undertaken further testing of referred patients from January 2011, whilst others will be seen in specialist allergy clinics.

The following represents a selected case series of women seen and assessed in the anaesthetic reaction clinics. This commentary does not include information either on milder reactions following which patients stop taking penicillin or other patients seen in the specialist allergy clinics. In relation to the latter, we are aware of 3 fatal cases of allergic reactions to intravenous co-amoxiclav (which contains penicillin) occurring in this region recently, one of which was an obstetric case <sup>(7)</sup>.

Between 01 January 2011 and 31 October 2012 five additional cases of severe antibiotic allergy have been diagnosed in pregnant women or immediately following delivery. The results of which are summarized in Table 26.

In 2007 there was a maternal and infant death following an unexpected acute anaphylactic reaction to co-amoxiclav (which contains penicillin) given during labour. The woman was not known to be allergic. This was included in the CEMACH Report 2006 – 2008 <sup>(8)</sup>.

**Table 26 - Cases of co-amoxiclav allergy in pregnancy or immediately following delivery in Northern Ireland from 01 January 2011 to 31 October 2012**

Case no	Signs and symptoms	Timing of reaction	Treatment required	Outcome	Mast cell tryptase	Penicillin specific IgE	Skin test results
1	Tachycardia Hypotension "Difficulty breathing"	C-section: Immediately following co-amoxiclav administration following delivery of baby	Epinephrine Chlorphenamine hydrocortisone	Survived	Elevated	N/A	Positive skin prick tests to co- amoxiclav
2	Flushing Severe hypotension	C-section: Immediately following co-amoxiclav administration following delivery of baby	Epinephrine Chlorphenamine hydrocortisone	Survived	Elevated	Elevated	N/A*
3	Tachycardia Severe hypotension	C-section: Immediately following co-amoxiclav administration following delivery of baby	Epinephrine Chlorphenamine hydrocortisone	Survived	Elevated	Elevated	Positive skin prick tests to co- amoxiclav
4	Tachycardia Severe hypotension	C-section: Immediately following co-amoxiclav administration following delivery of baby	Epinephrine Chlorphenamine hydrocortisone	Survived	Elevated	Elevated	N/A *
5	Tachycardia Severe hypotension	C-section: Immediately following co-amoxiclav administration following delivery of baby	Epinephrine Chlorphenamine hydrocortisone	Survived	N/A	Elevated	N/A Pregnant at time of clinic attendance

\* In cases 2 and 4 the onset of symptoms occurred immediately following intravenous co-amoxiclav administration. Both had raised mast cell tryptase and penicillin specific IgE. This was deemed adequate evidence to make diagnosis of co-amoxiclav allergy.

## Discussion

A maternal death in Northern Ireland is recorded within the 2006-2008 maternal mortality report <sup>(8)</sup> as a result of anaphylaxis to co-amoxiclav. The gravity of such a complication requires to be weighed against the possible benefits of antibiotic prophylaxis for neonatal GBS.

All five severe allergic reactions occurred at the time of caesarean section. Administration of antibiotics at delivery was recommended by NICE Caesarean Section guideline (2004) <sup>(9)</sup> at the clamping of the cord to reduce maternal postoperative infection. This has been superseded by the most recent update on this guideline in November 2011 <sup>(10)</sup> whereby antibiotic administration is now recommended at skin incision. The guideline states:

*'Offer women prophylactic antibiotics at CS before skin incision. Inform them that this reduces the risk of maternal infection more than prophylactic antibiotics given after skin incision, and that no effect on the baby has been demonstrated.'* (New Recommendation 2011)

Such a change in timing at Caesarean Section has necessitated an alteration in antibiotic regimen because of the association of co-amoxiclav with necrotizing enterocolitis if the newborn is exposed in utero. Thus a further recommendation is:

*'Do not use co-amoxiclav when giving antibiotics before skin incision.'* (New Recommendation 2011)

All documented cases occurred before the change in guideline recommendation.

The Obstetric Surveillance System (UKOSS) Annual Report 2012 has highlighted the increase in antibiotic prophylactic regimens in pregnancy (GBS and Caesarean Section) in addition to recent guideline changes on antibiotic timing <sup>(10)</sup>. The limited data on incidence of anaphylaxis within the UK is recognized. A study to collect 'information about the incidence, management and outcomes of anaphylaxis in pregnancy in the UK <sup>(11)</sup> has been approved by the UKOSS Steering Committee.

## Key messages

**At least five severe allergic reactions to co-amoxiclav occurred within the timeframe January 2011 – October 2012. All were at caesarean section following administration of co-amoxiclav at the clamping of the umbilical cord. One maternal death occurred following anaphylaxis after co-amoxiclav administration in 2007.**

**A study to collect information on the incidence of anaphylaxis in pregnancy in the UK is timely.**

## Recommendation

**All suspected anaphylactic reactions in pregnancy should be referred to the Regional Immunology Service for investigation.**

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# **Chapter 6**

## **Conclusions & Recommendations**

### **What are the aims of the Audit?**

The Audit aims to provide an understanding of the burden of EOGBS disease in Northern Ireland (2008 – 2010) and a measure of the observance of a guideline for prevention of neonatal infection during 2009 and 2010. During that period, preventative techniques used by health professionals focused on a risk based strategy as defined by the RCOG Guideline (2003) whereby antibiotics are considered for women in labour who have certain risks:

- fever in labour (>38 degrees)
- prolonged rupture of membranes (> 18 hrs)
- preterm labour (< 37 weeks)
- GBS detected in the urine or incidentally in the vagina following a clinical presentation
- a previous infant with GBS disease.

### **What challenges occurred within the information collection process?**

Measurement of the observance of the guideline against all of these risks was not possible from the Northern Ireland Maternity Information System (NIMATS). This database captures information relating to the maternity process. However, not all maternity units used NIMATS during the years assessed and thus the Audit also relied on the Patient Administration System (PAS) – an operational system in acute hospitals to record patient activity. The risk factors which could be assessed from both databases were: pre-term labour (<37 weeks), prolonged rupture of membranes and raised temperature in labour (>38 degrees). The duration of the risk 'prolonged rupture of membranes' was readjusted from 18 hours to >24 hours as this was the recorded measure on NIMATS and PAS systems. Information on other risk factors such as previous infant with GBS disease or a recording of microbiological swab results for GBS were not available within NIMATS or PAS.

Audit design limitations were present for the assessment of the antenatal workstream on laboratory confirmed GBS in a single unit. The Audit Tool (Proforma 1, Appendix 2) was inadequate to address matters such as timing of GBS testing in pregnancy, availability of results before labour, numbers with negative GBS swabs and their outcomes, length of stay of neonates and complications of therapy. On this basis, the authors regard this aspect of the Audit as preliminary and requiring further study, if feasible.

### **What is the incidence of GBS disease in Northern Ireland and how does this compare with elsewhere?**

The incidence of GBS disease in Northern Ireland is 0.57 per 1000 live births or 1 in every 1750 live births during the calendar years of 2008 – 2010. This is slightly higher than the combined England, Wales and Northern Ireland incidence of 0.41/1000 live births in 2010 as assessed by the Health Protection Agency. Whether this is a true difference of GBS infection incidence between Northern Ireland and other parts of the UK is uncertain. The Audit had strict criteria (blood or spinal fluid infection only) for assessing the presence of infection. Data were obtained from the microbiology laboratories in the five Trusts and the Public Health Agency. As such, asymptomatic infants were included, in addition to two blood results with a mixed growth of organisms which included GBS. The latter infants were included within the results for completeness although other studies may have omitted these as evidence of contamination. Health Protection Agency data

within the UK are from voluntary reports – thus some instances of GBS infection may not be reported which may underestimate the true incidence of infection.

### **In what proportion of GBS neonatal infections were risk factors identified in the mother?**

One or more of the risk factors for GBS were present in 55.8% of the mothers of infants with GBS infection. Thus the remaining women had no identifiable antenatal factor to allow prediction of the disease.

Would screening for GBS carriage with a vaginal swab test at 35 – 37 weeks for all pregnant women as used in the US, Canada and Australia and antibiotics offered in labour for GBS positive women resolve this deficiency?

Within the Audit approximately 1/3 of infected infants were delivered at less than 38 weeks and 1/4 less than 37 weeks. Thus universal screening for GBS at 35 – 37 weeks would have a reduced opportunity to identify these pregnancies at increased risk (other than due to preterm labour) as results of culture may not be available.

Screening will not prevent all instances of GBS disease. In the evaluation of universal antenatal screening undertaken in the US in 2009, a total of 61.4% of the GBS infected infants were born to women who had tested negative on antenatal screening at 35 – 37 weeks <sup>(1)</sup>. Similarly within this Audit, administration of antibiotics in labour is not a guarantee of GBS disease prevention. Approximately 1/4 of women who delivered infants with GBS infection received antibiotics in labour.

### **Why were risk factors not acted upon in labour?**

A trend exists within the 'at risk' sample of the Northern Ireland population whereby antibiotic prophylaxis increases with increasing numbers of risk factors. However, at best, 50% – 70% of at risk women received preventative measures for GBS leaving a considerable number of women with risk factors without antibiotics in labour.

Similarly, within the single unit that introduced an approach of opportunistic antenatal testing and post delivery infant swab testing, antibiotics were administered to women in labour in no more than 45% for GBS culture positive women with one or more additional risk factors.

Almost 56% of infants with EOGBS were delivered to women with one or more risk factors in labour. Antibiotics were administered to 31% of women with a single risk factor, 43% with two risk factors and 100% with 3 risk factors. Except for those with 3 risk factors, a considerable number of women did not receive antibiotics.

The RCOG guideline recommendation is that: *“The argument for (GBS) prophylaxis becomes stronger in the presence of two or more risk factors.”*

The Audit reflects this recommendation.

The authors can only speculate as to the reason for non adherence to the guideline in a proportion of cases. Possibilities include lack of time before delivery, allergy or lack of consent for antibiotic administration on admission. The language of the RCOG Guideline (2003) is non directive and

uses terms that are ambiguous. Terms such as '*antibiotics should be considered*' or '*antibiotics should be discussed*' results in uncertainty as to whether or not administration should take place at all.

Health professionals with a duty of care for the pregnant woman have a keen regard for an approach to pregnancy whereby no medication is administered without a sound indication. The Oracle Study <sup>(2, 3)</sup> exemplifies the possible risks of antibiotic administration. Concerns exist about increased antibiotic resistance and changes in types of neonatal infection secondary to widespread prophylactic regimens. There is an awareness of the possible deleterious effects of antibiotics, such as anaphylaxis, and this may also have played a role in reducing adherence to guidelines.

It is also possible that lack of knowledge of the detail of the guideline by health professionals played a part in the variable adherence to antibiotic prophylaxis in Northern Ireland.

### **What is the way forward for prevention of GBS in infants?**

A multifaceted approach to prevention to incorporate awareness amongst health care professionals and pregnant women about GBS, adherence to the 2012 RCOG Guidance, ongoing audits of management of risk factors in labour and audit/case note review of babies diagnosed with EOGBS, to identify if any missed opportunities exist for prevention. All of these are immediately achievable.

Further work is required on a rapid diagnostic test for use in labour to allow identification of the GBS vaginal carrier. Current rapid tests such as the nucleic acid amplification test (NAAT) have varied sensitivities and specificities. A disadvantage would be that NAAT does not have antimicrobial susceptibility testing for penicillin-allergic patients. The complexities of turnaround time in reality, availability of tests 24 hours a day, staffing requirements, costs and communication of results needs to be taken into consideration <sup>(4)</sup>. In addition other factors to take in to account would include the impact on length of stay of mother and infant and ensuing pressures on bed capacity.

### **Recommendations**

- Continue to raise the awareness of pregnant women and health professionals about GBS disease.
- Clinicians should be aware of the possible neonatal and maternal risks of antibiotic prophylaxis.
- Maternity Information Systems require revision. The information collected needs to be relevant to professional practice and able to support monitoring and audit of practice against clinical standards. This will assist in the future evaluation of outcomes of care.
- There is a need to improve the completeness and quality of data input to maternity information systems.
- A comprehensive retrospective evaluation of GBS testing, within a single maternity unit, for the prevention of GBS disease of the neonate should be undertaken, if feasible.



- An agreed pathway of care for the prevention of EOGBS infection in neonates.
- An agreed pathway of care for infants with suspected early onset sepsis e.g. the adoption of the recently published NICE guidelines on “Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection.”
- Maternal and neonatal case notes of all GBS culture positive neonates should be audited.
- An enhanced Regional Placental Pathology Service should be considered.
- Specific measures to enhance the identification of infection as a cause of Stillbirth:
  - Expedite the transport of infants for Post Mortem to the Regional Paediatric Pathology Centre.
  - Emphasis on technique of bacteriological culture of the infant and placenta at delivery.
  - Improvement of the uptake of autopsy examinations.
- All suspected anaphylactic reactions in pregnancy should be referred to the Regional Immunology Service for investigation.

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# Appendices

## Working Group Membership

Name	Designation	Organisation/Trust
Robin Ashe ( <b>Chair</b> )	Consultant Obstetrician & Gynaecologist	Northern HSC Trust
Denise Boulter	Nurse Consultant	Public Health Agency
Margaret Boyle	Senior Medical Officer	DHSSPS
Wendy Clarke	Labour Ward Sister	Southern HSC Trust
Stanley Craig	Consultant Neonatologist	Belfast HSC Trust
Caroline Gannon	Consultant Paediatric Pathologist	Belfast HSC Trust
Fiona Kennedy	Consultant in Public Health Medicine	Public Health Agency
Marina Lupari	Assistant Director of Nursing	Northern HSC Trust
Elaine Madden	Head of Midwifery & Gynaecology	South Eastern HSC Trust
Grace Ong	Consultant Microbiologist	Belfast HSC Trust
Nicola Porter	GAIN Manager	GAIN
Mohammed Sartaj	Specialist Registrar in Public Health	DHSSPS
Harmini Sidhu	Consultant Obstetrician & Gynaecologist	Southern HSC Trust
Ronan Strain	Regional Clinical Audit Facilitator	GAIN
Tom Trinick	Consultant Chemical Pathologist/GAIN	South Eastern HSC Trust
Martin Shields	Consultant Anaesthetist	Belfast HSC Trust
Sharon Jamison	Assistant Statistician	DHSSPS
Rachel Stewart	Assistant Statistician	DHSSPS
<b>Literature review undertaken by</b>		
Andrew Craven	ST2 in Obstetrics & Gynaecology	Northern HSC Trust

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Name	Designation
Lisa Bell	SHO in Obstetrics & Gynaecology
Josie Burns	Sister Midwife
Richard Bigger	Clinical Audit Facilitator – Northern HSC Trust
Elaine Corrigan	Specialist Registrar Microbiology, Belfast Health & Social Care Trust
Nuala Collins	NIMATS – Southern HSC Trust
Meabh Cosgrove	Specialist Registrar in Obstetrics & Gynaecology
Julie Dunlop	NIMATS – South Eastern HSC Trust
David Edgar	Consultant Immunologist, Royal Victoria Hospital, Belfast
Nazish Kanwal	Specialist trainee in Obstetrics & Gynaecology
Denise Kivelehan	NIMATS – Western HSC Trust
Julie Lewis	ST6 Paediatrics
Sarah Magowan	ST7 Paediatrics
Ruth McDonald	Clinical Audit Manager
Anne McGeown	Staff Midwife
Claire McGrath	NIMATS – Northern HSC Trust
Angela Mervyn	NIMATS – Belfast HSC Trust
Barbara Millar	NIMATS – South Eastern HSC Trust
Fionnuala Mone	Specialist Registrar in Obstetrics & Gynaecology
Anne Quinn	Clinical Effectiveness Manager
Rosie Steele	SHO in Obstetrics & Gynaecology
Ashlinn Stevens	SHO in Obstetrics & Gynaecology
Jonathan Wright	Clinical Audit Facilitator – Northern HSC Trust

**GBS Audit Proforma 1**

To be completed for women with antenatal risk factors for GBS	
<b>Audit Ref No:</b>	
1.	<b>Trust:</b> Belfast <input type="checkbox"/> Southern <input type="checkbox"/> Western <input type="checkbox"/> Northern <input type="checkbox"/> South Eastern <input type="checkbox"/>
2.	<b>Age of Mother:</b> <16 <input type="checkbox"/> 16-20 <input type="checkbox"/> 21-25 <input type="checkbox"/> 26-30 <input type="checkbox"/> 31-35 <input type="checkbox"/> 36-40 <input type="checkbox"/> 40+ <input type="checkbox"/>
3.	<b>Maternity unit where delivered:</b> _____
4a.	<b>Gestation at delivery:</b> _____ weeks _____ days
4b.	<b>Date of delivery:</b> _____
5.	<b>Mode of Delivery:</b> Vaginal Delivery <input type="checkbox"/> Emergency Caesarean Section in labour <input type="checkbox"/> Planned Caesarean Section <input type="checkbox"/>
6.	<b>Maternal Risk Factors (RCOG 2003):</b> <i>(Please tick all that apply)</i> Previous baby affected by neonatal GBS disease <input type="checkbox"/> GBS bacteruria detected during <i>current</i> pregnancy <input type="checkbox"/> Incidental finding of vaginal carriage of GBS during <i>current</i> pregnancy <input type="checkbox"/> Screen positive for GBS in current pregnancy (AAH only) <input type="checkbox"/> Preterm labour and delivery (<37 weeks) <input type="checkbox"/> Prolonged rupture of membranes >18hours in labour <input type="checkbox"/> Fever in labour (38°C) <input type="checkbox"/> <b>Number Risk Factors present:</b> One <input type="checkbox"/> Two <input type="checkbox"/> Three or More <input type="checkbox"/>
7.	<b>Was the woman given IV antibiotics?</b> Yes <input type="checkbox"/> No <input type="checkbox"/> If 'Yes' was this: Antenatal <input type="checkbox"/> Intrapartum <input type="checkbox"/>
8.	<b>What IV antibiotics were given during labour?</b> BenzylPenicillin <input type="checkbox"/> Clindamycin (due to penicillin allergy) <input type="checkbox"/> Other ( <i>please state</i> ) _____ None <input type="checkbox"/>

Primary Antibiotic Regime	
9.	<b>Benzylpenicillin with a 3 gm loading dose, followed by 1.5 g every 4 hours:</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
10.	<b>Clindamycin regimen (Woman allergic to Penicillin) 900mg 8 hourly:</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
11.	<b>Any evidence of maternal adverse reaction to antibiotics?</b> Yes <input type="checkbox"/> No <input type="checkbox"/> Not Known <input type="checkbox"/> If 'Yes', describe reaction _____
12.	<b>Time of first dose (24 hour clock):</b> ____: ____ Hrs <b>Time of Delivery (24 hour clock):</b> ____: ____ Hrs
To be Completed on all babies from Women with Risk factors for Group B Streptococcus Disease (Including information from women obstetric notes) Neonatal	
1.	<b>Birth Weight</b> _____gms
2.	<b>Signs &amp; Symptoms of Neonatal Sepsis/Infection:</b> <i>(please tick all that apply)</i> Pyrexia <input type="checkbox"/> Lethargy <input type="checkbox"/> "Poor handling" <input type="checkbox"/> Vomiting <input type="checkbox"/> Poor feeding <input type="checkbox"/> Sudden Collapse <input type="checkbox"/> Cyanosis <input type="checkbox"/> Tachypnoea <input type="checkbox"/> None <input type="checkbox"/>
3a.	<b>Did the baby have a positive gastric aspirate for GBS?</b> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/>
3b.	<b>Source of Positive GBS Culture:</b> Blood Culture <input type="checkbox"/> Lumbar Puncture <input type="checkbox"/> Urine <input type="checkbox"/> Skin <input type="checkbox"/> Other <input type="checkbox"/> (Please State) _____ No positive culture recorded in case note <input type="checkbox"/>
4.	<b>Age at Infection:</b> ____ Days ____ Hours
5.	<b>Antibiotic Given:</b> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <input type="checkbox"/>
6.	<b>Date Antibiotic started:</b> _____ <b>Time Antibiotic started (24hr clock):</b> ____:____Hrs <b>Date Antibiotic stopped:</b> _____ <b>Time Antibiotic stopped (24 hr clock):</b> ____:____Hrs
7a.	<b>Date admitted to NICU/NUU:</b> _____
7b.	<b>Date discharged from NICU/NUU:</b> _____
7c.	<b>Date of hospital discharge if different from question 7b:</b> _____
8.	<b>Outcome at Discharge:</b> Alive <input type="checkbox"/> Dead <input type="checkbox"/>
9.	<b>Developmental Status at most recent follow-up (if known):</b>

## GBS Audit Proforma 2

**To be completed on all babies with Confirmed GBS (including information from Women obstetric notes)**

### Part A – Neonatal GBS

**Audit Ref No:**

1.	<b>Trust:</b> Belfast <input type="checkbox"/> Southern <input type="checkbox"/> Western <input type="checkbox"/> Northern <input type="checkbox"/> South Eastern <input type="checkbox"/>
2.	<b>Birth Weight:</b> _____ gms
3.	<b>Signs &amp; Symptoms of Neonatal Sepsis/Infection:</b> <i>(please tick all that apply)</i> Pyrexia <input type="checkbox"/> Lethargy <input type="checkbox"/> "Poor handling" <input type="checkbox"/> Vomiting <input type="checkbox"/> Poor feeding <input type="checkbox"/> Sudden Collapse <input type="checkbox"/> Cyanosis <input type="checkbox"/> Tachypnoea <input type="checkbox"/> None <input type="checkbox"/>
4.	<b>Source of Positive GBS Culture:</b> Blood Culture <input type="checkbox"/> Lumbar Puncture <input type="checkbox"/> Urine <input type="checkbox"/> Skin <input type="checkbox"/> Other <input type="checkbox"/> (Please State) _____
5.	<b>Age at Infection:</b> _____ Days _____ Hours
6.	<b>Antibiotic Given:</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
7.	<b>Date Antibiotic started:</b> _____ <b>Time Antibiotic started (24hr clock):</b> ____:____ Hrs <b>Date Antibiotic stopped:</b> _____ <b>Time Antibiotic stopped (24 hr clock):</b> __:__ Hrs
8a.	<b>Date admitted to NICU/NUU:</b> _____
8b.	<b>Date discharged from NICU/NUU:</b> _____
8c.	<b>Date of hospital discharge if different from question 8b.:</b> _____
9.	<b>Outcome at Discharge:</b> Alive <input type="checkbox"/> Dead <input type="checkbox"/>
10.	<b>Developmental Status at most recent follow-up (if known):</b>

### Part B – Mother's Obstetric History

1.	<b>Age of Mother:</b> <16 <input type="checkbox"/> 16-20 <input type="checkbox"/> 21-25 <input type="checkbox"/> 26-30 <input type="checkbox"/> 31-35 <input type="checkbox"/> 36-40 <input type="checkbox"/> 40+ <input type="checkbox"/>
2.	<b>Maternity unit where delivered:</b> _____
3a.	<b>Gestation at delivery:</b> _____ weeks _____ days
3b.	<b>Date of delivery:</b> _____
4.	<b>Mode of Delivery</b> Vaginal Delivery <input type="checkbox"/> Emergency Caesarean Section in labour <input type="checkbox"/> Planned Caesarean Section <input type="checkbox"/>



	<b>Maternal Risk Factors (RCOG 2003):</b> ( <i>Please tick all that apply</i> )
	Previous baby affected by neonatal GBS disease <input type="checkbox"/>
	GBS bacteruria detected during <i>current</i> pregnancy <input type="checkbox"/>
	Incidental finding of vaginal carriage of GBS during <i>current</i> pregnancy <input type="checkbox"/>
5.	Screen positive for GBS in current pregnancy (AAH only) <input type="checkbox"/>
	Preterm labour and delivery (<37 weeks) <input type="checkbox"/>
	Prolonged rupture of membranes>18hours in labour <input type="checkbox"/>
	Fever in labour (38℃>) <input type="checkbox"/>
	<b>Number Risk Factors present:</b> One <input type="checkbox"/> Two <input type="checkbox"/> Three or More <input type="checkbox"/>
6.	<b>Was the woman given IV antibiotics?</b> Yes <input type="checkbox"/> No <input type="checkbox"/>  If ‘Yes’ was this:      Antenatal <input type="checkbox"/> Intrapartum <input type="checkbox"/>
7.	<b>What IV antibiotics were given during labour?</b> BenzylPenicillin <input type="checkbox"/> Clindamycin (due to penicillin allergy) <input type="checkbox"/> Other <input type="checkbox"/> ( <i>please state</i> ) _____ None <input type="checkbox"/>
<b>Primary Antibiotic Regime</b>	
8.	<b>Benzylpenicillin with a 3 gm loading dose, followed by 1.5 g every 4 hours</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
9.	<b>Clindamycin regimen (Woman allergic to Penicillin) 900mg 8 hourly</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
10.	<b>Any evidence of maternal adverse reaction to antibiotics</b> Yes <input type="checkbox"/> No <input type="checkbox"/> Not Known <input type="checkbox"/> If ‘Yes’, describe reaction _____
11.	<b>Time of first dose (24 hour clock):</b> ____: ____ Hrs <b>Time of Delivery (24 hour clock):</b> ____: ____ Hrs

### GBS Audit Proforma 3

To be completed on all GBS confirmed Still births	
Part A – Still Birth	
Audit Ref No:	
1.	Trust: Belfast <input type="checkbox"/> Southern <input type="checkbox"/> Western <input type="checkbox"/> Northern <input type="checkbox"/> South Eastern <input type="checkbox"/>
2.	Was <b>GBS</b> the: Main Cause of Death <input type="checkbox"/> Contributory cause of Death <input type="checkbox"/>
3.	Age of baby at Birth: _____ Weeks _____ Days
4.	Histological Signs of inflammation: Yes <input type="checkbox"/> No <input type="checkbox"/>
5.	GBS Identified from: Heart <input type="checkbox"/> Lungs <input type="checkbox"/> Stomach <input type="checkbox"/> Skin <input type="checkbox"/> Placenta <input type="checkbox"/> Other <input type="checkbox"/> (Please specify) _____
Part B – Mother’s History	
1.	Age of Mother: <16 <input type="checkbox"/> 16-20 <input type="checkbox"/> 21-25 <input type="checkbox"/> 26-30 <input type="checkbox"/> 31-35 <input type="checkbox"/> 36-40 <input type="checkbox"/> 40+ <input type="checkbox"/>
2.	Maternity unit where delivered: _____
3.	Mode of Delivery: Vaginal Delivery <input type="checkbox"/> Emergency Caesarean Section in labour <input type="checkbox"/> Planned Caesarean Section <input type="checkbox"/>
4.	Maternal Risk Factors (RCOG 2003): (Please tick all that apply) Previous baby affected by neonatal GBS disease <input type="checkbox"/>  GBS bacteruria detected during <i>current</i> pregnancy <input type="checkbox"/>  Incidental finding of vaginal carriage of GBS during <i>current</i> pregnancy <input type="checkbox"/>  Screen positive for GBS in current pregnancy (AAH only) <input type="checkbox"/>  Preterm labour and delivery (<37 weeks) <input type="checkbox"/>  Prolonged rupture of membranes >18hours in labour <input type="checkbox"/>  Fever in labour (38°C+) <input type="checkbox"/>  Number Risk Factors present: One <input type="checkbox"/> Two <input type="checkbox"/> Three or More <input type="checkbox"/>
5.	Was the woman given IV antibiotics? Yes <input type="checkbox"/> No <input type="checkbox"/> If 'Yes' was this: Antenatal <input type="checkbox"/> Intrapartum <input type="checkbox"/>

6.	<b>What IV antibiotics were given during labour?</b> BenzylPenicillin <input type="checkbox"/> Clindamycin (due to penicillin allergy) <input type="checkbox"/> Other <input type="checkbox"/> (please state) _____ None <input type="checkbox"/>
<b>Primary Antibiotic Regime</b>	
7.	<b>Benzylpenicillin with a 3 gm loading dose, followed by 1.5 g every 4 hour</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
8.	<b>Clindamycin regimen (Woman allergic to Penicillin) 900mg 8 hourly</b> Yes <input type="checkbox"/> No <input type="checkbox"/>
9.	<b>Any evidence of maternal adverse reaction to antibiotics?</b> Yes <input type="checkbox"/> No <input type="checkbox"/> Not Known <input type="checkbox"/> If yes, describe reaction _____
10.	<b>Time of first dose (24 hour clock):</b> ____: ____ Hrs <b>Time of Delivery (24 hour clock):</b> ____: ____ Hrs

## Testing for allergic anaphylaxis to antibiotics

Drug allergy testing is potentially complex both in terms of procedures and their interpretation and should only be undertaken by appropriately experienced specialists. The diagnosis of allergic anaphylaxis is best made using a combination of clinical history, laboratory and skin testing and direct provocative challenge where necessary. Good guidance regarding the investigation of intraoperative anaphylaxis is published and is of direct relevance to this report <sup>(1)</sup>.

## History

There is a spectrum of severity of reactions from mild (urticaria is the presenting feature in over 50% of cases of penicillin allergy) through to 23% of cases with additional systemic features and finally to 4% with anaphylactic shock. A thorough history is extremely useful to aid the diagnosis and assessment of severity of antibiotic allergy. This should include the following:

- 1) The reason for being prescribed an antibiotic. Antibiotic treatment for sore throats using penicillin is associated with a high incidence of maculo-papular rash. This is especially true with Epstein-Barr virus infections. In the absence of other signs, the diagnosis of allergy is very unlikely.
- 2) A full record of any other drugs administered at the time.
- 3) The temporal relationship between administration and the onset of symptoms. Immediate hypersensitivity reactions should occur within minutes of intravenous administration and mostly within 1 hour following oral administration. Reactions outside these times are unlikely to be allergic in nature.
- 4) The nature and severity of symptoms. Higher grades of severity are more likely to be due to allergic reactions.
- 5) The treatment required and how long this took to have effect.

Unfortunately clinical history is scant or unavailable in many cases. Many individuals remember being told never to take penicillin but have no recollection of an earlier reaction.

## Mast cell tryptase

This test should be performed on serial serum samples in suspected allergic reactions that occur in a hospital based setting. Serum mast cell tryptase increases within minutes in most allergic reactions and returns to normal within 24 hours. Mast cell tryptase measurement assists in the confirmation of an anaphylactic reaction, but does not, however, help with determining the causative drug or agent. Typically serum samples are recommended as soon as a reaction occurs, a second sample 2 hours later and a baseline sample at 24 hours after the reaction. Serum levels above 14 mcg/l are taken to indicate an allergic reaction.

## Specific IgE

Within Northern Ireland tests are available to measure serum concentrations of specific IgE against ampicillin, amoxicillin, penicillin V and penicillin G. This is performed using the UniCAP-system<sup>®</sup> (Phadia, Uppsala, Sweden). Concentrations greater than 0.35 kUA/l are used to define a positive test. The test only measures specific IgE against major penicillin determinants (not minor

determinants) and sensitivity is therefore poor (10-50%). Measurement of specific IgE is of itself inadequate as a diagnostic test for penicillin allergy <sup>(2, 3)</sup>.

### **Skin testing**

Following administration of penicillin,  $\beta$ -lactams bind to carrier molecules leading to the formation of antigenic determinants. The major determinant is benzylpenicilloyl poly-L-lysine (PPL). There are other minor determinants classified as minor determinant mixtures (MDMs). Using both these determinants to test for penicillin allergy is more sensitive than using the parent drugs. Amoxicillin and the culprit  $\beta$ -lactam should also be added to the list of agents to be tested.

Several skin-testing protocols are used worldwide to assess likelihood of penicillin allergy. They involve initial skin prick testing with PPL, MDMs, amoxicillin and culprit  $\beta$ -lactam. A positive response is indicated by the development of a wheal of greater than 3 mm within 15 minutes following the prick. These tests have an extremely low risk of inducing allergic symptoms in sensitized individuals.

If skin prick testing is negative, intradermal testing may be performed. This involves injecting 0.02 ml of test drug into the dermis and again looking for the development of a larger wheal 15 minutes later. There is a 1:1000 chance of inducing mild to moderate allergic symptoms with this test. The test is repeated several times using increasing concentrations of drug until neat drug is tested.

Diagnostic performance of drug skin testing is uncertain, however in an unselected population, negative predictive values as high as 85 - 99% <sup>(4)</sup> have been reported. Lower negative predictive values are associated with the broad spectrum antibiotics which are presently used in community and hospital based settings. For this reason, in a condition such as allergic anaphylaxis to penicillin, there is risk in accepting the results of skin testing alone <sup>(5)</sup>.

Skin reactivity may also reduce with time. Five years following positive test results 40 - 100 % of patients exhibit no persisting skin reactivity. A substantial proportion of such patients test positive using drug provocation tests when skin reactivity has resolved <sup>(6)</sup>.

### **Drug provocation test (DPT)**

This test should only be performed if all others are negative. In this context it involves the supervised, incremental administration of oral antibiotic in increasing doses. It typically starts with a lip rub followed by doses of 5 mg (penicillin) up to 250 mg of drug at 30 min intervals. Several protocols exist with 3 - 4 steps used to reach the 250 mg dose. DPT has an increased chance of inducing moderate to severe signs of allergy.

### **Outcomes**

Outcomes are dependent on integrating the detailed clinical history and results of a range of investigative strategies. On average 16% of cases of penicillin allergy will be confirmed using specific IgE titres, 62% using skin testing and 21% using DPT. These testing protocols have significant implications for resources as the time taken to perform the full battery of tests can be well over 3 hours and may need split into several consultations <sup>(1)</sup>.

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**Glossary of Terms**

<b>Abbreviation/Term</b>	<b>Meaning / Organisation</b>
BPSU	British Paediatric Surveillance Unit
CEMACH	Confidential Enquiry into Maternal & Child Health
CMACE	Centre for Maternal and Child enquiries
DHSSPSNI	Department of Health Social Services & Public Safety Northern Ireland
GAIN	Guidelines & Audit Implementation Network
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NICORE	Neonatal Intensive Care Outcomes Research & Evaluation
NIMATS	Northern Ireland Maternity System
NSC	UK National Screening Committee
RCM	Royal College of Midwives
RCOG	Royal College of Obstetricians and Gynaecologists
RCPCH	Royal College of Paediatrics and Child Health
RPPC	Regional Paediatric Pathology Centre
UKOSS	UK Obstetric Surveillance System
<b>Condition Specific</b>	
Anaphylaxis	A life threatening allergic reaction
Antenatal	Taking place before birth
Chorioamnionitis	Inflammation of the fetal membrane
EOGBS	Early Onset Group B Streptococcus
EOS	Early Onset Sepsis
GBS	Group B Streptococcus
Gestational Age	Duration of pregnancy measured in weeks
HVS	High Vaginal Swab
IAP	Intrapartum antibiotic prophylaxis
Intraventricular Haemorrhage	Bleeding into the brain. A complication of prematurity
Intrapartum	During labour and delivery
LB	Live Births
LOGBS	Late Onset Group B Streptococcus
Neurodevelopmental	Relates to the development of the brain and central nervous system
Placenta	The organ that connects the fetus to the wall of the uterus
Postpartum	Time period beginning immediately after birth
Preterm Labour	Labour prior to 37 weeks



PROM	Prolonged Rupture of Membrane (more than 18 hours)
ROM	Rupture of membranes
SROM	Spontaneous rupture of membranes
Tachypnoea	Rapid breathing due to pathology
<b>General Terms</b>	
Adverse Reaction	Any harmful, unintended effect of a medication, diagnostic test, or therapeutic intervention
Anaphylaxis	Rapidly progressing, life-threatening allergic reaction
Aspirate	Removal by suction of a fluid from a body cavity using a needle
Autopsy	Post Mortem examination
Bacteriuria	Presence of bacteria in the urine
BPD	Broncho-Pulmonary Dysplasia
CSF	Cerebrospinal fluid
Epidemiology	Study of the determinants of disease events in populations
ICU	Intensive Care Unit
IV	Intravenous
Lethargy	sluggishness or fatigue; a feeling of listlessness
Live birth	Born alive
Morbidity Rate	Incidence of disability
Mortality Rate	Incidence of death
Nasopharyngeal	Pertaining to the nasal and pharyngeal cavities
Pathology	Medical science concerned with all aspects of disease with an emphasis on the essential nature, causes, and development of abnormal conditions, as well as with the structural and functional changes that result from disease processes
Perinatal	Period of time from 24 weeks gestation to one month after delivery.
Post Mortem	Examination to determine cause of death
Prophylaxis	Measure taken to maintain health and prevent the spread of disease
Pyrexia	Fever
RDS	Respiratory Distress Syndrome
Stillbirth	No sign of life at delivery after 24 weeks gestation.
Sensitivity	Ability of a test to correctly diagnose a disease
Specificity	Ability of a test to correctly diagnose those without disease