

## Current Status and Problems of Newborn Infection Management at a Regional Hospital in Japan

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**PURPOSE:** To clarify neonatal bacterial infection management in near term and term infants at a regional hospital in Japan. **METHODS:** Between 2018 and 2020, of 729 births, 236 patients who underwent blood examination at least twice by the age of 3 days, were included. Data from the medical records were analyzed retrospectively. **RESULTS:** Median gestational age was 39 weeks, with 116 boys (49.1%) and 202 vaginal deliveries (85.6%). There were 37 cases of maternal group B streptococcus, 24 cases of premature rupture of membranes for more than 24 hours (PROM group), and 107 cases of amniotic fluid turbidity at birth (AFT group). Comparing groups, C-reactive protein (CRP) was significantly lower in the cesarean section (C/S) group (median 0.22 mg/dL;  $p < 0.05$ ), and higher in the AFT group (0.44 mg/dL;  $p < 0.05$ ). There were 77 positive cultures, ( $p < 0.05$ ). Antibiotics were administered more frequently in cesarean section (19 cases;  $p < 0.001$ ) and less in the PROM group (2 cases;  $p < 0.01$ ). **CONCLUSIONS:** There were no asymptomatic cases of CRP  $>2$  mg/dL, and no cases of severe sepsis in normal neonatal deliveries. CRP levels were elevated in the AFT group, where culture was positive, but few antibiotics were administered. In the C/S group, antibiotics were administered if respiratory symptoms occurred unless the CRP level was high. Further, all patients in PROM group who received antibiotics had any symptoms, suggesting that routine blood tests may not be necessary.

### INTRODUCTION

Neonatal bacterial infections may lead to a very poor prognosis, accounting for 13% of neonatal deaths worldwide (1). Infection is established mainly as transplacental or birth canal infection via mothers, with a high mortality rate in early onset sepsis (2). Since the mortality rate in premature infants or low body weight infants (LBWIs) is worse than that in term infants (born between 37–42 weeks), various studies have been conducted by neonatal intensive care units (NICUs), and the timing of antibiotic administration has been debated (3). However, most of the reports have focused on premature babies, so the research results could not be directly applied to term infants who are cared for in normal regional hospitals.

Since term infants usually receive maternal immunoglobulin G (IgG), infection is generally prevented. Therefore, antibiotics are rarely administered to the mother, unless there is a high risk of maternal fever, maternal group B Streptococcus (GBS) infection or premature rupture of membranes (PROM), and amniotic fluid turbidity (AFT). In addition, blood or culture examinations are rarely examined if term newborns do not present with symptoms such as respiratory distress, jaundice, fever, convulsions, and poor feeding (3). However, once these symptoms appear, it is sometimes difficult for general community pediatrics to deal with them because the infection has already been established or treatment would be too late. However, the current situation and problems concerning infection in term infants are still unclear due to the lack of studies conducted in hospitals without NICUs.

At our facility, one pediatrician managed nearly 250 newborn babies per year. Prompt intervention was performed for symptoms such as mild respiratory distress, and for births from high-risk pregnant women with infectious diseases. Blood examinations including C-reactive protein (CRP) and the immature-to-total (IT) ratio in white blood cells (WBCs) were analyzed for 2 consecutive days with monitoring cultures of the ears and nose. Cases with aggregated symptoms or data were transferred to the NICU in an advanced hospital.

In this study, it was difficult to diagnose neonatal sepsis and judge the effects of treatment, as in previous studies from NICUs. However, there have been no reports of frequent blood examinations in term newborns at high risk of infection, and the data and clinical course were considered as extremely valuable. In addition, we thought that it could be useful information for general pediatricians who work away from NICUs.

## MATERIALS AND METHODS

### **Clinical setting**

Even though pregnant women had a high risk of diabetes, hyperthyroidism, or hypertension, near term and term newborns were managed in our hospital. Newborns with diseases such as respiratory disorders, jaundice, and infectious diseases are difficult to contain, and they are transferred to an advanced hospital. Bacterial cultures were collected from the nose and ears if newborns were at risk of infection from maternal infections such as GBS, PROM, or ATF. Blood tests were routinely performed on days 1 and 2 after birth.

### **Research Design**

Of the 729 infants born in our hospital between April 2018 and March 2021, the 236 infants who underwent blood tests for infectious diseases for more than two consecutive days were included in this study. Data such as maternal background, delivery modes, birth findings, results of blood tests, bacteriological (ear/nose) tests, and treatment were collected retrospectively from medical records and examined. We usually have the criteria of administering antibiotics to patients who have breathing or feeding problems, and/or patients with CRP >2mg/dl even if they are asymptomatic. The study was approved by the ethical committee of Steel Memorial Hirohata Hospital (number 3-176, approved at 17th of November, 2021). The need for written informed consent was not required owing to the retrospective nature of this study. The study procedures were in accordance with the ethical standards of the responsible committee on human studies and the Declaration of Helsinki of 1975, as revised in 2008.

### **Risk evaluation**

The risks of infection were analyzed based on the maternal condition which was divided into four groups, namely, PROM group, ATF group, maternal GBS group, and the “other” groups. The type of delivery, classified as the vaginal delivery (VD), vacuum extraction delivery (VED), and Cesarean section (C/S), was also analyzed to determine the current management. The other groups included patients with fever, respiratory distress, poor feeding, jaundice, and hypoglycemia.

### **Statistical analysis**

Each data point was examined and statistically analyzed using JMP 10.0. The data were expressed as the median (range), and comparisons between one group and the other group were analyzed using the Mann-Whitney U or Wilcoxon’s paired-order test. Statistical significance was set at  $P < 0.05$ .

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## RESULTS

### **Patients’ background**

The median maternal age was 31 (16–45) years and the median gestational age was 39 (34–42) weeks, with 50.4% being primiparas. VD was performed in 202 cases (85.6%), of which 17 were VED. There were 37 cases (15.3%) of maternal GBS, 24 cases (9.7%) of PROM for 24 hours or more, and 107 cases (45.5%) of ATF. 116 infants (49.1%) were boys. Reported median Apgar score was 1 minute 9 (2–10) points, 5 minutes 10 (7–10) points, and their median length and weight were 48.2 (42.6–53.5) cm, and 3056 (2124–4036) g, respectively. Respiratory disorders occurred in 52 patients (22%), and feeding disorders occurred in 16 patients (6.8%). Phototherapy was administered to 45 patients (19.1%). Bactericide administration was performed using ampicillin + cefotaxime in 30 patients (27.5%). Culture was performed in 182 patients, of which 121 (66.5%) were positive. No cases were sent for further treatment because of suspected severe sepsis (Table I).

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Table I. Clinical characteristics of mothers and neonates

n = 236	Median or n	(range) or %
<b>Background of mother</b>		
age (y)	31	(16–45)
Primipara (n)	119	50.4%
Gestational age (w)	39	(34–42)
Vaginal delivery (n)	185	78.4%
Vacuum extraction delivery (n)	17	7.2%
Caesarean section (n)	34	14.4%
Induced delivery (n)	61	25.8%
GBS (n)	37	15.3%
PROM (n)	24	9.7%
Amniotic fluid turbidity (n)	107	45.5%
Male neonate (n)	116	49.1%
Apgar score 1min	9	(2–10)
Apgar score 5min	10	(7–10)
Birth height (cm)	48.2	(42.6–53.5)
Birth weight (g)	3056	(2124–4036)
Respiratory disorder	52	22.0%
Feeding disorder	16	6.8%
Photo therapy	45	19.1%

GBS, Group B streptococcus; PROM, Premature rupture of membranes for more than 24 hours; g, gram; cm, centimeter; n, number; y, year; w, weeks.

### Classified bacteria

In previous reports, coagulase negative *Staphylococcus* (CNS), GBS, *Escherichia coli*, and *Listeria monocytogenes* were generally mentioned (4), and generally in this study similar bacteria were detected. (Table II).

Table II. Results of culture

From ear	N=187	From nose	N=87
<i>Staphylococcus</i> spp.	62	<i>Staphylococcus</i>	40
coagulase negative <i>Staphylococcus</i> (CNS)	13	CNS	7
MRCNS	28	MRCNS	14
MRSA	2	MRSA	1
GBS	6	GBS	3
<i>Escherichia. Coli (E.coli)</i>	21	<i>E.coli</i>	5
<i>Enterococcus</i> spp.	3	<i>Enterococcus</i> spp.	1
<i>Corynebacterium</i> spp.	6	<i>Corynebacterium</i> spp.	3
<i>Bacillus</i> spp.	1	<i>Bacillus</i> spp.	2
<i>Pseudomonas aeruginosa</i>	1	<i>Pseudomonas aeruginosa</i>	0
<i>Candida</i>	2	<i>Candida</i>	1
<i>E.coli</i> (ESBL)	3	Other	0
Other	4	Multiple bacteria	10
Multiple bacteria	35		

MRCNS, multiple resistant CNS; MRSA, Methicillin-resistant *Staphylococcus aureus*; GBS, Group B *Streptococcus*; ESBL, Extended spectrum  $\beta$ -lactamases.

### Outcomes

The outcomes of the infection control are summarized in Table III. Maternal antibiotics were administered to 70 patients, and intravenous and oral antibiotics were administered to all patients with GBS and PROM. Bactericide administration to infants was performed in 65 cases (27.5%), and culture was positive in a total of

274 cases (121 persons), the breakdown of which is shown in Table III. The high CRP level which was set to 2 mg/dL in newborns, occurred in 33 cases, 27 infants were administered antibiotics. In 24 of the 27 cases, the peak CRP level was on the newborns' first day. Asymptomatic CRP elevation was observed in 13 patients (5.5%). There were no cases of severe illness requiring transfer to a higher hospital.

Table III. Clinical characteristics about infectious control

n = 236	n	%
History of maternal antibiotic administration	70	30.0%
Antibiotic administration to newborns	65	27.5%
Total number of culture positives (Total cases)	274(n = 121)	51.3%
From ear	187	69.0%
From nose	87	31.0%
CRP >2mg/dl	33	14.0%
CRP >2mg/dl and antibiotic administration	27	11.4%
The peak days of CRP elevation		
1 <sup>st</sup> day	24	88.9%
2 <sup>nd</sup> day	3	11.1%
-CRP >2mg/dl at 1 <sup>st</sup> day	2	66.7%
Antibiotic administration without symptoms	13	5.5%
Transferred to advanced hospital	0	0%

CRP, C-reactive protein.

### Analysis by infection risk

Patient information was mainly compared with the infection risk. There was no difference in the proportion of boys, gestational age, or birth weight in any group. The mode of delivery was significantly higher in the AFT group than the others, but there was no significant difference in induced delivery in any group. CRP levels were significantly higher in the AFT group, but WBC, IT ratio, and IgM values were not significantly different in any group. Regarding the culture results, bacteria were detected more frequently in the PROM and AFT groups, but antibiotic administration was lower in the PROM group, where maternally administered antibiotics were significantly higher (Table IV).

Table IV. Profile of mothers and newborns

	PROM (n = 24)	GBS (n = 37)	AFT (n = 107)	The others (n = 73)
Male	12	23	53	34
GA	39.5(35–41)	39(36–41)	40(37–41)	38(34–42)
VED	1	2	22**	3
Induced delivery	17	5	14	18
Birth weight	3248 (2474–3878)	3136 (2428–3896)	3098 (2278–4036)	2884 (2124–3926)
Respiratory distress	1	2	14	35*
Phototherapy	4	4	19	18
Sucking disorder	1	1	6	8
CRP (mg/dL)	0.36 (0.06–3.72)	0.37 (0.04–4.21)	0.44* (0.04–6.09)	0.23 (0.02–6.79)
CRP >2mg/dL	2	2	18	11
WBC (X10 <sup>3</sup> )	229(109–313)	229(97–388)	216(119–354)	217(91–379)
IT (%)	6.25(0–22)	4.5(0–45)	5.3(0–27)	5.2(0–33)
Immunoglobulin M (mg/dL)	14(6–22)	12.5(6–40)	13(5–40)	12(5–25)
Culture positive	10*	25	77*	14
Antibiotics	2**	6	23	34
Antibiotics w/o symptom	0	3	8	2

PROM, infant from premature rupture of membranes; GBS, Group B *Streptococcus*; AFT, Amniotic fluid turbidity; GA, Gestational age; VED, vacuum extraction delivery; CRP, C-reactive protein; WBC, white blood cells; IT, immature-to-total (IT) ratio in white blood cells (WBCs), \*p < 0.05, \*\*p < 0.01.

**Analysis by delivery style**

There was no gender difference, but infants born by C/S had a lower gestational age. It was considered that elective C/S accounted for most cases. There was no difference in induced labor among the three groups, but the AFT group had significantly higher VED. Respiratory disorders were more common with C/S and VED. Laboratory values showed low CRP, creatine kinase (CK), lactate dehydrogenase (LDH), calcium (Ca), and high phosphate (P) levels in cesarean infants. In contrast, the CK was high in the VED group, whereas bactericide administration was significantly higher in the C/S group (Table V).

Table V. Clinical profile of patients

	VD (n = 185)	VED (n = 17)	C/S (n = 34)
Male	97	5	18
GA	39(34–42)	40(38–41)	37(35–41) ***
Induction	50	4	7
AFT	86	14**	7
Respiratory distress	25	6*	21***
Suck disorder	13	1	2
Phototherapy	36	4	5
Culture positive	106	14	1***
Antibiotics	39	7	19***
CRP	0.37(0.02–6.79)	0.51(0.04–3.65)	0.22(0.03–6.01) *
CK	631(138–2898)	871(244–2591) *	452(137–1560) **
LDH	682(377–2054)	744(551–1604)	588(393–1241) **
Ca	9.1(6.4–11)	9.2(8.4–9.8)	8.5(7.6–9.8) ***
P	6.4(4.5–8.3)	5.9(5.4–7.3) *	6.65(4.9–7.9) *
WBC	221(97–388)	223(161–329)	206(91–333)
IT	5.2(0–45)	5.6(2.7–20)	4.95(0–20)
IgM	13(6–36)	12.5(5.1–40)	11.5(5–27)

VD, vaginal delivery; VED, vacuum extraction delivery; C/S, Cesarean section; GA, Gestational age; AFT, Amniotic fluid turbidity; GA, Gestational age; \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001.

**DISCUSSION**

This report describes typical neonatal care in a regional hospital in Japan. Because many hospitals focus mainly on adults, medical care for children especially newborns, is not friendly. This is for instance, because blood tests and blood cultures require a large amount of blood. On the other hand, the provision of safe delivery, even if there is a risk for the pregnancy, tends to be considered a prerequisite. Therefore, providing neonatal care in a safe, non-invasive manner without enough human resources is a difficult issue in many local hospitals. This study provides a valuable source of information for pediatric practitioners.

First, we provided useful data on identifying neonatal infectious diseases. Although true sepsis could not be detected in this report, CRP has been used for the early detection of infectious diseases (5–8). CRP is not only known as an early marker of sepsis in previous reports, but can be measured easily and inexpensively. As a result, since PROM and GBS mothers for 24 hours or more were properly managed, many antibiotics were administered when required (2, 9). Under such circumstances, the significant increase in CRP level was not statistically significant. There were few cases of elevated CRP, and their management was successful. After excluding respiratory and feeding disorders, CRP was elevated by >2 mg/dL in 13 cases (5.5% of all): [PROM, 0; GBS, 3; ATF, 8; others, 2], without any symptoms. In addition, 14 patients received antibiotics for respiratory distress and other symptoms, and 24 of these 27 cases (88.9%) reached the peak CRP on the first day. In the past, it has been said that CRP peaks physiologically on the first day, and conversely, if an increase is observed beyond that, it is necessary to administer antibiotics prophylactically on the premise of sepsis (10–12). From the above findings, routine blood tests may not be necessary for PROM children, and even for GBS children and amniotic fluid opaque children, clinicians can almost determine the necessity of antibiotics by blood tests at 1 d of age. In terms of IT, although it has been reported to be useful for the early detection of infection, it would hardly be useful for the patients in our study. Many biomarkers have recently been explored for the treatment of early onset sepsis (8, 13–16).

The next topics are culture and antibiotics. Since ear and nose cultures are non-invasive, they are performed as surveillance cultures in many facilities. However, the result only reflected the culture of the amniotic fluid, which is different from blood culture for the disclosure of infection. The frequency of resistant bacteria was

interesting, since these were detected in 48 cases, accounting for 22.1% of the infants' ears and 19.5% of the infants' noses. Ear and nose culture tests have implications for active surveillance and antibiotic administration. Since the culture is performed only on newborns at high risk of infection, the positive rate is considered to be high, but it should be noted that resistant bacteria can be produced even if the infection is not through horizontal infection as in NICU (4). However, we did not know whether a real infection occurred, moreover, this study was retrospectively undergone by a single hospital; therefore, verification of the correct method of surveillance and correct antibiotic selection, an addition to prospective study, is mandatory in further studies.

Second, there are surprisingly few cases of respiratory distress or jaundice in which inflammatory reaction increases suggest infection. In our study, there were 52 cases of respiratory distress who received antibiotics, but only 8 (15.3%) of them had CRP levels >2 mg/dL. Most respiratory disorders in term delivery are transient tachypnea of the newborn (TTN), and infections are not always involved. In the future, we should discuss whether to routinely add antibiotics to cases judged to be TTN, and we look forward to the development of biomarkers (17, 18).

Finally, this report provides valuable information on the rise in CK and LDH levels. As is often noted in clinical practice, these markers are known as stress markers and are known to increase in asphyxia. This time, severe asphyxia cases were not included because serial blood tests were not performed before transfer. However, CK and LDH levels in VD were significantly lower than those in the C/S group. The reason for the significant decrease as in Ca this time is unknown, but immaturity of the parathyroid gland is suspected because of the significantly lower gestational age in the C/S group.

In summary, this study provides a great deal of valuable data on near term and term neonates cared for in a regional hospital. It was clarified that the CRP value differed depending on the risk of maternal infection and mode of delivery. In asymptomatic cases, only 1 d of age is enough for a CRP check, and it is considered necessary to reconsider the routine blood sampling itself for newborns, for infection control in PROM. Larger studies are needed on antibiotic administration due to the risk of infection.

#### CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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