Title

Intrapartum antibiotics for prolonged rupture of membranes at term to prevent Group B Streptococcal sepsis

Authors

Ruppa Mohanram Geethanath[1], Imran Ahmed[1], Majd Abu-Harb[1], Chike Onwuneme[1], Kenneth McGarry[2]

Kim Hinshaw[3]

Institutions:

[1]Department of Neonatology, Sunderland Royal Hospital, UK

[2]Department of Statistics, Sunderland University, UK

[3]Department of Obstetrics and Gynaecology, Sunderland Royal Hospital, UK

Corresponding author:

Ruppa Mohanram Geethanath, Consultant Neonatologist, Department of Neonatal Paediatrics,

Sunderland Royal Hospital, UK

Email:Ruppa.geethanath@chsft.nhs.uk

Tel: 01915699978

Fax: 01915699233

Word count: 1658

Abstract:

Background: Group B streptococcus (GBS) is the most common cause of neonatal sepsis in United Kingdom (UK). Early onset sepsis (EOS), but not late onset sepsis (LOS) can be prevented by providing intrapartum antibiotic prophylaxis (IAP). In spite of national guidelines since 2003, the incidence of neonatal GBS infections is increasing in UK.

Aim: To assess the incidence of culture proven GBS infections before and after a change of practice on antepartum management of GBS in babies <3 months of age, born at Sunderland Royal Hospital between 1st Jan 2008 and 31st December 2017.

Setting: Tertiary neonatal unit

Study design: Retrospective cohort study

Methods: Babies presenting with signs of sepsis from birth up to 3 months of age were included. Data regarding risk factors, intrapartum antibiotic prophylaxis and outcome of babies were collected.

Results: 29 cases were identified and presented in two epochs – before and after changing guidelines for antepartum and intrapartum management. There was a statistically significant reduction in EOS rates and no difference in LOS rates.

Conclusion: Prolonged rupture of membranes is a risk factor at any gestation. It is possible to reduce the neonatal early onset GBS disease burden by adherence to guidelines and timely targeted administration of IAP.

Key words: Group B streptococcus, intrapartum antibiotics, neonates, sepsis

Introduction

Group B Streptococcus (GBS), a common inhabitant of bowels and vagina is the commonest cause of serious neonatal infections. GBS infections in newborns are classified as early onset which occurs within the first 7 days of life and late onset which usually occurs between 8 days and 90 days of life. Early onset is vertically transmitted and can be prevented by intrapartum antibiotic prophylaxis (IAP). Late onset disease is horizontally transmitted and cannot be prevented by IAP[1].

There are two preventative strategies to reduce early onset GBS infections in newborn babies. One is based on routine screening of pregnant women and the second is based on risk factors. Both strategies involve administration of IAP to selected groups of pregnant women. If GBS is isolated in screening or if risk factors are present, they should be given IAP.

The common risk factors for early onset infections are

1. Previous infant with invasive GBS disease
2. GBS bacteriuria in pregnancy
3. Intrapartum temperature of $>38^0$ C
4. Prolonged rupture of membranes (PROM)>18 hours
5. Preterm delivery <37 weeks gestation

Centres for Disease Control (CDC) introduced guidelines on the prevention of group B streptococcus (GBS) infection in 1996. They are based on routine screening strategy in United States of America and have successfully reduced the rate of GBS infections from 1.7/1000 livebirths in 1993 to 0.24/1000 livebirths in 2014[1, 2]. In UK,

we follow risk factors based strategy and national RCOG guidelines have been in existence since 2003 and they have been revised in 2012 and recently in 2017. In spite of the guidelines, the British Paediatric Surveillance Unit (BPSU) data shows the rates of early onset GBS infections have been increasing from 0.48/1000 livebirths (BPSU 2002)[3], to 0.57/1000 livebirths (BPSU 2015)[4]. The exact reason for increasing rates of GBS infection is not known but there is evidence about the missed opportunities to prevent infection by incomplete adherence of the guidelines and missing to administer IAP to eligible mothers.

Methods

This is a retrospective cohort study done in a tertiary neonatal unit setting. All babies who were born between 1st January 2008 and 31st December 2017 at Sunderland Hospital and developed GBS sepsis during this period were identified from Badgernet database (National neonatal database) and cross checked with microbiology laboratory by getting a print out of all positive blood and CSF cultures at Sunderland Royal Hospital (SRH). We included babies from birth up to 3 months of age to identify babies admitted to Paediatric wards with late onset GBS sepsis. All babies presented with signs of sepsis were mostly admitted to the neonatal unit and few babies with late onset sepsis were admitted to the Paediatric wards at SRH. Those who became ill within the first 7 days of age were regarded as early onset sepsis and those who present between 8 days and 90 days were regarded as having late onset sepsis.

Based on a previous audit, guidelines on antepartum management of GBS infections were changed in early 2012. Therefore data has been analysed in 2 epochs - before (epoch 1, 2008 -2011) and after (epoch 2, 2012-2017) guideline change. In epoch 1,

IAP was not considered if PROM was the only risk factor particularly at term gestation. In our analysis we identified PROM as the main risk factor in babies who presented with early onset GBS sepsis in epoch 1 and most of them presented within the first 24-48 hours of discharge from the hospital. The change in the guidelines were

1. To give IAP if there is PROM>18 hours (irrespective of gestation)
2. To observe babies for at least 24 hours if there is PROM in hospital

This study was registered as a quality improvement programme with the clinical governance department at Sunderland Royal Hospital.

Results

A total of 29 cases of confirmed neonatal GBS sepsis were identified between 1st January 2008 and 31st December 2017. There were 16 cases – 12 early onset sepsis (0.86/1000 livebirths) and 4 late onset sepsis (0.28/1000 livebirths) in epoch 1 (2008-2011). In epoch 2 (2012-2017) there were 13 cases – 7 were early onset sepsis (0.35/1000 livebirths) and 6 late onset sepsis (0.29/1000 livebirths). We also noticed a higher mortality (12.5% vs 7.5%) and morbidity (31.25% vs 0%) in epoch 1 when compared to epoch 2.

In epoch 1, two babies who had GBS sepsis and meningitis died (12.5% mortality) one at the age of 13 months and the other baby at the age of 5.5 years. Both these babies had significant morbidities – both had 4 limb cerebral palsy, hydrocephalus needing VP shunt, epilepsy, optic atrophy and deafness. A third baby with EO GBS sepsis developed mild dystonic cerebral palsy (18% risk of cerebral palsy). 3 babies had deafness (18%) and 2 babies had optic atrophy and visual problems (12.5%) and 2 babies had cranial diabetes insipidus (12.5%). 5/16 (31.25%) had some form of morbidity in this cohort.

In epoch 2, of the 7 babies with early onset sepsis, 1 died (preterm baby born at 25 weeks) within an hour of birth (7.5% mortality) and we did not notice any morbidity in this cohort.

The chi-squared test for two proportions (epoch 1 and epoch 2) was statistically significant There was a statistically significant reduction in EOS rates in epoch 2 (p value 0.04) and there were no differences in LOS rates.

Tables – Epoch 1 and Epoch 2

Discussion

The incidence of early onset sepsis (EOS) due to GBS is increasing in UK in spite of national guidelines to reduce the burden of EOS. Intrapartum antibiotic prophylaxis (IAP) has been shown to reduce 80-90% of the early onset sepsis. There is some evidence the rising rate of EOS due to GBS could be due to failure to adhere to guidelines, lack or delay in communication of results leading to missed opportunities to give adequate intrapartum antibiotic prophylaxis[6]. Prolonged rupture of membranes (PROM>18 hours) is one of the important risk factors in predisposing babies for EOS. Stewardson-Krieger etal[7] (1978) demonstrated a direct relationship between the duration of rupture of membrane and sepsis rate in newborns. They demonstrated the neonatal sepsis rate increased from 0.7/1000livebirths if the duration of ROM was 0-9 hours to 16.8/1000 livebirths if the duration of ROM was over 19 hours, increasing to 18.3/1000 live births if duration of ROM was more than 30 hours. Embleton etal[8] (2002) in their case control study have shown the odds ratio for developing EOS is 25 times higher if there is PROM. Also there is a direct relationship between GBS load, risk of vertical transmission and the likelihood of serious disease in neonates. IAP reduces the bacterial load thereby reducing the incidence and severity of EOS. Our

national guideline (RCOG) continues to be vague on this risk factor in term babies which is open to interpretation. In 2003 version of the guidelines, it recommended to 'consider' IAP if there was PROM and in the subsequent revisions, the recommendation for IAP is not clear[9]. Centres for Disease Control (CDC), Canadian, Australian and New Zealand guidelines clearly recommend giving IAP if there is prolonged rupture of membranes for >18 hours and if GBS status is not known at any gestation. A recent metaanalysis of randomized trials on antibiotic prophylaxis for term or near term premature rupture of membranes has shown not only a reduction in neonatal sepsis but also a significant reduction in maternal chorioamnionitis and endometritis when the latency was longer than 12 hours (Berghella etal 2015)[10]. The recent revision of RCOG guidelines identifies prolonged rupture of membranes as risk factor and recommends induction of labour for term prelabour rupture of membranes but is evasive in clearly recommending IAP if the latency is more than 18 hours. It clearly recommends giving IAP for preterm PROM but it is not clear for PROM at term. For any national clinical guidelines to be effective, it needs to be correctly interpreted and implemented. This will happen only when the guidelines are clear and consistent.

In our cohort of babies in epoch 1, we could have given IAP for 5 mothers for PROM and therefore missed opportunity to prevent GBS infections. Probably the increased mortality and morbidity of babies in epoch 1 could be due to increased bacterial load which is however difficult to prove retrospectively. We identified PROM as a risk factor in our babies and we decided to give IAP to mothers if there is PROM of >18 hours in epoch 2. We believe that has contributed in reducing the early onset GBS neonatal sepsis in epoch 2.

Conclusions

Though IAP reduces EOS due to GBS there are drawbacks as well. As it is given at the time of labour it will not be able to prevent stillbirths, preterm births and miscarriage due to GBS. Also there are concerns related to antibiotic exposure during the neonatal period influencing neonatal intestinal microbiome and an association between early antibiotic exposure in newborns and increased rate of allergies in babies including cow's milk protein allergy.[11, 12, 13] The ideal way for preventing neonatal GBS is through maternal immunisation with GBS vaccines which will reduce neonatal sepsis, miscarriage, preterm births and still births. Until we have a good GBS vaccine, IAP remains the best effective strategy in preventing GBS infections in neonates. There is some evidence that though IAP does not prevent late onset sepsis, it delays the onset and reduces the severity of late infection[14]. The major limitation of our study is our small sample size. It will be interesting to do a subgroup analysis on recent BPSU data on GBS sepsis which included 856 babies with GBS sepsis to look for PROM as an isolated risk factor at term gestation. We request our national guidelines group on prevention of neonatal GBS sepsis to consider recommending IAP for PROM at term gestation as well. It is possible to reduce GBS disease burden in UK if the guidelines are correctly interpreted and implemented by timely administration of IAP to eligible mothers.

Acknowledgements

We thank our junior doctors Kim Simpson and Rebecca Hannah for helping us collect data.

Abbreviations

GBS – Group B Streptococcus, EOS- early onset sepsis, LOS – late onset sepsis, UK- United Kingdom, ROM – rupture of membranes, PROM – prolonged rupture of membranes, RCOG – Royal College of Obstetrics and Gynaecology, IAP – intrapartum antibiotic prophylaxis, CDC – Centre for disease control, BPSU – British Paediatric Surveillance Unit, CSF – cerebrospinal fluid, SRH- Sunderland Royal Hospital.

References

1. Verani JR, McGee L, Schrag SJ (2010). Prevention of perinatal Group B Streptococcal disease. MMWR Recomm Rep 59,1-36.
2. https://www.cdc.gov/groupbstrep/clinicians/clinical-overview.html (Accessed 2nd December 2017)
3. Heath PT etal (2004). Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet 363, 292–94.
4. https://www.rcpch.ac.uk/system/files/protected/page16/AnnualReport201415_web.pdf (Accessed 2nd December 2017)
5. Newcombe R.G. (1998) Interval estimation for the difference between independent Proportions: Comparison of Eleven Methods. Statistics in Medicine 17, 873–890.
6. Vergnano S etal (2010). Missed opportunities for preventing group B streptococcus infection. Arch Dis Child Fetal Neonatal Ed 95, F72–F73.
7. Stewardson-Krieger PB, Gotoff SP (1978). Risk factors in early-onset neonatal group B streptococcal infections. Infection 6, 50-53.
8. Oddie S, Embleton N (2002). Risk factors for early onset neonatal group B streptococcal sepsis: case control study. BMJ 325, 308-12.
9. Hughes RG, Brocklehurst P, Steer PJ, Heath P, Stenson BM on behalf of the Royal College of Obstetricians and Gynaecologists (2017). Prevention of early-onset neonatal group B streptococcal disease. Green-top Guideline. No. 36. BJOG, DOI: 10.1111/1471-0528.14821.
10. Saccone G, Berghella V (2015). Antibiotic prophylaxis for term or near-term premature rupture of membranes: metaanalysis of randomized trials. Am J Obstet Gynecol 212, 627 e1-9.

11. Love BL, Mann JR, Hardin JW, Kevin ZL, Cox C, Amrol DJ (2016). Antibiotic prescription and food allergy in young children. Allergy Asthma Clin Immunol 12, 41 DOI 10.1186/s13223-016-0148-7.
12. Hirsch AG, Pollak J, Glass TA, Poulsen MN, Bailey-Davis L, Mowery J, Schwartz BS (2017). Early life antibiotic use and subsequent diagnosis of food allergy and allergy diseases. Clin Exp Allergy 47(2): 236-244.
13. Yamamoto-Hanada K, Yang L, Narita M, Saito H, Ohya Y (2017). Influence of antibiotic use in early childhood on asthma and allergic diseases at age 5. Ann Allergy Asthma Immunol 119, 54-58.
14. Berardi etal. Group B Streptococcal late-onset disease: 2003-2010 (2013). Pediatrics 131, e361.

Conflicts of Interest: The authors declare no conflict of interest

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose

Epoch 1 (2008-2011)

Year	Live births	EOS (Number)	EOS/1000 live births	LOS (Number)	LOS/1000 live births
2008	3546	4	1.12	3	0.84
2009	3328	1	0.3	0	0
2010	3436	0	0	1	0.3
2011	3574	7	2	0	0
Cumulative	13884*	12	0.86*	4	0.28

Epoch 2 (2012-2017)

Year	Live births	EOS (Number)	EOS per 1000 live births	LOS (Number)	LOS per 1000 live births
2012	3384	1	0.3	1	0.29
2013	3295	1	0.3	1	0.3
2014	3436	1	0.3	2	0.6
2015	3158	3	0.9	1	0.3
2016	3334	1	0.3	0	0
2017	3228	0	0	1	0.3
Cumulative	19835*	7	0.35*	6	0.29

*The chi-squared test for two proportions (epoch 1 and epoch 2) was statistically significant with X = 3.8, df = 1, p-value = 0.04, the 95% CI [4.62e-05, 1.0][5]; since we calculate EOS rate per thousand live births, the two proportions are 0.86 and 0.35.

The exact 1-sided significance value was chosen based on our confidence of the new guidelines on prevention of GBS infection methods in Epoch2.