*HK J Paediatr (new series)* 2005;**10**:3-9

# *Original Articles*

# Reducing Hospitalisation and Antibiotic Use in Suspected Early Neonatal Sepsis through Serial Measurements of C-reactive Proteins

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**Abstract**

***Objective:*** To evaluate whether a standard practice of serial measurements of C-reactive protein (CRP) would reduce the duration of hospitalisation and antibiotic use in newborn infants with birth weight 2.2 kg or more and having clinical features of suspected early neonatal sepsis. ***Study design:*** This is a retrospective observational study comparing two groups of newborns with birth weight 2.2 kg or more managed for suspected early neonatal sepsis before and after adoption of a clinical protocol of measuring two serial CRP to guide stopping antibiotics in 1999. The protocol involved checking the first CRP 8 to 16 hours after the initial evaluation and the second CRP one day after the first one. A cut-off value of less than 10 mg/L for the serial CRP was used as a guide to stop the antibiotics. The mortality, duration of hospitalisation and antibiotics of 76 infants managed in 2000 were compared to those of a group of 80 infants in 1998. ***Results:*** One infant in the study group died but the death was unrelated to sepsis. The median hospital stay was shorter in the study group (7.0 vs 8.0 days, p=0.03). The median duration of antibiotics was also shorter in the study group (3.0 vs 7.0 days, p<0.005). Three infants (3.9%) in the study group and none in the control group required repeated sepsis evaluation and new antibiotics within one week of cessation of the initial antibiotics (no statistical significance). No infants in either group were readmitted within one week of discharge. ***Conclusion:*** After applying a protocol of measuring C-reactive protein serially in the management of suspected early neonatal sepsis, the duration of hospitalisation and antibiotic use may be reduced for infants with birth weight 2.2 kg or more.

**Key words** Acute phase reactant and protocol; C-reactive protein; Infection; Newborn

## Introduction

Infection is a significant cause of mortality and morbidity in neonates.[1,2] The clinical features of early onset bacterial infection can be subtle and non-specific.[3] Therapeutic use of antibiotics is suggested for those infants with clinical features of sepsis.[4] However, such empirical approach could result in unnecessary use of antibiotics in 90% to 96% of such infants who are not genuinely infected.[5,6] This over-treatment would lead to unnecessary intravenous catheterisation, prolonged length of hospitalisation as well as mother-infant separation. Prolonged use of antibiotics also increases risk and cost. Antibiotic therapy for longer than 72 hours has been found to be associated with increased colonisation by pathogenic gram-negative organisms and emergence of drug-resistant strains.[7,8] Minimising exposure of bacteria to antibiotics and thus reducing the risk of the emergence of resistance by a shorter length of therapy was suggested.[9] Hence, it is important for neonatologist to determine the optimal length of antibiotic therapy so that infants with genuine infection would be adequately treated while those without infection would not be over-treated.

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*Received July 29, 2003*

The level of C-reactive protein (CRP) may be used as a guide. CRP is an acute phase reactant which was found to be elevated in neonates with systemic bacterial infections.[10,11] Studies showed that CRP was probably the best available single diagnostic test for infection.[12] It was suggested that antibiotics could be safely discontinued when CRP values remained normal 24 hours after initial clinical suspicion of infection.[13] The present study was undertaken to determine the outcome of the patients with suspected early neonatal sepsis after implementation of a protocol of using CRP for decision making.

## Method

### *Control Group*

All newborns with birth weight 2.2 kg or more admitted in 1998 for suspected sepsis within 72 hours of life were included as control for the present study. The clinical features of suspected sepsis included any of the following: (1) fever: rectal temperature more than 38 degree Celsius; (2) respiratory condition: tachypnoea, chest retraction, apnea, grunting, etc; (3) cardiovascular condition: tachycardia, hypotension, hypertension, poor peripheral circulation, etc; (4) neurological condition: lethargy, bulging fontanelle, hypotonia or hyper-reflexia, seizure, etc; (5) gastrointestinal condition: poor feeding, vomiting, abdominal distension, etc; (6) haematological condition: petechiae, pallor, etc. The routine investigations included blood culture, complete blood count with differential (CBP) and chest radiographs (CXR). CRP might be checked but not as a routine. If it was checked, the first sample was usually taken at the initial evaluation whereas the second one was usually taken next morning, i.e., 8 to 24 hours after the initial evaluation. The decision of performing other investigations such as lumbar puncture and suprapubic aspiration for urine was subject to clinical condition. BACTEC system was used for the blood culture. CRP was analysed with the method of rate nephelometry by the laboratory and reported two to three times a week. Antibiotics, usually ampicillin and gentamicin, were started after the initial evaluation. Other antibiotics might be considered in individual patients. For example, cefotaxime instead of gentamicin would be given for cases with suspected meningitis or existing renal impairment. The in-charge physicians would decide on the duration of antibiotics based on the clinical progress.

### *Study Group*

The study group comprised all newborns with birth weight 2.2 kg or more admitted in 2000 for suspected sepsis within 72 hours of life. During this period, a new clinical protocol for management of neonatal sepsis was applied. Admission criteria were the same as before. Blood culture, CBP and CXR were all taken at the initial clinical evaluation. CRP was checked as a routine. The major difference from the control group was that blood samples for CRP were obtained at standard times. If the initial clinical assessment was done from 8am to 12 midnights, the first CRP would be checked on the following morning and then the second one on the morning one more day later. If the initial clinical assessment was done between 12 midnights and 8am, the first CRP would be checked at 4pm on the same day and the second one on the next morning. It meant that the first and second CRP would be taken 8 to 24 hours and 24 to 48 hours respectively after the initial clinical assessment. In addition, the results were reported before 6pm daily except on Sundays or public holidays. Time of commencement and choice of antibiotics were similar to the control group. However, antibiotics would be stopped if two serial CRP were less than 10 mg/L and blood culture was negative by the time of CRP report. Otherwise, antibiotics would be given for at least seven days. The in-charge physicians could however make the final decision on the duration of the therapy after evaluating the individual clinical condition irrespective of the investigation result.

The infants would be discharged when they were medically well and when antibiotics had been stopped. They would also be followed in our outpatient clinic after the discharge. The practice remained the same over these two periods. Since we discharged low birth weight well infants at 2.2 kg, the cut-off birth weight of 2.2 kg was arbitrarily chosen to exclude low birth weight infants whose duration of hospitalisation were affected by other co-existing problems.

### *Data Collection*

Patients and controls meeting the inclusion criteria were identified from the discharge summaries and then medical records of patients admitted in these periods. Baseline data on gestation age, birth weight, sex, mode of delivery, Apgar score and the clinical features of suspected sepsis were collected. The maximal respiratory support of each patient was also grouped into high frequency oscillatory

ventilation, conventional ventilation, nasal continuous airway pressure, oxygen alone and none. The results of the total white blood cell count, absolute neutrophil count, immature cell percentage, platelet count, CRP and blood culture were all recorded. Attending physicians' comments on the chest radiograph were classified as normal or abnormal. The final diagnoses were according to the discharge summary. The choice of the antibiotics was also identified.

### *Outcome Measures*

Primary outcomes were mortality and duration of hospitalisation. Secondary outcomes included: (1) duration of antibiotics; (2) the need for sepsis evaluation and new antibiotics within one week of the cessation of the antibiotics; (3) readmission and sepsis evaluation within one week after discharge. Data of the outcomes could be collected from the in-patient as well as the outpatient clinic medical records.

### *Statistical Analysis*

Continuous variables such as the gestational age, birth weight, duration of hospitalisation and antibiotics were reported as median with range and they were compared by Mann-Whitney test. Continuous variables such as the laboratory results were reported as mean with standard deviation and they were compared by Student's *t* test. Categorical variables were reported as numbers or percentages and they were compared by Chi squared test or Fisher's exact test. CRP values were not compared because they were taken at different times of the clinical course. P-value of less than 0.05 was regarded as statistically significant. Statistical analysis was performed with SPSS version 11.0.

## Results

Seventy-seven and 80 infants met the inclusion criteria in the study and control groups respectively. One patient in the study group was not included in the analysis as the medical record was lost. As shown in Table 1, the two groups were similar in gestational age, birth weight, mode of delivery, clinical features of suspected sepsis and maximum

**Table 1** Clinical characteristics of the patients

| Variable | Control group (N=80) | Study group (N=76) | P-value |
|---|---|---|---|
| Gestational age in weeks: median (range) | 39.0 (33-42) | 39.0 (31-41) | NS |
| Birth weight in gm: median (range) | 3277 (2240-4270) | 3165 (2270-4220) | NS |
| Female sex | 25.0% | 46.1% | 0.006 |
| Mode of delivery | | | NS |
| Normal vaginal delivery | 43.8% | 46.1% | |
| Vacuum extraction | 22.5% | 28.9% | |
| Forceps | 1.3% | 1.3% | |
| Caesarean section | 31.3% | 22.4% | |
| Breech | 1.3% | 1.3% | |
| Clinical features of sepsis | | | |
| Fever | 13.8% | 7.9% | NS |
| Respiratory | 77.5% | 84.2% | NS |
| Cardiovascular | 15.0% | 26.3% | NS |
| Neurological | 5.0% | 1.3% | NS |
| Gastrointestinal | 12.5% | 14.5% | NS |
| Haematological | 7.5% | 5.3% | NS |
| Maximal respiratory support | | | NS |
| High frequency oscillatory ventilation | 0.0% | 1.3% | |
| Conventional ventilation | 7.5% | 3.9% | |
| Nasal continuous positive airway pressure | 0.0% | 2.6% | |
| Oxygen supplement alone | 35.0% | 46.1% | |
| None | 57.5% | 46.1% | |

NS: no statistical significance

level of care. The study group however contained more female infants.

All the blood cultures were negative. Other investigation results are shown in Table 2. The total white cell count, absolute neutrophil count, immature cell percentage, platelet count and CXR were comparable in both groups. In the study group, 19.4% and 16.7% of the first and second CRP respectively were increased. In the control group, 7.9% and 31.1% of the first and second CRP respectively were increased. Statistical analysis of CRP is not applicable.

The final diagnoses and choice of antibiotics were shown in Table 3. The proportion diagnosed as sepsis was similar in both groups. However, in the study group, fewer patients were labeled as pneumonia or meconium aspiration syndrome but more as transient tachypnoea of newborn or no relevant diagnosis when compared to the control group. The difference was statistically significant. The majority in both groups (more than 93%) received ampicillin and

**Table 2** Results of the sepsis evaluation

| Variable | Control group (N=80) | Study group (N=76) | P-value |
|---|---|---|---|
| Total white cell count ($x10^9$/L) | 20.5±5.7 (n=80) | 21.0±6.6 (n=76) | NS |
| Platelet count ($x10^9$/L) | 245.7±67.8 (n=80) | 266.0±66.4 (n=75) | NS |
| Absolute neutrophil count ($x10^9$/L) | 12.4±4.2 (n=72) | 14.5±15.6 (n=61) | NS |
| Immature cells (%) | 0.7±1.5 (n=65) | 0.6±1.6 (n=56) | NS |
| Increased 1st CRP more than 10 mg/L | 7.9% (n=63) | 19.4% (n=72) | Not applicable |
| Increased 2nd CRP more than 10 mg/L | 31.1% (n=45) | 16.7% (n=66) | Not applicable |
| Abnormal chest X-ray | 60.8% (n=79) | 50.7% (n=75) | NS |

Plus: minus values are means±standard deviation; NS: no statistical significance.
The values in the bracket are the actual number of individual tests performed and reported.

**Table 3** Final diagnosis and the choice of antibiotics

| Variable | Control group (N=80) | Study group (N=76) | P-value |
|---|---|---|---|
| Final diagnosis | | | <0.005 |
| Sepsis | 40.0% | 38.2% | |
| Pneumonia | 25.0% | 11.8% | |
| Meconium aspiration syndrome | 27.5% | 9.2% | |
| Respiratory distress syndrome | 0.0% | 1.3% | |
| Transient tachypnoea of newborn | 5.0% | 26.3% | |
| Spontaneous pneumothorax | 0.0% | 5.3% | |
| No relevant diagnosis | 2.5% | 7.9% | |
| Choice of antibiotics | | | 0.03 |
| Ampicillin and gentamicin | 93.8% | 94.7% | |
| Ampicillin and cefotaxime | 6.3% | 0.0% | |
| Ampicillin, gentamicin and metronidazole | 0.0% | 1.3% | |
| Penicillin and gentamicin | 0.0% | 3.9% | |

gentamicin. A few in the control group received ampicillin and cefotaxime whereas a few in the study group received penicillin and gentamicin.

There was one death in the study group: an infant with giant exomphalos died because of uncontrolled bleeding from the exomphalos and it was believed to be unrelated to sepsis. The median length of hospital stay was shorter in the study group (7.0 vs 8.0 days, p=0.03). Furthermore, the median duration of the antibiotics was also shorter in the study group (3.0 vs 7.0 days, p<0.005) (Table 4).

Three out of 76 infants in the study group and none in the control group required repeated sepsis evaluation and new antibiotics within one week of cessation of the initial antibiotics (no statistical significance). One of them was the infant with giant exomphalos. Antibiotics were initially given for 14 days. Repeated sepsis evaluation and new antibiotics were given within one week afterwards. For the second infant, initial antibiotics had already been given for seven days. Repeated sepsis investigation was negative. The need for sepsis re-evaluation was therefore not related to early cessation of antibiotics in these two cases. The third infant was born normal vaginally at term with birth weight 3.05 kg and normal Apgar scores. His mother had no routine antenatal follow up. He presented with repeated vomiting but no fever, any abdominal sign or cardiorespiratory distress on the day of birth. CBP and CRP were normal. Vomiting subsided next day and three days of antibiotics were initially given. Lumbar puncture was performed on day 4 of life to test for VDRL titre because the maternal VDRL was subsequently found to be positive. He did not have any clinical features of meningitis but *E. Coli* was found in the cerebrospinal fluid. Cefotaxime was then started (Table 4).

No patient in either group required readmission within one week of discharge (Table 4).

## Discussion

This study showed that the duration of hospitalisation and antibiotic use might be reduced after applying a clinical protocol involving standard measurement of CRP. Early cessation of the antibiotics in the study group might not lead to significant adverse outcomes. The only case of death in the study group was not related to sepsis or the early cessation of antibiotics. Though three cases required sepsis re-evaluation in the study group, the proportion was not statistically significantly different from the control group. In the case where meningitis was diagnosed after early cessation of antibiotics, it was not known whether it would have been prevented by continuation of initial antibiotics.

In our protocol, we used CRP as a guide to decide when to stop the antibiotics after they were started. However, we could not tell whether the patients had genuine sepsis or not and it was not our objective in the study. A positive blood culture is microbiologic confirmation of the diagnosis of sepsis and traditionally, it was regarded as the gold standard. However, technical pitfalls of performing blood

**Table 4** The outcomes of the patients

| Variable | Control group (N=80) | Study group (N=76) | P-value |
|---|---|---|---|
| Death | 0 | 1 | NS |
| Length of hospitalisation: median (range) | 8.0 (3-18) | 7.0 (3-108) | 0.03 |
| Female | 8.0 (3-18) (n=20) | 8.0 (4-108) (n=35) | NS |
| Male | 8.0 (4-18) (n=60) | 7.0 (3-27) (n=41) | <0.005 |
| Duration of antibiotics: median (range) | 7.0 (2-10) | 3.0 (1-14) | <0.005 |
| Female | 7.0 (2-10) (n=20) | 3.0 (2-14) (n=35) | 0.025 |
| Male | 7.0 (3-10) (n=60) | 3.0 (1-10) (n=41) | <0.005 |
| Repeated sepsis evaluation and new antibiotics within 1 week of cessation of initial antibiotics | 0 | 3 | NS |
| Readmission and sepsis evaluation within 1 week of discharge | 0 | 0 | NS |

NS: no statistical significance

culture exist. Insufficient volume of the blood sample and the use of intrapartum antibiotics in mothers may affect the results. The reliability of the test was questioned and it was suggested that a negative blood culture should not be used as the sole criteria for discontinuing antibiotics.[3] As shown in our study, the blood cultures from all the infants were negative. Genuine sepsis might be present in some of our patients although it could not be proven. Indeed, the term 'clinical sepsis',[2] 'clinical septicemia',[10] 'infection likely',[14] 'probable sepsis/infection',[15-17] 'very probable sepsis/infection'[6,18] and 'deep culture negative sepsis',[19] etc. have been described for these situations and antibiotics were continued despite the negative blood cultures.

Several uncontrolled studies on the application of CRP in neonates have shown that most of the patients who received antibiotics for only two to five days did not have significant relapse of clinical features of sepsis.[14,20,21] With the use of a control group in the present study, there may be more evidence to show the benefit of reduction of hospital stay and antibiotic use.

The following two major differences in the practice between the study and the control groups may explain why the protocol was useful. Firstly, the first CRP was taken at the initial clinical assessment in the control group but at a delayed time of 8 to 24 hours after initial assessment in the study group. As shown in a previous study, the diagnostic value of CRP measured at a delayed time rather than at the initial evaluation was more satisfactory.[15] Secondly, during the control period, CRP was only reported two to three times a week but during the study period, the CRP was reported daily except on Sundays and public holidays. The earlier report of the results enabled earlier stop of antibiotics in the study period. Moreover, on following a clearly defined protocol, the physicians might be more confident to stop the antibiotics earlier.

There were some limitations of our study due to its retrospective nature. Firstly, we could not exactly tell whether the two groups of patients were really comparable. The record of the obstetrical history of any prolonged rupture of membranes, intrapartum fever and use of maternal antibiotics, etc. was incomplete. Screening for group B streptococcus was not performed routinely. In addition, there were more female infants in the study group. It would not be certain how these existing and potential differences in the risk factors for early neonatal sepsis could affect the final outcome. Nevertheless, there was no proven sepsis in all patients. Hence there might not be a direct influence to the final outcome. It may be interesting to notice that when the sex subgroups were analysed separately, there was no difference in hospital stay for females but it was shorter in the study group for males (7.0 vs 8.0 days, $p<0.005$). The reason for this observed variation in different sex is not certain. On the other hand, the duration of antibiotic use was shorter in the study group for either sex (both 3.0 vs 7.0 days, $p<0.05$) (Table 4).

Secondly, the proportions of final diagnoses were different between two groups, i.e., fewer pneumonia or meconium aspiration syndrome but more transient tachypnoea of newborn or no relevant diagnosis in the study group. There might be a primary difference in the etiology between the two groups. On the other hand, it may only indicate that the final diagnoses made by the physicians were simply affected by their decision to continue or discontinue antibiotics. For example, it may be difficult to differentiate pneumonia from transient tachypnoea of newborn only by clinical features or CXR. But the physician would make a diagnosis of transient tachypnoea of newborn rather than pneumonia when they decided to stop the antibiotics earlier. Simply speaking, the more objective diagnosis that could be easily compared would be the sepsis confirmed by blood culture, which was not found in both groups of infants.

Lastly, the small sample size of each group may not be large enough to detect any difference in the adverse outcomes such as mortality.

In conclusion, a standardised protocol of measuring CRP for newborns with suspected early sepsis was associated with a reduction in hospitalisation and antibiotic use. A larger prospective study may be necessary to address the issues.

## References

1. Jason JM. Infectious disease-related deaths of low birth weight infants, United States, 1968 to 1982. Pediatrics 1989;84:296-303.
2. Stoll BJ, Gordon T, Korones SB, et al. Early-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1996;129:72-80.
3. Kaftan H, Kinney JS. Early onset neonatal bacterial infections. Semin Perinatol 1998;22:15-24.
4. Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention. MMWR Recomm Rep 1996;45(RR-7):1-24.
5. Hammerschlag MR, Klein JO, Herschel M, Chen FC, Fermin R. Patterns of use of antibiotics in two newborn nurseries. N Engl J Med 1977;296:1268-9.
6. Philip AG, Hewitt JR. Early diagnosis of neonatal sepsis. Pediatrics 1980;65:1036-41.
7. Goldmann DA, Leclair J, Macone A. Bacterial colonization of neonates admitted to an intensive care environment. J Pediatr

1978;93:288-93.
8. Lacey RW. Evolution of microorganisms and antibiotic resistance. Lancet 1984;2:1022-5.
9. Low DE, Scheld WM. Strategies for stemming the tide of antimicrobial resistance. JAMA 1998;279:394-5.
10. Mathers NJ, Pohlandt F. Diagnostic audit of C-reactive protein in neonatal infection. Eur J Pediatr 1987;146:147-51.
11. Pourcyrous M, Bada HS, Korones SB, Barrett FF, Jennings W, Lockey T. Acute phase reactants in neonatal bacterial infection. J Perinatol 1991;11:319-25.
12. Da Silva O, Ohlsson A, Kenyon C. Accuracy of leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis: a critical review. Pediatr Infect Dis J 1995;14:362-6.
13. Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. Pediatr Infect Dis J 1997;16:735-47.
14. Ehl S, Gering B, Bartmann P, Hogel J, Pohlandt F. C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics 1997; 99:216-21.
15. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics 1998;102:E41.
16. Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr 1988;112: 761-7.
17. Singh M, Narang A, Bhakoo ON. Predictive perinatal score in the diagnosis of neonatal sepsis. J Trop Pediatr 1994;40:365-8.
18. Dobson SR, Isaacs D, Wilkinson AR, Hope PL. Reduced use of surface cultures for suspected neonatal sepsis and surveillance. Arch Dis Child 1992;67(1 Spec No):44-7.
19. Wagle S, Grauaug A, Kohan R, Evans SF. C-reactive protein as a diagnostic tool of sepsis in very immature babies. J Paediatr Child Health 1994;30:40-4.
20. Bomela HN, Ballot DE, Cory BJ, Cooper PA. Use of C-reactive protein to guide duration of empiric antibiotic therapy in suspected early neonatal sepsis. Pediatr Infect Dis J 2000;19: 531-5.
21. Philip AG, Mills PC. Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery. Pediatrics 2000;106:E4.