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ORIGINAL ARTICLE

Limited Diagnostic Value of Routine Screening of Neonates with the Urinary Group B Streptococcal Antigen Tests

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Background: A urinary latex test for detection of antigens from group B Streptococcus (GBS) has been used for the diagnosis of invasive GBS disease. However, the value of routine screening of infants with this test has not been determined.
Methods: All infants admitted to Linkou Chang-Gung Memorial Hospital (Taoyuan, Taiwan) from January 2005 to May 2013 were screened with a urinary GBS antigen test (Wellcogen Strep B). Medical records were retrospectively reviewed to determine the diagnostic value of this test.
Results: A total of 14,277 infants were tested and 38 cases had confirmed diagnoses of invasive GBS disease (34 bacteremia, 18 meningitis, 14 both), corresponding to a prevalence of 0.27% among our admitted infants. A total of 106 infants had positive results, but only 26 had confirmed disease. Among infants with confirmed disease, 12 had negative antigen results. These data allowed calculation of the sensitivity (68.4%), specificity (99.4%), positive predictive value (24.5%), and negative predictive value (99.9%). Adjusting for prevalence, the disease probability of a positive test result was 23.6%, and the probability of a negative post-test result was 0.09%. The absolute risk reduction of a negative result was very small (0.18%). Analysis of demographic, clinical, and laboratory parameters indicated that late age of onset (≥7 days-old), presence of seizure, fever, respiratory distress, leukopenia, bandemia, thrombocytopenia, coagulopathy, metabolic acidosis, and elevated levels of C-reactive protein (CRP) were significantly related to the presence of a true positive test result.
Conclusion: In our study population, the positive predictive value of the GBS antigen test was poor and the risk reduction of a negative result was weak. These results indicate that routine

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screening with this test has a limited diagnostic value. However, GBS antigen testing appears to be useful for early detection of disease in infants with certain demographic, clinical, and laboratory risk factors.

1. Introduction

Group B Streptococcus (GBS, *Streptococcus agalactiae*) is a major pathogen in neonatal care units which is responsible for many severe infections.[1–3] There is increasing attention to such infections because they are associated with unfavorable complications and poor outcomes.[4] Neonatal early-onset GBS disease (from birth to 6 days old) usually manifests as pneumonia or bacteremia, and late-onset GBS disease (from age 7 days to 89 days) usually manifests as bacteremia, osteomyelitis, septic arthritis, or meningitis.[5] In a recent review of pediatric meningitis in Northern Taiwan, GBS was the leading pathogen for infants <1 month old.[6] Recent research estimated the case-mortality ratio as 4.4% for early-onset disease and 3.3% for late-onset disease.[7] Considering the serious nature of this disease, health care institutions have implemented numerous prevention policies. Maternal GBS screening and intrapartum antibiotic prophylaxis led to declines in the incidence of early-onset GBS disease to 0.25 cases per 1000 live births in the United States in 2010.[8] Despite the success of these and other prevention strategies, neonatal GBS disease remains a serious problem, and the incidence of late-onset GBS disease is unchanged.[3,8]

A latex agglutination test for rapid identification of GBS has been commercially available for more than 30 years.[9,10] This qualitative test can be used to test samples of serum, cerebrospinal fluid (CSF), or urine for the presence of GBS antigens. Urine is the most commonly used sample because it can be easily and noninvasively acquired. Thus, many hospitals and referral centers in Taiwan routinely use a urinary GBS antigen test to screen infants upon admission (personal communication: Kai-Hsiang Hsu, 2014). However, the diagnostic value of routine urinary GBS antigen testing of neonates has been questioned.[11–14]

The purpose of the present study is to test the diagnostic value and statistical power of the urinary GBS antigen test for routine screening of neonates upon admission, based on retrospective analysis of patients from a single institution in Taiwan from January 2005 to May 2013.

2. Methods

2.1. Participants

This study is a retrospective review of patients admitted to the Neonatal Department at Linkou Chang-Gung Memorial Hospital (Taoyuan, Taiwan) from January 2005 to May 2013. This unit is a referral center in Northern Taiwan with 37 neonatal intensive care units (NICU) and 70 sick-baby nursery beds, and an annual admission of approximately 1800 infants who are ≤3 months old. The hospital database has all medical information from admission to discharge. The Institutional Review Board of our institution approved this study.

The database allowed analysis of the demographic and clinical characteristics of the admitted infants. Infants with various respiratory illnesses, including tachypnea, rapid O_2 desaturation, grunting, retraction, or respiratory failure that necessitated intubation, were considered to have respiratory distress. Fever was defined as rectal or axillary temperature >38°C. Feeding intolerance was defined as gastrointestinal discomfort, including decreased appetite, frequent vomiting, large gastric residual content, or abdominal distension. Hyperbilirubinemia was diagnosed only if phototherapy was necessary to lower serum bilirubin level. Seizure was diagnosed based on subtle manifestations to apparent myoclonic movement according to observations of the health care staff. Participants were classified as having multiple clinical manifestations if all sufficient criteria were present.

Upon admission, blood cultures, hemograms, and levels of C-reactive protein (CRP) were determined for all infants as part of routine sepsis workups. CSF was examined according to the physician's discretion if meningitis was suspected. Arterial acid-base status was assessed if there were indications of a respiratory or metabolic condition. The following abnormalities were recorded within 24 hours of admission: leukocytosis [white blood cell (WBC) > 30,000/uL], leukopenia (WBC < 5000/uL), bandemia (band form WBC > 5% of total WBC), thrombocytopenia (platelet count < 100,000/uL), coagulopathy requiring plasma transfusion, and metabolic acidosis indicating $NaHCO_3$ correction. Confirmed invasive GBS disease was defined as isolation of GBS from the blood or CSF, and it was classified as early-onset disease if the infant was <7 days old and late-onset disease if the infant was ≥7 days old.

2.2. Urinary GBS antigen test

In our institution, all infants admitted to either the NICU or the sick-baby nursery, regardless of diagnosis, were examined for the presence of the urinary GBS antigen upon admission as part of routine screening. All urine samples were collected within 24 hours of admission in a sterilized urine bag and sent for immediate testing with the Wellcogen Strep B latex agglutination test (Remel, Thermo Fisher Scientific, Lenexa, KS, USA). Standard preparation procedures, including heating, cooling, and centrifugation, were performed according to the manufacturer's guidelines.

2.3. Statistical analysis

We determined the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio (LR) of the urinary GBS antigen test to assess its diagnostic value. The LR is the probability of a specific finding in patients with disease divided by the probability of the same finding in patients without disease, an indication of diagnostic accuracy.[15,16] Post-test odds were calculated as:

$$\text{pretest odds} \times (\text{prevalence}/1 - \text{prevalance}) \times \text{LR}$$

and post-test probability was calculated as:

$$\text{post} - \text{test odds}/(\text{post} - \text{test odds} + 1).$$

Statistical analysis was performed with SPSS Statistics version 20 (International Business Machines Corporation, IBM, Armonk, New York, United States). Categorical data were analyzed with a χ^2 test or Fisher's exact test where appropriate. Logistic regression was used to determine the correlation of categorical dependent variables with continuous parameters. A p value <0.05 was considered statistically significant.

3. Results

3.1. Incidence and demography

Table 1 shows the distribution of infected infants by age at the time of positive test results and clinical presentations. During the 8-year study period, a total of 14,277 infants were tested and 38 cases had confirmed invasive GBS disease (34 with bacteremia, 18 with meningitis, and 14 with both), corresponding to a prevalence of 0.27%. Among these 38 infants, 18 were males and 20 were females, seven were preterm (gestational age 29—34 weeks), and six had low birth weight (1160—2460 g). A total of 31 of the infants were born elsewhere and transferred to our institution. Among those inborn infants, six manifested early-onset disease, which could help in estimating our institution's case-births ratio to be 2/3668 for 2006, 2/3852 for 2007, and 2/4248 for 2011, and this gave to an annual incidence of 0.5/1000 live births.

Figure 1 shows the annual occurrence of early- and late-onset disease. There were 14 infants with early-onset disease and 24 infants with late-onset disease. More specifically, three infants were diagnosed at birth, 11 were diagnosed before they were 7 days old, 14 were diagnosed between age 7 days and 30 days, and 10 were diagnosed between age 31 days and 89 days. The only death was in an early-onset infant, corresponding to a mortality rate of 2.6%.

3.2. Urinary GBS antigen test

Table 2 summarizes the evaluation of the urinary GBS antigen test. A total of 106 infants had positive urinary GBS antigen tests, but only 26 had confirmed disease (true positive results). This allowed calculation of the sensitivity (68.4%), positive predictive value (24.5%), and false positive rate (75.5%). Among the 38 infants with confirmed disease, 12 had negative antigen results (false negative results); the number of true negative cases was 14,159. This allowed calculation of the specificity (99.4%), negative predictive value (99.9%), and false negative rate (0.08%). The LR for a positive result was 114 and the LR for a negative result was 0.318. Adjusting for prevalence, the post-test probability of confirmed disease after a positive test result was 23.5%, and the post-test probability after a negative post-test was 0.09%. The absolute risk reduction of disease probability of a negative result was 0.18% (0.27—0.09%).

3.3. Risk factors

The positive predictive value of the test was low (24.5%), so we further analyzed the risk factors associated with "true positive" results. Table 3 summarizes demographic,

Table 1 Age and clinical presentation of infants who tested positive for the urinary group B Streptococcus (GBS) antigen.

Age at positive test result		Number of positive results	Clinical presentation, *n*		Number of positive tests among infected patients, *n* (sensitivity)	True positive *n* (%)	False positive *n* (%)
Early onset	Immediately after birth	23	Bacteremia	3	3 (100)	3 (13)	20 (87)
			Meningitis	1	1 (100)		
			Bacteremia + meningitis	1	1 (100)		
	<7 days	48	Bacteremia	10	7 (70)	7 (14.6)	41 (85.4)
			Meningitis	4	4 (100)		
			Bacteremia + meningitis	3	4 (100)		
Late onset	7—30 days	27	Bacteremia	12	7 (58)	9 (33)	18 (67)
			Meningitis	7	6 (86)		
			Bacteremia + meningitis	5	4 (80)		
	31—89 days	8	Bacteremia	9	5 (56)	6 (75)	2 (25)
			Meningitis	6	5 (83)		
			Bacteremia + meningitis	5	4 (80)		
Overall		106	Bacteremia	34	22 (65)	26 (24.5)	80 (75.5)
			Meningitis	18	16 (89)		
			Bacteremia + meningitis	14	12 (86)		

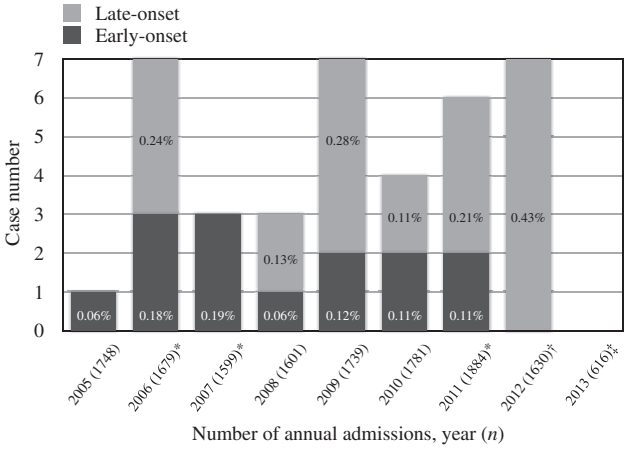

Figure 1 Number of annual cases at our institution who tested positive in the urinary group B Streptococcus (GBS) antigen test, with early-onset (black) or late-onset (gray) disease. * In 2006, 2007, and 2011, respectively, two inborn infants were diagnosed as early-onset GBS disease. The corresponding case-births ratios were 2/3668 for 2006, 2/3852 for 2007, and 2/4248 for 2011 at our institution. † Universal maternal GBS screening was adopted as a health care policy in Taiwan in 2012. ‡ The data of 2013 was only reviewed until May 2013, at which time there were no cases.

clinical, and laboratory data of infants with true and false urinary GBS antigen test results. Sex, mode of delivery, and gestation time (full-term or preterm) were not significantly related to the presence of positive results. Interestingly, 75% of younger infants (age $<$ 7 days) but only 42% of older infants (age $\geq$ 7 days) had false positive results. Further analysis indicated that late-onset infants were significantly more likely to have true positive results than early-onset infants [$p = 0.002$, odds ratio (OR) = 4.09]. Analysis of symptoms indicated that seizure was a powerful indicator for GBS meningitis, and that all infants with seizures and positive test results had confirmed GBS meningitis (no false positives). However, only 6/18 infants (33%) with GBS meningitis had seizures, which was compatible with a previous pediatric study of seizure and acute phase of bacterial meningitis.[17] Infants with fever and positive test results ($p < 0.001$, OR = 9.2) and infants with respiratory distress and positive test results ($p < 0.001$, OR = 5.34) had significantly greater probabilities of true positive test results. In otherwise healthy infants, the presence of hyperbilirubinemia or feeding intolerance was not significantly related to the presence of positive results.

Numerous laboratory parameters were also important in distinguishing true positive test results (Table 3). In particular, leukopenia ($p < 0.001$, OR = 16.8) was the strongest indicator, followed by thrombocytopenia ($p = 0.012$, OR = 14.4), coagulopathy ($p < 0.001$, OR = 7.7), elevated CRP ($p < 0.001$, OR = 7.2), metabolic acidosis ($p = 0.015$, OR = 4.5), and bandemia ($p = 0.003$, OR = 4.2).

4. Discussion

Burden of neonatal GBS disease varied across countries.[18] A previous study reported that the overall incidence of neonatal GBS infection among live births was 0.11% in Taiwan, and 0.17% at Linkou Chang-Gung Memorial Hospital.[19] In the present study, the case-admission ratio of culture-proven invasive GBS disease was 0.27% and case-births ratio of early-onset disease was 0.05%. This higher case-admission incidence may be because it included

Table 2 Diagnostic evaluation of the urinary group B Streptococcus (GBS) antigen test.

Total (n=14277)	With invasive GBS disease (n=38)	Without invasive GBS disease (n=14239)	
Positive (n=106)	26	80	Positive predictive value = 26/106 = **24.5%**
Negative (n=14171)	12	14159	Negative predictive value = 14159 / 14171 = **99.9%**
	Sensitivity = 26/38 = **68.4%**	Specificity = 14159 /14239 = **99.4%**	

Pre-test	Probability (Prevalence) = 38/14277 = **0.27%**	
	Odds = prevalence /(1-prevalence) = 0.27% /(1-0.27%) = **0.27%**	
GBS Antigen	LR for a positive result (LR+) = sensitivity / (1-specificity) = 68.4%/(1-99.4%) = **114**	
	LR for a negative result (LR-) = (1-sensitivity) /specificity = (1-68.4%) /99.4% = **0.318**	
Post-test	Positive result	Odds for a positive result = Pretest odds x LR+ = 0.27% x 114 = 30.8%
		Probability of disease = posttest odds/(posttest odds+1) = 30.8% /130.8% = **23.5%**
	Negative result	Odds for a negative result = Pretest odds x LR- = 0.27% x 0.318 = 0.09%
		Probability of disease = posttest odds/(posttest odds+1) = 0.09% /1.09% = **0.09%**

GBS, group B streptococcal; LR, likelihood ratio

Table 3 Demography, symptoms and signs, and laboratory parameters of infants with true- and false-positive results in the urinary group B Streptococcus (GBS) antigen test.

	True positive (26) *n* (%)	False positive (80) *n* (%)	*p*	Odds ratio (95% CI)
Demography				
Sex, male	9 (35)	42 (53)	0.113	N.S.
Method of delivery, VD	18 (69)	60 (75)	0.562	N.S.
Term (≥37 wk)	20 (77)	48 (60)	0.118	N.S.
Symptoms and signs				
Onset ≥7 days old	15 (58)	20 (25)	0.002*	4.09 (1.62–10.35)
Seizure	6 (23)	0 (0)	0.001*	∞
Fever	14 (54)	9 (11)	0.001*	9.20 (3.26–25.96)
Respiratory distress	12 (46)	11 (14)	0.001*	5.34 (1.98–14.6)
Hyperbilirubinemia	0 (0)	9 (11)	0.109	N.S.
Feeding intolerance	0 (0)	8 (10)	0.195	N.S.
Laboratory parameters				
WBC ≤5000/uL	15 (58)	6 (8)	0.001*	16.8 (5.38–52.54)
WBC ≥ 30,000/uL	2 (8)	4 (5)	0.634	N.S.
Bandemia ≥5%	11 (42)	12 (15)	0.003*	4.2 (1.54–11.19)
Platelets < 100,000/uL	4 (15)	1 (1)	0.012*	14.4 (1.53–135.15)
Coagulopathy	10 (38)	6 (8)	0.001*	7.7 (2.45–24.28)
Metabolic acidosis	6 (23)	5 (6)	0.015*	4.5 (1.25–16.27)
CRP ≥ 10 mg/L	18 (69)	19 (24)	0.001*	7.2 (2.71–19.23)

CI = confidence interval; CRP = C-reactive protein; N.S. = nonspecific; VD = vaginal delivery.
*$p < 0.05$ indicates statistical significance.

admitted infants as denominator, instead of births at our institution alone. We used the Wellcogen Strep B test to test concentrated urine samples and identify GBS disease. The sensitivity and specificity of our urinary antigen test were 68.4% and 99.4%, respectively. These statistics are comparable to those of previous studies that used the same assay kit (sensitivity of 68–88%, specificity of 99–99.5%).[20,21] Thus, we have confidence in our examination procedures and the quality of our test results.

The sensitivity of the urinary GBS antigen test was 68.4% and the positive LR was 114. However, the low positive predictive value (24.5%) indicates that about 75% of the positive antigen results were false positives. Thus, routine use of this test may result in unnecessary and prolonged hospitalizations and the administration of treatments that are not needed. Restriction of the test in clinical practice had been proposed.[11–14] The high false positive rate may be due to urine bag contamination from perineal or rectal colonization.[22,23] However, collection of urine by a catheter or aspiration to reduce skin contamination is highly invasive for most infants, and the results would still not be conclusive.[23] On the other hand, our low post-test positive probability (23.5%) means that the accuracy of a positive result was only about one-fourth. The positive predictive value increased and the false positive rate decreased in infants who experienced onset at an age of ≥7 days, although there were no apparent differences in sensitivity (Table 1). The higher positive predictive value among late-onset infants may be because most were admitted for symptoms that correlated with invasive GBS infection. By contrast, routine urinary GBS antigen screening for younger infants, especially immediately after birth, had the lowest positive predictive value, so this practice appears to be unnecessary from a clinical point of view.

The specificity (99.4%) and negative predictive value (99.9%) of the urinary GBS test were both satisfactory. However, for a disease with low prevalence, it is also important to consider the negative LR and the post-test probability to assess the diagnostic value of a test. The negative LR was 0.318, and there was a small decrease in post-test probability.[24] The post-test probability for a negative result was 0.09%, and the absolute risk reduction was merely 0.18%. Thus, for every 556 infants tested for the urinary GBS antigen, only one would benefit from a negative result to exclude invasive disease. This indicates that the value of universal screening for exclusion is very small. However, for infants with increased risk of sepsis, the high negative predictive value means that this test remains a valuable adjunct for exclusion of GBS disease.[14,21]

Risk-based interpretation of the results of the urinary GBS antigen test could assist in clinical decision-making. Although sex, mode of delivery, and gestation period had no effect on the number of true or false positive cases, age at testing was discriminative. With a positive urinary GBS antigen test, infants who were at least 7 days old had a higher risk for true positive results. In the present study, as in previous studies, fever, seizure, and respiratory distress are the major symptoms associated with invasive GBS disease.[5,19] We also found that additional laboratory abnormalities were also associated with GBS disease (Table 3). Thus, infants with any of these cardinal signs have an increased risk of invasive infection and deserve more attention. In these circumstances, the urinary GBS antigen test appears to be valuable because of its large positive LR and its high negative predictive value.

Analysis of the cost-effectiveness of the urinary GBS antigen testing also indicates that routine screening is

probably unsuitable. In particular, each test (code: 12125C) costs 90 National Health Insurance (NHI) points in Taiwan[25] (approximately 76–105 Taiwan dollars[26] or 2.6–3.6 US dollars as of October 2013). Thus, during the study period, 1,284,930 NHI points were spent for 14,277 urinary GBS antigen tests. For each specific condition, it cost 58,406 NHI points to correctly diagnose one case of GBS bacteremia, 80,308 points for one case of GBS meningitis, and 49,420 points for one case of invasive infection. However, even with our routine screening, 12 cases of bacteremia, two cases of meningitis, and 12 cases of invasive infections were missed, and there were many cases of overdiagnosis. Because the risk of bacterial infection in asymptomatic infants is low,[27] we believe that the use of a risk-based strategy to test suspected infants, instead of routine screening of all infants, would increase diagnostic accuracy and would be more cost-effective.

There were some limitations in this retrospective study. First, only one blood or CSF sample was typically taken from each infant, so it was inevitable that some samples simply failed to yield growing pathogens, even for severely ill infants. This may have led to an underestimation of the sensitivity and an overestimation of the specificity. However, our use of a large sample size and a long study period would minimize this limitation. Second, the case-births ratio of early-onset disease may be underestimated. Because most inborn infants left hospital before they were 3 days old and there was a lack of follow-up information in this retrospective study, some early-onset cases may have fallen ill later (i.e., aged between 3 days and 6 days) but may have been missed in the current database. Third, we failed to determine the impact of maternal GBS screening and prophylaxis with intrapartum antibiotics on the occurrence of early-onset GBS disease. Although these procedures have been performed on selected women for years in Taiwan, and they are known to effectively lower disease occurrence,[28] universal screening did not become a health policy in Taiwan until 2012.[29] In our study, the occurrence of early-onset GBS infection per admission was 0.105% (15/14,277), corresponding to about two cases/year. The occurrence of early-onset GBS infections seems to have declined since 2012 (Figure 1). However, because many study infants were born outside of our facility, it was difficult to calculate the occurrence based on live births, as in previous surveillance studies. Finally, we were unable to perform an adequate analysis of maternal risk factors. Again, because many of the study infants were outborn, we could not consider some important maternal conditions, such as preterm rupture of the membrane, maternal fever, or chorioamnionitis.[30] We believe that maternal factors may have an important impact on the clinical value of the urinary GBS test, and these should be considered in future studies.

In conclusion, based on statistical evidence of a poor positive predictive value of a positive result and the weak risk reduction of a negative result, we believe that routine screening of neonates with the urinary GBS antigen test is unnecessary. However, for infants with known risk factors, a positive urinary GBS antigen test may aid in the early detection of disease, and negative results may be useful for exclusion of GBS disease.

Conflicts of interest

There were no conflicts of interest stated by the authors.

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