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Research Article

# Observation *Versus* Prophylactic Antibiotics in Late Preterm Infants with Premature Rupture of Membranes: A Pragmatic Randomized Controlled Trial

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**Abstract**

**Background:** There is no general accepted strategy for the management of asymptomatic neonates born to mothers with Premature Rupture of Membranes (PROM).

**Objectives:** To compare expectant observation versus prophylactic antibiotics in the management of infections in late preterm infants born to mothers with PROM.

**Methods:** Infants between 34 and 36 weeks gestation weighting ≥1500 grams born to mothers with PROM were randomized to prophylactic antibiotic or expectant observation groups. Primary outcomes were the incidence of bacterial sepsis, and the incidence of systemic bacterial infection during hospitalization.

**Results:** A total of 120 infants were enrolled. No significant difference in sepsis or systemic bacterial infections was found (RR 0.25, 95% CI 0.01 to 5.66, P=0.48; RR 0.80, 95% CI 0.23 to 2.84, P=0.73). The risk of readmission due to infection seemed higher in expectant group, without statistically significant difference (RR 5.10, 95% CI 0.58 to 45.12, P=0.14).

**Conclusions:** Expectant observation strategy could be considered in late preterm infants born to mothers with PROM to reduce unnecessary consumption of antibiotics.

**Keywords:** Antibiotic; Late preterm infant; Premature rupture of membrane; Randomized controlled trial

## Key Messages

There is no general accepted strategy for the management of asymptomatic neonates born to mothers with Premature Rupture of Membranes (PROM). From this trial, we find that expectant observation strategy did not does not increase the risk of infection in late preterm infants born to mothers with PROM during hospitalization in NICU. Expectant observation strategy could be considered in late preterm infants born to mothers with PROM to reduce unnecessary consumption of antibiotics.

## Introduction

Premature Rupture of Membranes (PROM), defined as the rupture of membranes before the onset of labor is the most common cause of preterm birth [1]. Following rupture of the membranes, ascending bacterial invasion can lead to intrauterine infection in up to 60% of cases in the absence of antibacterial therapy [2]. The incidence of neonate sepsis following PROM varied from 4 to 20% [3]. Current guidelines of PROM focus on the role of intrapartum antibiotics in pregnant women without giving recommendations of whether or not to use antibiotics in asymptomatic neonates after birth [4]. A Cochrane systematic review-comparing prophylactic versus selective antibiotics to neonates of mothers with risk factors for neonatal infection found that previous small trials failed to provid enough evidence to guide practice, and thus suggested further pragmatic Randomized Controlled Trial (RCT) to address the question [5]. Guidelines of the prevention of early-onset neonatal Group B Streptococcus (GBS) infection can be used [6]. However, these guidelines are inappropriate for countries where GBS is not the main colonizing microorganism in pregnant women with PROM [7]. Some pediatricians routinely prescribe antibiotics to neonates if PROM was present [8], while others prefer to observe and selective antibiotics strategies [9]. There is no general accepted strategy for the management of asymptomatic neonates born to mothers with PROM.

In addition, recommendation from current guidelines on intrapartum antibiotic use is gestational-age dependent. There is insufficient evidence to justify the routine use of intrapartum prophylactic antibiotics for the late preterm (34-37 weeks gestation) [10].Therefore, the use of intrapartum antibiotic in women with late preterm is more variable often depending on the preference of institutions, which causes the management of late preterm infants more complicated [11]. The aim of our study is to assess the effect of expectant observation versus prophylactic antibiotics for late preterm infants born to mothers with PROM.

## Methods

### Study design

This study is a prospective, open-labelled, randomized controlled




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trial performed at NICU of West China Second University Hospital (WCSUH), Sichuan University, from November 2015 to August 2017. The hypothesis is that expectant observation is not inferior to prophylactic antibiotics in the management of late preterm neonates born to mothers with PROM. This trial was approved by the Chinese Ethics Committee of Registered Clinical Trials. The parents or legal guardians were informed before the start of interventions and given the option to withdraw at any time. This trial was registered at Chinese Clinical Registry (ChiCTR-IOR-15006744), which is the primary registry of International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO). The Consolidated Standards of Reporting Trials (CONSORT) statement was considered in the report of study design, results, abstract and flow diagram [12].

### Participants and interventions

We recruited late preterm infants according to the inclusion criteria as follows: (1) born to mothers with PROM at 34 through 36 weeks gestation; (2) age ≤24 hours at enrollment. Infants were excluded if they met one of the following criteria: (1) confirmed diagnosis of infectious disease before enrollment; (2) antibiotic use before enrollment; (3) allergy to cefuroxime; (4) any condition considered inappropriate to be included by physicians. The infants were allocated in a 1:1 ratio to expectant observation or prophylactic antibiotic group according to a randomization list generated by SPSS 13.0. The group allocation and randomization sequence were concealed from investigators by a coordinator who was blinded to the participants' characteristics. The coordinator assigned the participants to groups. Clinicians and investigators were not blinded to the group assignment, because of the obvious difference of interventions between groups. A statistician who conducted the data analysis was blinded to the group assignment. No prophylactic antibiotic was given at enrollment to infants in the expectant observation group, while cefuroxime sodium (30mg/kg q12h) was administered for 48 hours to infants in the prophylactic antibiotic group. The initiation of antibiotics, prolonged antibiotics use or changing of antibiotics decided by physicians were allowed in both groups when suspected or confirmed infection was considered. To carefully monitor all participants, blood culture and sputum culture were performed in both groups within 24 hours after enrollment. Blood routine and C-Reaction Protein (CRP) were monitored every 3 days during the first week and every week after the first week during hospitalization.

A follow-up was performed by telephone interview of the parents at 2 months after birth to assess the long-term outcomes. Medical records from the Hospital Information System (HIS) of WCSUH were also used to verify the information from parents if the participants visited the outpatient department of WCSUH after discharge.

### Primary and secondary outcomes

The primary outcomes were: (1) the incidence of early- and late-onset sepsis before discharge, and (2) the incidence of early- and late-onset systemic bacterial infection before discharge. Early-onset infection was defined as occurring in the first 72 hours of life. Late-onset infection was defined as occurring >72 hours after birth [13]. Sepsis included both definite and clinical sepsis. Definite sepsis was diagnosed when a pathogen was isolated from blood, urine, or cerebrospinal fluid, and the infant was treated with antibiotics for ≥5 days. Clinical sepsis was diagnosed when a blood culture was negative, but the C-reaction protein was >10mg/L, and the infant was treated with antibiotics for ≥5 days [14]. The diagnosis of systemic bacterial infection including sepsis, bacterial meningitis, urinary tract infection, and infectious pneumonia was made by physicians based on clinical symptoms, Cerebrospinal Fluid (CSF) analysis, urine analysis, etiological examinations and imaging examinations [15-16].

The secondary outcomes were: (1) all-cause mortality before discharge; (2) the incidence of fungal infection before discharge; (3) the incidence of bacterial infection during follow-up; and (4) the incidence of readmission during follow-up. Fungal infection included both mucocutaneous and invasive fungal infection [17]. Bacterial infection during follow-up included both local and systemic bacterial infection. Bacterial infection was counted when a diagnosis of bacterial infection was made by physician and the infant received antibiotics for ≥3 days. Study data was collected and managed using ResMan Clinical Trial Management Public Platform (http://www.medresman.org/register.aspx).

### Sample size

The sample size was calculated based on the incidence of sepsis before discharge. According to the aim of study, non-inferiority test was used with an expected maximum difference of 10% [18]. The estimated incidences of infection were based on both previous prospective studies and experience from physicians, since no previous trials could give a robust estimation. The estimated incidence of sepsis was 6% in expectant observation group, and 4% in prophylactic antibiotics group [19-20]. With a one-tailed $\alpha$ error of 0.05 and a $\beta$ error of 0.20, the power analysis resulted in a total sample of ≥58 participants per group (multiplied by 2 groups=116 infants). We included 120 participants, 60 in each group.

### Statistical analysis

Continuous value was described by mean and Standard Deviation (SD), while discontinuous value was described by number and percentage. Difference at baseline was assessed by Student's test or the Mann-Whitney U test if the variable was not normally distributed for continuous variable, and Chi-squared test for binary variable [21]. Adjusted analysis of binary outcome was performed using logistic regression. Prognostic factors adjusted included gestational week, birth weight, length of PROM, invasive operation and antibiotics use before delivery [22]. We conducted Intention-To-Treat (ITT) analysis with all participants analyzed in the study arm to which they were randomly assigned. To assess the potential impact of lost to follow-up, we performed a "best case worst case" sensitivity analysis [23]. All analyses used the individuals as the unit of analysis. Data were analyzed by using SPSS software version 21 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

## Result

### Enrollment procedure and characteristics of participants

From November 2015 to August 2017, we approached parents of a total of 187 potential neonates; of these, 26 (13.9%) were considered as inappropriate to be randomized due to the suspected infection by physicians, and 41(21.9%) were not interested. Finally, 120 eligible neonates were recruited. The baseline demographic, clinical characteristics of neonates and mothers were presented in (Table 1). No significant difference was found between the 2 groups. The mean

**Table 1:** Baseline characteristics participants.

| Characteristics | Total (n=120) | Expectant observation (n=60) | Prophylactic antibiotic (n=60) |
|---|---|---|---|
| **Neonates** | | | |
| Gestational week, w (mean±SD) | 36.11±2.09 | 36.35±2.20 | 35.87±1.95 |
| Gender, male, n (%) | 79 (65.83%) | 44 (73.33%) | 35 (58.33%) |
| Birth weight, g (mean±SD) | 2556.13±573.92 | 2590.75±587.60 | 2521.50±562.72 |
| Length of PROM, d (mean±SD) | 1.02±3.23 | 1.15±3.78 | 0.90±2.56* |
| Invasive operation, n (%)[b] | 16 (13.33%) | 7 (11.67%) | 9 (15.00%) |
| **Mothers** | | | |
| Age, y (mean±SD) | 31.28±4.60 | 31.43±4.53 | 31.12±4.69 |
| Alcohol, n (%) | 1 (0.83%) | 0 (0.00%) | 1 (1.67%) |
| Smoking, n (%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Caesarean section, n (%) | 86 (71.67%) | 41 (68.33%) | 45 (75.00%) |
| Antibiotics use before delivery, n (%) | 82 (68.33%) | 36 (60.00%) | 46 (76.67%) |

**Note:** *Length of PROM was unclear in one participant. Invasive operations included umbilical vein catheters, lumbar puncture, and central venous catheter.

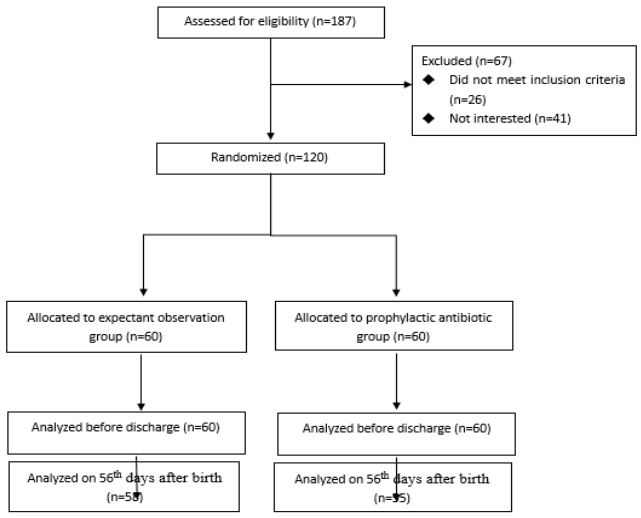


**Figure 1:** Flow diagram of participants.

duration of hospitalization of all participants was 6.1±2.7 days. One hundred and thirteen participants (94.2%; 58 in expectant observation group, and 55 in prophylactic group) completed the follow-up and 34 (30.1%) of them were back to visit outpatient department of WCSUH after discharge. The number of infants followed (n=116) was almost consistent with the estimated sample size. All participants were included in the Intention-To-Treat (ITT) analysis (Figure 1).

### Primary and secondary outcomes

No significant difference was found in terms of sepsis during hospitalization between the two groups (RR 0.25, 95% CI 0.01 to 5.66, P=0.48). Similarly, there was no significant difference in terms of systemic infections during hospitalization between the two groups (RR 0.80, 95% CI 0.23 to 2.84, P=0.73). Four pneumonia was detected in the expectant observation group, while 3 pneumonia and 2 sepsis was diagnosed in the prophylactic antibiotic group during. All cases had negative results of blood culture and sputum culture. No death or fungal infection occurred in all participants during hospitalization (Table 2). It was worth noting that twelve (20.0%) infants in the expectant observation group received antibiotics during hospitalization. Eight of them initiated the antibiotics within 48 hours after birth. The mean durations of antibiotics were 2.2±3.5 days in the expectant observation group and 4.0±3.7 days in the prophylactic antibiotic group, respectively (MD-1.77, 95% CI-3.07 to -0.46, P=0.01). In addition, 1 (1.7%) and 2 (3.3%) infants in the expectant observation and prophylactic antibiotic groups received prophylactic fluconazole, respectively.

During the follow-up, a total of 21 (17.5%) infants were reported to have bacterial infection. Pneumonia was the most frequent diagnosis (16/21). The risk of bacterial infection seemed to be higher in expectant group, but without statistically significant difference (23.3% *vs* 11.7%, RR 2.24, 95% CI 0.83 to 6.10, P=0.11). Twenty-one (17.5%) infants were readmitted to hospitals within 56 days after birth. However, only 6 participants (5.0%) were readmitted due to infectious diseases, while the others were readmitted because of jaundice. The risk of readmission due to infection seemed to be higher in expectant group, but without statistically significant difference (8.3% *vs* 1.7%, RR 5.10, 95% CI 0.58 to 45.12, P=0.14). Results were unchanged when adjusted for the prespecified confounding variables. However, in the "worst case" of sensitivity analysis, the risk of infection during follow-up in expectant observation group was 2.8 times than that of prophylactic group with statistically significant difference (26.7% *vs* 11.7%, RR 2.84, 95% CI 1.07 to 7.57, P=0.04).

## Discussion

### Summary of findings

In this study, we provide the evidence that compared with the prophylactic use of antibiotics, expectant observation did not increase the risk of either bacterial sepsis or systemic bacterial infection in late preterm infants born to mothers with PROM during hospitalization. Although one fifth of the participants in expectant observation group received antibiotics, expectant observation still reduced the rate and duration of antibiotic use. The risk of infection and readmission due to infection after discharge seemed to be higher in expectant observation group but without statistically significant difference.

**Table 2:** Outcomes of expectant observation and prophylactic antibiotic groups.

| Characteristics | Total (n=120) | Expectant observation (n=60) | Prophylactic antibiotic (n=60) | RR (95% CI) | *P* Value | $RR_{adj}$ (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|
| **Primary outcomes** | | | | | | | |
| Sepsis before discharge, n (%) | 2 (1.7%)* | 0 (0.0%) | 2 (3.3%) | 0.25 (0.01, 5.66)** | 0.48 | - | - |
| Systematic bacterial infection during before discharge, n (%) | 9 (7.5%)*** | 4 (6.7%) | 5 (8.3%) | 0.80 (0.23, 2.84) | 0.73 | 0.75 (0.16, 3.45) | 0.71 |
| **Secondary outcomes** | | | | | | | |
| All-cause mortality before discharge, n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1.00 (0.02, 2.72)** | 1 | - | - |
| Fungal infection before discharge, n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1.00 (0.02, 2.72)** | 1 | - | - |
| Bacterial infection during follow-up, n (%) | 21 (17.5%)**** | 14 (23.3%) | 7(11.7%) | 2.24 (0.83, 6.10) | 0.11 | 2.70 (0.91, 8.06) | 0.07 |
| Best case | 26 (21.7%) | 14 (23.3%) | 12(20.0%) | 1.25 (0.52, 3.00) | 0.62 | 1.31 (0.51, 3.35) | 0.58 |
| Worst case | 23 (19.2%) | 16 (26.7%) | 7(11.7%) | 2.84 (1.07, 7.57) | 0.04 | 3.56 (1.22, 10.34) | 0.02 |
| Readmission during follow-up, n(%) | 21 (17.5%)e | 11 (18.3%) | 10(16.7) | 1.38 (0.51, 3.73) | 0.53 | 1.56 (0.53, 4.62) | 0.42 |
| Best case | 25 (20.8%) | 11 (18.3%) | 15(25.0%) | 0.81 (0.33, 1.99) | 0.65 | 0.83 (0.32, 2.14) | 0.7 |
| Worst case | 23 (19.2%) | 13 (21.7%) | 10(16.7%) | 1.80 (0.69, 4.74) | 0.23 | 2.15 (0.76, 6.10) | 0.15 |
| Readmission due to infection during follow-up, n (%) | 6 (5.0%) | 5 (8.3%) | 1(1.7%) | 5.10 (0.58, 45.12) | 0.14 | 6.54 (0.61, 70.65) | 0.12 |
| Best case | 11 (9.2%) | 5 (8.3%) | 6(10.0%) | 0.82 (0.24, 2.84) | 0.75 | 0.74 (0.20, 2.75) | 0.65 |
| Worst case | 8 (6.7%) | 7 (11.7%) | 1(1.7%) | 7.81 (0.93, 65.60) | 0.06 | 9.70 (1.06, 89.24) | 0.045 |

**Notes:**

*One early-onset sepsis and one late onset sepsis.

**Zero point five was added to the incidence of event in expectant observation group in the calculation RR and its 95% CI.

***In expectant observation group: 4 early-onset pneumonia; in prophylactic antibiotic group: 3 early-onset pneumonia, 1 early-onset sepsis; 1 late-onset sepsis.

****In expectant observation group: 10 pneumonia, 2 conjunctivitis, and 2 pneumonia combined with conjunctivitis; in prophylactic antibiotics group: 4 pneumonia, 2 conjunctivitis, and 1 suspected sepsis combined with conjunctivitis.

*****The reason for readmission in expectant observation group: 6 jaundice, 4 pneumonia, and 1 intestinal infection; in prophylactic antibiotic group: 1 pneumonia, and 9 jaundice.

### Comparison with previous studies

A previous RCT (n=49) compared prophylactic penicillin G and kanamycin given immediately after birth with selective antibiotics in infants with prolonged rupture of fetal membranes (≥24 hours) [20]. This study found no statistical difference between the two groups (RR 0.12, 95% CI 0.01, 2.04; RD-0.16, 95% CI-0.32, 0.00). Similarly, another quasi-random trial (n=67) evaluating the comparative effect of postnatal selective versus prophylactic penicillin in neonates with maternal history of GBS found that there was no event of death or neonatal sepsis in both groups (RD 0.00, 95% CI-0.08 to 0.08; RD 0.00, 95% CI -0.06 to 0.06) and 42% (16/38) infants in selective group received antibiotics [24]. However, these two trials were under-powered due to limited sample sizes.

### Strength and limitations

One of the main strengths of this study was its randomized controlled design that balanced both baseline characteristics and unknown bias between the two groups. The sample size calculation also overcame the shortage of previous trials. Moreover, the pragmatic design improved the applicability of study results for clinical practice in the real-life context. And the reproducible definition of primary outcomes allowed the study repeatable.

Several limitations should also be noted. First, the physicians and nurses were not blinded due to ethical considerations in this pragmatic RCT. Nevertheless, lab tests (pathogen culture, CRP) were used in the diagnosis of primary outcomes. And the statistician was also blinded to the group assignment to minimize detection bias. Second, the incidence of sepsis in prophylactic antibiotics group was consistent with the estimated incidence used in sample size calculation. However, a lower than expected incidence was observed in the expectant observation group. One possible reason was that 20% of the infants in the expectant observation group received antibiotics when infection was considered. The exclusion of infants who were considered as suspected infection might also decrease the prevalence of sepsis. Furthermore, the results during follow-up were mainly parents-reported with only 30% of followed patients having records in HIS.

## Conclusion

In summary, compared with prophylactic antibiotics, expectant observation does not increase the risk of infection in late preterm infants born to mothers with PROM during hospitalization in NICU. This result assists neonatal units considering expectant observation strategy rather than prophylactic use for late preterm population to reduce the unnecessary consumption of antibiotics. Future study with sufficient sample size should compare the long-term outcomes following these two approaches.

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