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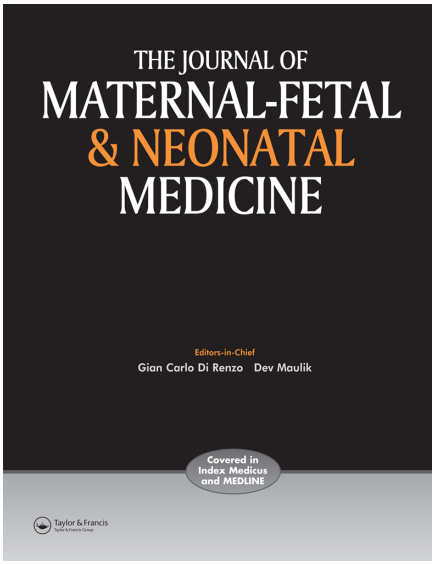

Replacing risk-based early-onset-disease prevention with intrapartum group B streptococcus PCR testing

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Abstract

Objective: To evaluate the effect of a rapid PCR-based group B streptococcus (GBS) test on length of stay in hospital among newborns, antibiotic use, and GBS-early-onset-disease (EOD) incidence.

Methods: We conducted a before and after service evaluation including term deliveries between January 1st and November 12th, 2014 (6688 deliveries). Length of stay in the hospital, GBS-EOD incidence and antibiotic use were evaluated.

Results: We recorded 3 confirmed and 74 possible cases of GBS-EOD in Phase 1, and 85 possible cases in Phase 2. In newborns with suspected infection, the introduction of the rapid test was related to a decreased length of stay on the pediatric care unit by 1.16 days ($p=0.01$), and an increase in the length of stay on the mother-and-baby ward by 1.11 days ($p<0.001$). No increase in antibiotics was noted.

Conclusion: The introduction of a point of care test was associated with a reduction in length of stay in the pediatric care unit, without an increase in antibiotic use. This test could improve the accuracy of GBS colonisation detection, and help to prevent intrapartum transmission as no verified GBS-EOD cases were recorded with the intrapartum PCR algorithm.

Replacing risk-based early-onset-disease prevention with intrapartum group B streptococcus PCR testing

Short title: Intrapartum GBS PCR

Keywords: **neonates, observational study, group B streptococcus, rapid diagnostic test, GBS early onset disease**

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INTRODUCTION

Group B streptococcal infection (GBS) is the leading cause of early-onset disease (EOD) in newborns. GBS is acquired from the colonized maternal birth canal after membranes rupture or during labor. Intrapartum antibiotic prophylaxis (IAP) administered to GBS-colonized mothers has been shown in several studies to be efficient in preventing GBS-EOD in newborns [1–3]. The main challenge has been how to identify those women who should receive IAP. In the absence of an intrapartum test, in 2010 the Center of Disease Control in the United States recommended that all women have a vaginal/rectal sample taken for culture screening of GBS at 35–37 weeks of gestation to determine IAP and manage GBS-EOD [4]. Several countries such as Germany and France have implemented this approach [4,5], yet other countries such as the UK have used a different strategy, and have chosen to implement IAP based on a risk assessment rather than universal screening [6,7].

Recently, a specific and sensitive PCR-based rapid test for intrapartum testing for GBS has been developed [8–14]. The on-demand Xpert GBS test (Cepheid, Sunnyvale, California) provides results in 30 to 50 minutes, is easy to perform and can be used as a point of care test, near-patient in the delivery unit. Prior literature shows that GBS intrapartum screening is superior to antepartum culture [4,5,15]. It has been shown to be effective and cost-neutral, with superior efficacy on preventing GBS disease [8,9,11]. Historically, in Finland, most maternity hospitals used risk-based IAP (RB-IAP) to identify women who should receive prophylaxis at time of birth. Decision criteria for IAP in full term deliveries were: premature rupture of membranes for more than 18 hours, history of GBS-positive vaginal or urine culture earlier during the pregnancy, or a previous birth in which the child developed GBS-EOD. In recent years, doubts about the efficiency of risk-based IAP have been raised and several hospitals have considered changing to screening.

We performed an observational service evaluation to compare neonatal outcomes in a large maternity hospital in Finland using the new PCR-based intrapartum testing approach to determine IAP (PCRB-IAP) compared to a RB-IAP as standard of care. Verified GBS-EOD cases with positive GBS culture from blood or CSF in Kätilöopisto maternity hospital are rare events. Given the very large sample size needed to see a statistically significant difference in GBS-EOD reduction between the two phases, we chose to primarily examine the two following endpoints: total hospitalization days on the pediatric care unit, the mother-and-baby ward and the Neonatal Intensive Care Unit (NICU), and the total administration of antibiotics to mothers. Feasibility and ease-of-use of the test were evaluated by questionnaire for midwives (results reported in the Supplemental Web File).

METHODS

Data were collected between the 1st of January and the 12th of November, 2014 in the Kätilöopisto Maternity Hospital in Helsinki, Finland, which has on average 8,000 births annually. In this hospital, deliveries occur after the gestational age of 32 weeks. Deliveries at less than 32 weeks of gestation [16], complicated deliveries, and elective Cesarean Sections are referred to the nearby University Hospital. The study was approved by the "Naisten, lasten ja psykiatrian eettinen toimikunta" (Women's, children's and psychiatric ethical committee) of Kätilöopisto Maternity Hospital.

The evaluation was performed in two phases. During Phase 1 (Jan 1 – May 26, 2014), RB-IAP was used; prophylactic antibiotics were given to mothers with premature rupture of membranes for more than 18 hours, history of GBS-positive vaginal or urine culture earlier during the pregnancy, or a previous child with culture-positive GBS-EOD. This was a continuation of standard practice.

In Phase 2 (May 27 – November 12, 2014), intrapartum vaginal/rectal PCR screening for GBS infection was performed (PCRB-IAP). On admission to hospital for delivery, a double-swab was taken by a trained midwife (lower third of vagina and rectum) from every woman during the initial clinical exam. Then, the attending midwife immediately performed the assay on one of the three GeneXpert systems placed on the antenatal and delivery units. A positive Xpert GBS result was available within 36 to 52 minutes, and a negative result in 52 minutes. The midwives then initiated IAP for women who either screened positive for vaginal/rectal GBS colonization, or, if there was no result of the vaginal/rectal sample (e.g. PCR invalid or error) and the women presented risk factors (as described above). At the initiation of the study all 130 midwives were trained in small groups in the use of running the Xpert and acting on results. Midwives who joined at a later stage were trained individually.

IAP administration

Penicillin G was used for intrapartum antibiotic prophylaxis (5 million international units followed by 2.5 million international units every 4 hours until delivery) as per hospital guidelines. If penicillin allergy was known or suspected, cefuroxime (1.5 g, followed by 750 mg every 8 hours until delivery) or clindamycin (900 mg every 8 hours until delivery) was administered instead of penicillin.

Eligibility criteria

All term vaginally delivered live births occurred at the Kätilöopisto Maternity Hospital between January 1st and November 12th, 2014 were included. Women giving birth to preterm infants (<37 weeks) were given cefuroxime prophylaxis as standard of care. Preterm births were therefore excluded from the analysis, as the new algorithm would not lead to a change in patient management.

Data collection

We extracted data from the electronic medical records from the hospital's medical information department and the microbiology laboratory. These data were completed by an analysis of paper notes in the patients' medical files. Data on antibiotic use were obtained from the Hospital Pharmacy database.

All newborns aged under three days with proven GBS-EOD were identified in the clinical records database by searching for ICD code P36.0 (sepsis with GBS) [17]. We also wanted to identify all newborns with possible or suspected, but not proven, GBS-EOD. We therefore included newborn notes with codes P39.9 (undefined perinatal infection), P36.90 (suspected bacterial sepsis of the newborn) and P36.99 (undefined bacterial sepsis of the newborn). We grouped the codes P36.99 and P36.90 into the root 36.9 ICD-code (bacterial sepsis of

newborn, unspecified). The babies' and the corresponding mothers' medical records were extracted and matched, and both sets of data were analyzed together. Data on the length of stay by location of the newborns were also extracted. Locations were defined as: the 'mother-and-baby ward' (where newborns in good health stay with their mothers), the 'pediatric care unit' (specific ward for sick newborns), or the neonatal intensive care unit, 'NICU', in the nearby University hospital (where newborns with critical illnesses are referred). In order to assess the potential impact of the change in practice on antibiotic use, we extracted data on the three antibiotics prescribed for intrapartum prophylaxis (penicillin G, cefuroxime and clindamycin) for five months in each study phase. To calculate the total amounts of antibiotics given to mothers for each phase, we converted penicillin G international units into grams.

Data analysis

The number of births, the antibiotics administered to mothers (total grams of antibiotics administered per 100 deliveries), and number of proven and suspected cases of GBS-EOD were tabulated.

The length of stay in hospital of newborns identified with ICD-10 codes of proven or possible GBS-EOD was evaluated using descriptive statistics for each study phase. We also conducted regression analyses of the effect of the phase on the number of days of hospitalization using two different link functions: ordinary least squares (OLS) and generalized linear models (GLM). The former assumes the data are normally distributed, and the latter accounts for possible non-normality conditions of data. The dependent variable was length of stay in each ward. After conducting simple regressions using the OLS and GLM functions, we further controlled for gestational age in days and ICD-10 diagnosis of the child. No other control variables were accounted for due to data restrictions. Regression results including the GLM

specification and the additional covariates are available upon request. Chi square and t-tests were performed, where appropriate, to compare between the two phases (**Tables 1 and 2**).

RESULTS

Phase 1 – deliveries, IAP and GBS-EOD

During Phase 1 (RB-IAP), there were 3,157 deliveries at the hospital. Of these, 3,028 (95.9%) were term deliveries to 3,049 babies and were included in the analysis (**Figure 1**). 119 (3.8%) were preterm deliveries and therefore excluded from the analysis. An additional 10 birth events were also excluded as they did not fulfill the eligibility criteria (described in Methods). Of the term deliveries, 536 women (17.7%) received IAP based on risk factor evaluation alone, 284 women (9.4%) were given antibiotics due to verified or suspected maternal infections, and 2,208 women (72.9%) did not receive antibiotics.

Three newborns developed blood culture positive GBS-EOD, (incidence of 0.95/1000 babies) (**Figure 1**). None of the three mothers had known risk factors and they had not received IAP or other antibiotic treatment. In total, 77 newborns (2.5%) were identified as having ICD-10 codes (**Table 1)** that indicated confirmed, possible or suspected GBS-EOD cases and were treated with parenteral antibiotics.

Phase 2 – deliveries, GBS test results, IAP and GBS-EOD

During Phase 2 (PCRB-IAP), 3,841 deliveries took place at the hospital. Of these, 3,660 (95.3%) were term deliveries, resulting in 3,681 babies, and were included in the analysis. 154 (3.7%) were preterm deliveries and therefore excluded. An additional 27 birth events were excluded from the analysis as they did not fulfill the eligibility criteria (described in Methods). Out of the 3,660 term deliveries, 843 women (23.0%) tested GBS positive, 2,637

women (72.1%) tested GBS negative, and 180 women (4.9%) had invalid or no results. Among the 843 GBS positive women, 750 received IAP, and 16 received antibiotic treatment due to infection or suspected infection. 77 mothers who had a positive test result did not receive IAP because labor progressed rapidly and there was no time to give IAP. Among the 2637 women with negative GBS colonization status, 235 received antibiotic treatment due to infection or suspected infection, and 14 received IAP due to known risk factors as described above. Of the 180 women with unknown GBS status, 3 received antibiotic treatment due to infection or suspected infection and 13 received IAP.

During Phase 2, no proven GBS-EOD cases in newborns were recorded (**Figure 2**). 85 newborns (2.3%) identified as having ICD-10 codes suggesting possible or suspected GBS-EOD were treated with parenteral antibiotics (**Table 1)**.

Comparison of antibiotic use and length of stay

The administration of penicillin G to mothers was 228.4 IU per 100 deliveries during Phase 1 and 241.6 IU per 100 deliveries during Phase 2. The consumption figures for cefuroxime were 67.5g/100 deliveries and 50.0g/100 deliveries, respectively, and the consumption of clindamycin was 2.4g/100 deliveries and 1.8g/100 deliveries, respectively. The mothers' total antibiotic consumption was 208.3g/100 deliveries for Phase 1 and 198.2g/100 deliveries for Phase 2.

The mean lengths of stay (LOS) in the pediatric care unit were 3.82 days in phase 1 and 2.69 days in phase 2 ($p=0.02$), and on the mother-and-baby ward, mean LOS were 3.48 days in phase 1 and 4.59 days in phase 2 ($p<0.01$). Some babies were only on one of the wards, and others were on more than one ward during their stay. Eight babies (6 in Phase 1 and 2 in Phase 2) were also transferred to the NICU in the nearby University Hospital.

Subsequent regression analyses were carried out in order to estimate the relationship between the introduction of the test and length of stay while controlling for the covariates mentioned in the methods (**Table 3**). When using linear simple regression, the introduction of the Xpert GBS was related to a reduction in length of stay of 1.16 days (p=0.01) in the pediatric care unit and an increase of 1.11 days (p<0.001) on the mother-and-baby ward. When controlling for ICD-10 diagnosis and gestational age (285 days [SD 8.01] in Phase 1 versus 283 days [SD 9.72] in Phase 2), the introduction of the Xpert GBS was related to a reduction in the length of stay of 1.20 days (p<0.001) in the pediatric care unit and an increase in the length of stay in the mother-and-baby ward of 0.95 days (p<0.001).

These results were robust to sensitivity analyses such as the change of functional form by using Generalized Linear Model estimation, and the introduction of the additional control variables of 'any complication' during birth and 'hospital stay only at one ward' with no significant change to the results.

No statistically significant differences were seen in the probability of proven or possible GBS-EOD across the two phases (77 perinatal infections/3,049 babies (2.5%) vs 85 perinatal infections/3,681 babies (2.3%), p=0.89). Also, the distribution was unchanged in each ICD-10 category (**Table 1**). Although not statistically significant, 3 confirmed GBS cases were observed in Phase 1, and none in Phase 2.

DISCUSSION

To our knowledge this is the first service evaluation that compares RB-IAP to intrapartum PCR-based IAP. A strength of the study was the number of babies included in the dataset, 6,688 sequential births, which allowed for the measurement of the effect of PCR-based IAP on length of stay in the hospital. Hospitalization days among newborns with proven or possible GBS-EOD on the pediatric care unit significantly decreased by around one day in Phase 2 compared to Phase 1. An increase of similar magnitude (1 day) on the mother-and-baby ward was observed. This finding suggests that newborns were less sick or not sick at all, staying instead with their mothers on the mother-and-baby ward. It could also be related to changes in patient management over time. Though the study was not powered to measure changes in incidence, there were no cases of proven GBS-EOD when PCRB-IAP was implemented compared to a GBS-EOD incidence of 0.95/1000 (3/3157) during the RB-IAP phase. According to the results of the midwives' questionnaire, the test's clinical relevance in preventing GBS-EOD and its ease-of-use near the patient were positively affirmed (results reported in the Supplemental Web File). The Kätilöopisto Maternity Hospital adopted the technology as hospital protocol and one year after the study concluded, there had been no GBS-EOD cases.

We did not observe an increase in the overall amounts of antibiotics administered to mothers between the study phases. This is encouraging because a previous study comparing intrapartum PCR to antepartum GBS culture found an increase of prophylactic antibiotics for mothers with the introduction of intrapartum testing [11]. One of the goals in implementing PCRB-IAP is to minimize the unnecessary use of antibiotics in GBS-negative mothers. Targeted antibiotic use means improved antimicrobial stewardship and a potential reduction in hospital costs.

A main reason for exploring new ways of identifying newborns at risk of GBS-EOD is that a risk-based approach for IAP has significant disadvantages, the most important one of which is that only half of newborn children with GBS-EOD are born to women with known risk-factors [7,18]. As many GBS-positive women without risk factors are not screened, they do not receive prophylaxis to prevent transmission during birth. We did not evaluate the effect of the rapid test compared to antepartum screening as this was not the standard of care in the hospital before the study and several papers have already been published on this topic [4,5]. Whilst many countries currently conduct antepartum screening, there are several reasons why it was not considered for this setting. Between 10% and 12% of women change GBS status between the antepartum screening date and birth, with a positive predictive value below 60%, and antepartum results are therefore less useful at birth for IAP decisions than intrapartum GBS status results [11,18,19]. Women who deliver before weeks 35-37 will not benefit from antepartum screening, and their GBS status remains unknown [20]. Finally, for successful implementation of antepartum testing, extensive coordination between Obstetrics/ Gynecology practitioners, laboratories and hospitals is required, which is challenging.

Due to the hospital electronic database's data restrictions, we were unable to perform a statistical analysis comparing the length of stay of healthy babies on the mother-and-baby ward with the neonates with perinatal infections. In Phase 1, when mothers received antibiotics for any suspected or proven infection, the midwives did not attempt to assess any other risk factors that could lead to IAP as the mothers were already under antibiotic treatment. This means that we did not have data on the number of women who would have been offered IAP based on identifying risks only. In the future, a hospital or country with the ability to set up a larger study might consider looking at the directly measurable effect that this strategy has on the incidence of early onset GBS infections. There seems to be an association between the adoption of the GBS-PCR rapid test and a decrease in the length of

stay of neonates on the pediatric care unit. This would imply a real-world clinical impact of the test.

In conclusion, the availability of an accurate point of care test for GBS is important to improve the accuracy of GBS colonization detection and prevention of intrapartum transmission. It could reduce patients' length of stay, without an increase in antibiotic use. Future research should focus on prospectively evaluating the benefits of the test, and directly evaluating the test's effect on GBS-EOD in a larger cohort.

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DECLARATION OF INTEREST AND FUNDING

V. Björklund, T. Nieminen, VM Ulander, T. Ahola and H. Saxén declare no conflict of interest.

Cepheid provided the Xpert GBS test cartridges and supplied the 3 GeneXpert systems for the duration of the study.

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Table 1. Distribution of ICD-10 codes of the newborns identified with suspected or confirmed GBS-EOD by phase

Three-digit ICD-10 codes	Phase 1 (RB-IAP)		Phase 2 (PCRB-IAP)-		p-value
	Total newborns with confirmed or possible GBS-EOD = 77		Total newborns with confirmed or possible GBS-EOD = 85		
	N	Proportion (%)	N	Proportion (%)	
Total	77	100	85	100	0.89
P36.0	3	3.9	0	-	NA
P36.9 *	32	41.6	29	34.1	0.33
P39.9	42	54.6	56	65.9	0.14

* The ICD-10 P36.9 category comprises : P36.90 (Suspected bacterial sepsis of newborn) and 36.99 (Bacterial sepsis of newborn, unspecified) (18), which were grouped for the purpose of this analysis.

Table 2. Length of stay of the newborns identified with suspected or confirmed GBS-EOD by ward and phase

	Phase 1 (RB-IAP)		Phase 2 (PCRB-IAP)		p-value
	Newborns with confirmed or possible GBS-EOD = 77		Newborns with confirmed or possible GBS-EOD = 85		
	N	Mean of number of days (SD)	N	Mean of number of days (SD)	
Pediatric care unit	65	3.82 (3.34)	84	2.69 (2.3)	0.02
Mother-and-baby ward	63	3.48 (1.34)	76	4.59 (1.85)	<0.01
Neonatal Intensive Care Unit	6	6.83 (4.45)	2	5 (1.41)	NA

Note: some newborns spent time in more than one ward.

Table 3. Linear regression on length of stay (days) in Phase 2 compared to Phase 1 by ward.

Selected characteristics	Pediatric care unit (n=149)		Mother-and-baby ward (n=139)	
	Length of stay*	*p*	Length of stay*	*p*
Xpert GBS Test	-1.16	0.01	1.11	<0.001
Xpert GBS Test + Control variables	-0.94	0.04	0.86	<0.001

Note: For clarity purposes, we only show the results of the length of stay variable. The results for the covariates are available upon request.

*A negative value represents a reduction in length of stay in Phase 2 compared to Phase 1

Figure 1: Phase 1 - Risk-based intrapartum antibiotic prophylaxis

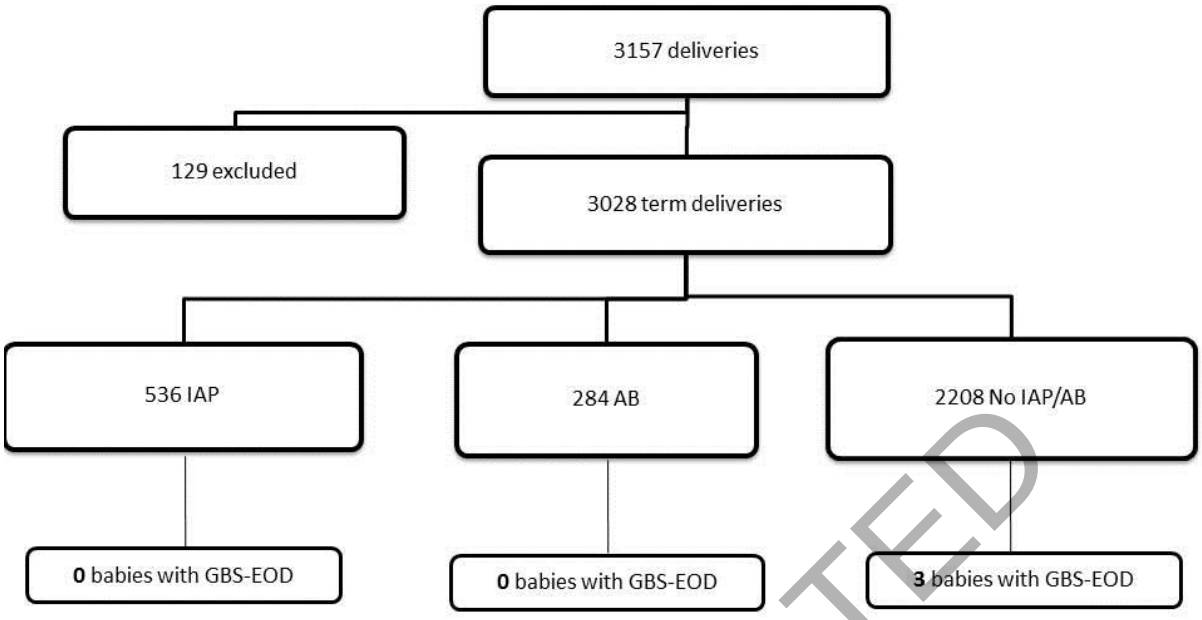

Figure 2: Phase 2 - PCR-based intrapartum testing for antibiotic prophylaxis