Duration of empirical therapy in neonatal bacterial meningitis with third generation cephalosporin: a multicenter retrospective study

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Abstract

Introduction: The duration of treatment is not well established, especially in the negative cerebrospinal fluid (CSF) culture. The aim of this study is to explore the influence of duration of treatment in neonatal bacterial meningitis.

Material and methods: This is a retrospective analysis of 200 CSF specimens. Two hundred full-term neonates with bacterial meningitis admitted to the clinical status were evaluated using the Glasgow Outcome Scale (GOS) on the day of discharge.

Results: Neonates were identified as having bacterial meningitis based on the results of CSF culture tests of all suspected cases. According to the GOS, neonates were divided into two outcome groups: 77.5% good (GOS = 5) (shorter than 3 weeks’ administration) and 22.5% unfavorable (GOS = 1–4) (longer than 3 weeks’ administration). The duration of antibiotic treatment ranged from 4 to 43 days, and the mean therapy time was 19.74 ±7.32 days. Duration longer than 3 weeks for neonatal bacterial meningitis with negative CSF culture had no impact on prognosis. The unfavorable outcome group had more prenatal infections and premature rupture of membranes cases than the good outcome group. High CSF protein and CSF glucose and CSF cell count increase were associated with unfavorable outcome in 167 non-prenatal infection infants. High CSF cell count increase was associated with unfavorable outcome in 33 prenatal infection infants. In term infants, the positive rate of blood cultures was 24.5%.

Conclusions: Third generation cephalosporin therapy does not have a different prognosis for negative CSF culture of neonatal bacterial meningitis in term infants in this study.

Key words: multicenter, bacterial meningitis, term infant, retrospective study.

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Introduction

Bacterial meningitis occurs more commonly in the first month of life than any other period, and frequently in infants associates with early onset sepsis (EOS) and late onset sepsis (LOS). The morality from meningitis is close to 100% in untreated individuals and is still up to 40% in children who receive appropriate antibiotic treatment in developing countries [1–3]. Although in the United Kingdom the case fatality associated with neonatal meningitis declined from 25% to 10% between the 1980s and 1990s, long-term sequelae rates did not change, with up to 50% of survivors having long-term neurodevelopmental complications [4–6]. Early identification and prompt antibiotic treatment are essential for reducing mortality and morbidity. Decisions on the choice of a specific antimicrobial agent are based on knowledge of its activity against the causative pathogen and relative penetration into cerebrospinal fluid (CSF) in the presence of meningeal inflammation. In 2004, the Infectious Disease Society of America published practice guidelines for treatment of meningitis. A 14-day course is sufficient for neonates with uncomplicated group B streptococcus (GBS) meningitis and for other Gram-positive organisms, while a 21-day course of therapy is required for neonates with complicated GBS meningitis and Gram-negative microorganisms. If abscesses, multiple areas of infarction, or ventriculitis occur, it is suggested to administer antibiotics for 6–8 weeks [7–10]. However, in this practice’s guidelines the duration of antimicrobial therapy has often been based more on tradition than on evidence-based data. Isolation of a pathogen in culture is a prerequisite for proven bacterial meningitis. Culture results take at least 48–72 h to be reported. In addition, its positivity rate is low, especially in the CSF, and is affected by sample volume inoculated, prenatal antibiotic use, level of bacteremia and laboratory capabilities. The early and appropriate initiation of antimicrobial agents in high risk neonates before the result of blood and (or) CSF culture susceptibilities is defined as “empirical antibiotic therapy”. With the worldwide increase in the prevalence of penicillin-resistance pneumococci, combination therapy with a third-generation cephalosporin (ceftiraxone sodium used in this study) plus vancomycin has become the standard approach to empirical antimicrobial therapy. The purpose of this study was to evaluate the effect of ceftiraxone treatment. Ceftriaxone sodium was used with penicillin partially plus vancomycin at the beginning of the treatment, which was immediately stopped if the clinical manifestations or test results improved (generally in 3–5 days). Hence, the cases included in this study were treated with ceftriaxone sodium only in the maximum period for treatment.
5 – good recovery or only minor sequelae [23]. Moderate or severe disability was defined as any of the following conditions: spasticity or muscle weakness in one or more limbs, hydrocephalus, seizures disorder and hearing loss. According to the criteria of GOS, patients were classified into two prognosis groups: good (155 cases, 77.5%, GOS = 5) or adverse (45 cases, 22.5%, GOS = 1–4). Five was considered favorable and 1–4 as unfavorable.

**Statistical analysis**

All statistical analyses were performed using SAS9.4. Clinical characteristics of the two groups were described by mean values and standard deviations (median and interquartile ranges were used for non-normally distributed variables) or rate and column percentages, according to the type of variable. Student’s t-test was used to compare continuous variables between the groups (Mann-Whitney U test was used for non-normally distributed variables) and the χ² test and Fisher’s exact test were used for categorical variables. P-values < 0.05 were considered statistically significant.

**Results**

During the study period, 200 neonates with meningitis were identified among 407 referred infants. There were 126 male infants and 74 female infants. There were 167 non-prenatal infections and 33 prenatal infections. The mean birth weight was 3253 ±485 g. There were 11 (5.5%) neonates with low birth weight (< 2500 g) and 9 (4.5%) with high birth weight (> 4000 g). The mean age at onset of meningitis was 12.1 ±8.6 days. The average duration of hospital stay was 21.0 ±7.3 days (range: 4–43 days). There were 33 (16.5%) cases identified as EOM and 167 (83.5%) as LOM. The overall prenatal infection rate was 16.5% (33 of 200 patients) including 19 cases of maternal fever greater than 38°C, 11 cases of prolonged rupture of membranes over 18 h, and vaginal colonization with group B Streptococcus was noted in 3 cases.

In the investigation of the final outcome of patients, it was observed that the mortality rate was 5.5%. The mortality among infants in 2 cases was due to failure to control the worsening of the disease, and in 9 cases treatment was stopped by their families. There were no other infections during the treatment. However, 10 cases were complicated with polyelectrolyte disorder and another 10 cases were complicated with lung dysfunction.

Ceftriaxone is active against most bacteria causing neonatal sepsis and meningitis including some resistant to first line therapy. However, ESBL (extended spectrum β-lactamase) mediated resistance to third-generation cephalosporin has appeared among neonatal pathogens. Complications due to ventriculitis, hydrocephalus, convulsions, and relapse were reported in 64/200 (32%) of infants.

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**Table I. Study criteria for enrolment and diagnosis**

| Exclusion criteria at enrolment |
|---------------------------------|
| Gestation age < 37 weeks        |
| Pre-existing seizure disorders, cerebral palsy, degenerative neurological disorders |
| Known immunodeficiency states   |
| Active viral infections         |
| Known hypersensitivity to cephalosporins |
| Cyanotic congenital heart disease |
| Positive CSF culture            |

| Diagnostic criteria for bacterial meningitis |
|---------------------------------------------|
| **Clinical variables:**                      |
| Temperature instability                      |
| Heart rate ≥ 180 beats/min or ≤ 100 beats/min |
| Respiratory rate > 60 breaths/min plus grunting or desaturations |
| Lethargy/altered mental status               |
| Glucose intolerance (plasma glucose > 10 mmol/l) |
| Feed intolerance                             |
| Positive CSF Gram stain                      |

| Inflammatory variables:                      |
| Leukocytosis (WBC count > 34 × 10⁹/l) or leukopenia (WBC count < 5 × 10⁹/l) |
| CSF absolute neutrophil count 1000/µl or above |
| Thrombocytopenia < 100 × 10⁹/l                |
| CRP > 10 mg/l or 2 SD above normal value     |
| Procalcitonin > 8.1 mg/dl or 2 SD above normal value |
| WBC counts in CSF exceeding 21 × 10⁹/l       |
| CSF protein concentration > 1500 mg/l        |
| CSF glucose concentration < 30 mg/dl or less than 50% of blood glucose |

**CSF** – cerebrospinal fluid, **WBC** – white blood cells, **CRP** – C-reactive protein.
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Peripheral blood leukocytes varied between $3.0 \times 10^9/l$ and $40.19 \times 10^9/l$ with a mean of $15.61 \times 10^9/l$ including 30 cases of leukocytosis and 5 of leukopenia. Neutrophils varied between 10% and 93% with a mean of 49.85%. There were 105 cases with a C-reactive protein (CRP) level over 8 mg/l and 97 cases with procalcitonin (PCT) over 0.5 ng/ml.

Positive cultures of blood were obtained in 49 (24.5%) cases, with 28 (57.1%) cases of Gram-negative bacilli infections. Escherichia coli (13/49), Klebsiella pneumoniae (9/49) and Staphylococcus haemolyticus (5/49) were the commonest pathogenic bacteria. Other organisms were Staphylococcus epidermidis (4/49), Streptococcus agalactiae (3/49), Staphylococcus aureus (2/49), Acinetobacter baumannii (2/49), and Enterococcus faecium (2/49) (Table II).

Cerebrospinal fluid cell count varied between 0 and $9680 \times 10^6/l$ with a median of $76 \times 10^6/l$, including 93 cases with the number of cells more than $100 \times 10^6/l$. Cerebrospinal fluid protein concentration varied between 148 and 6670 mg/l, with a median of 1265 mg/l. Mean CSF glucose level was 2.08 ±0.96 mmol/l, CSF glucose level varied between 0.1 and 5.96 mmol/l, and there were 66 cases with CSF glucose < 1.7 mmol/l.

### Glasgow Outcome Scale and neurological complications

According to the criteria of the GOS, patients were divided into two outcome groups: good (155 cases, 77.5%, GOS = 5) or unfavorable (45 cases, 22.5%, GOS = 1–4) when we analyzed the effect of the duration of treatment in term infants on prognosis. Twenty-nine infants (64.4%) had moderate disability and other neurologic complications evidenced by cranial sonography or magnetic resonance imaging/computed tomography (CT) scan in unfavorable outcome patients including 6 (13.3%) cases of hydrocephalus, 3 (6.7%) of encephalomalacia, 3 (6.7%) of ependymitis, 2 (4.5%) of subdural effusion and 2 (4.5%) of mortality. There was higher frequency of poor outcome for patients with prenatal infection. Thus we separated the patients with prenatal infections from those without prenatal infections when analyzing the effects of other factors on prognosis.

### Table II. Distribution of bacterial pathogens detected in blood culture in early-onset meningitis (EOM) and late-onset meningitis (LOM)

| Pathogenic bacteria EOM (n = 8) | N       | Pathogenic bacteria LOM (n = 41) | N       |
|---------------------------------|---------|----------------------------------|---------|
| Gram-positive bacilli (n = 4):  |         | Gram-negative bacilli (n = 23):   |         |
| Staphylococcus haemolyticus     | 1       | Escherichia coli                 | 12      |
| Staphylococcus epidermidis      | 1       | Klebsiella pneumoniae            | 6       |
| Streptococcus agalactiae        | 1       | Acinetobacter baumannii          | 2       |
| Listeria monocytogenes          | 1       | Stenotrophomonas maltophilia     | 1       |
|                                |         | Pseudomonas aeruginosa           | 1       |
|                                |         | Serratia marcescens              | 1       |
| Gram-negative bacilli (n = 4):  |         |                                  |         |
| Klebsiella pneumoniae           | 3       |                                  |         |
| Escherichia coli                | 1       |                                  |         |
Clinical prognosis and duration of antibiotic treatment

The duration of antibiotic treatment ranged from 4 to 43 days, and the mean therapy time was 19.74 ± 7.32 days. Table III presents the relationship between prognosis and duration of 10, 14, 16, 18 and 21 days, respectively. We found that longer than 21 days of third-generation cephalosporin therapy had no impact on clinical prognosis (p > 0.05). Table IV presents the outcomes of our study. We found that shorter hospital stay was associated with unfavorable outcome in 33 prenatal infection infants. The CSF white blood cell and CSF protein and CSF glucose were predictors of unfavorable outcome in 167 non-prenatal infection infants. High CSF cell count increase was associated with unfavorable outcome in 33 prenatal infection infants (Tables III and IV).

Discussion

Optimal duration of empiric antimicrobial therapy decreases the development of antimicrobial resistance, prevents unwanted changes in flora found in the Neonatal Intensive Care Unit (NICU), and minimizes unnecessary expenses for infants who have negative blood cultures [24]. Prolonged duration of initial empirical antibiotic therapy is associated with an increased risk of necrotizing enterocolitis and death in extremely low birth weight infants [25]. Other adverse effects of prolonged empirical antibiotic therapy include increased risk of neonatal candidiasis and alteration of gut microflora [26–28]. Maintenance of intravenous access for a long period in neonates is difficult and is a burden in many developing countries. Hence, it seems prudent to restrict the duration of empirical antibiotic therapy when blood or CSF cultures are sterile and the neonate is asymptomatic.

These survey data have clinical relevance for the hospital, local health authority as well as for the regional health bureau to implement appropriate meningitis surveillance against this invasive bacterial disease. Clinical and demographic characteristics of study infants segregated into initial empirical antibiotic treatment groups are presented.

The incidence of CSF culture-confirmed meningitis is not high. Nevertheless, there is a strong association between meningitis and sepsis with positive blood cultures [29]. Therefore, many studies report that meningitis is associated with a positive culture from the blood or abnormal cerebrospinal fluid parameters [16, 30–32]. Third generation cephalosporin was first reported for the treatment of neonatal bacterial meningitis in 1985, when four neonates presented no sequelae afterward, and it shows several advantages that make it the first-line treatment of meningitis in most developed and developing countries [33–36]. Ceftriaxone is active against most bacteria causing neonatal sepsis and meningitis including some resistant to first line therapy, and synergistic interactions against a variety of micro-organisms have been demonstrated.

The pathogenic microorganism of meningitis cases differs according to the geographic region. The most frequently reported etiology is Gram-positive bacilli such as group B streptococci in the developed countries [9, 10, 16]. In our study, the positive blood culture rate was 24.5% and the most common bacteria are Gram-negative bacilli such as in early onset meningitis Klebsiella pneumoniae and Escherichia coli in late onset meningitis. The prognosis and outcome in our study were

### Table III. Influence of duration of antibiotic treatment on prognosis

| Duration of antibiotic treatment [days] | Good outcome (n = 155) | Poor outcome (n = 45) | \( \chi^2 \) value | P-value |
|----------------------------------------|------------------------|-----------------------|---------------------|---------|
| 4–10                                   | 10                     | 14                    | 20.083              | < 0.001 |
| 10–43                                  | 145                    | 31                    |                     |         |
| 4–14                                   | 39                     | 21                    | 7.979               | 0.009   |
| 14–43                                  | 118                    | 24                    |                     |         |
| 4–16                                   | 57                     | 25                    | 5.085               | 0.027   |
| 16–43                                  | 98                     | 20                    |                     |         |
| 4–18                                   | 74                     | 30                    | 5.004               | 0.028   |
| 18–43                                  | 81                     | 15                    |                     |         |
| 4–21                                   | 104                    | 33                    | 0.629               | 0.471   |
| 21–43                                  | 51                     | 12                    |                     |         |
Table IV. One factor analysis in prognosis of 200 bacterial meningitis infants

| Factor                                      | Non-prenatal infection (n = 167) | Prenatal infection (n = 33) | P-value | Good outcome | Poor outcome | P-value | Good outcome | Poor outcome | P-value |
|---------------------------------------------|----------------------------------|----------------------------|---------|---------------|--------------|---------|---------------|--------------|---------|
| Sex, male                                   | 81 (59.12%)                      | 23 (76.67%)                | 0.0726  | 11 (61.11%)    | 23 (73.33%)  | 0.4583  |
| Birth weight < 2500 g                       | 9 (6.57%)                        | 1 (3.3%)                   | 0.6922  | 1 (5.57%)      | 0 (0.00%)    | 1.0000  |
| Age at onset [days]                         | 13.03 ±8.84                      | 12.20 ±8.14                | 0.6354  | 10.11 ±6.15    | 9.60 ±8.13   | 0.8393  |
| Hospital stay [days]                        | 21.11 ±7.11                      | 20.46 ±8.23                | 0.3617  | 21.88 ±5.92    | 16.22 ±7.22  | 0.0212  |
| PROM > 18 h                                 | 4 (2.92%)                        | 5 (10.00%)                 | 0.1105  | 18 (100.00%)   | 15 (100.00%) |         |
| Delivery way:                               |                                  |                            |         |               |              |         |               |              |         |
| Natural delivery                            | 89 (64.96%)                      | 19 (63.33%)                | 0.5265  | 8 (44.44%)     | 8 (53.33%)   | 0.6109  |
| Delivery acouche                            | 4 (2.92%)                        | 2 (6.67%)                  | 0 (0.00%)| 0 (0.00%)      | 0 (0.00%)    |         |
| Cesarean                                    | 44 (32.12%)                      | 9 (30.00%)                 | 0.5215  | 10 (55.56%)    | 7 (46.67%)   | 0.8047  |
| Antibiotic treatment                        | 0 (0.00%)                        | 0 (0.00%)                  | 4 (22.22%)| 8 (53.33%)     | 0.0643       |         |
| Clinical symptoms:                          |                                  |                            |         |               |              |         |               |              |         |
| Fever                                       | 108 (78.83%)                     | 20 (66.67%)                | 0.1537  | 13 (72.22%)    | 12 (80.00%)  | 0.6037  |
| Apnea                                       | 4 (2.92%)                        | 2 (6.67%)                  | 0.2939  | 3 (16.67%)     | 0 (0.00%)    | 0.2330  |
| Poor feeding                                | 25 (18.25%)                      | 7 (23.33%)                 | 0.5215  | 3 (16.67%)     | 3 (20.00%)   | 0.8047  |
| Jaundice                                    | 26 (18.98%)                      | 5 (16.67%)                 | 0.2011  | 3 (16.67%)     | 5 (33.33%)   | 0.4184  |
| Seizures                                    | 26 (18.98%)                      | 9 (30.00%)                 | 0.1791  | 2 (11.11 %)    | 3(20.00%)    | 0.4782  |
| Abnormal neuroimaging:                     |                                  |                            |         |               |              |         |               |              |         |
| Cranial sonography                          | 32 (58.19%)                      | 11 (55.00%)                | 0.8054  | 2 (40.00%)     | 0 (0.00%)    | 0.1515  |
| MRI/CT                                      | 60 (67.42%)                      | 18 (72.00%)                | 0.6631  | 8 (57.14%)     | 4 (57.14%)   | 1.0000  |
| Positive cultures of blood:                 |                                  |                            |         |               |              |         |               |              |         |
| Gram-negative bacilli                       | 27 (20.00%)                      | 9 (33.33%)                 | 0.1282  | 9 (69.23%)     | 4 (30.77%)   | 0.2208  |
| CSF parameters:                             |                                  |                            |         |               |              |         |               |              |         |
| WBCs [× 10⁹/l]                              | 49.53                            | 151.65                     | < 0.001 | 56.45          | 159.34       | < 0.001 |
| CSF glucose [mmol/l]                        | 2.18 ±0.99                       | 1.78 ±0.90                 | 0.0456  | 1.72 ±0.73     | 2.19 ±0.79   | 0.0871  |
| CSF protein [mg/l]                          | 1419 ±745.64                     | 2022 ±1508.09               | 0.0015  | 1726 ±890.87   | 1283 ±900.00 | 0.4047  |
| Blood parameters:                           |                                  |                            |         |               |              |         |               |              |         |
| White blood cells [× 10⁹/l]                 | 13.67 ±3.09                      | 15.23 ±5.98                | 0.3480  | 13.77 ±6.98    | 16.79 ±6.33  | 0.3211  |
| Neutrophil [%]                              | 49.35 ±19.89                     | 48.60 ±27.67               | 0.8627  | 58.08 ±20.99   | 48.50 ±18.33 | 0.2111  |
| Lymphocyte [%]                              | 35.54 ±15.23                     | 38.35 ±18.54               | 0.4553  | 30.58 ±9.45    | 35.16 ±12.67 | 0.5163  |
| Platelets [× 10⁹/l]                         | 361 ±97.87                       | 432 ±120.97                | 0.1177  | 284.4 ±78.33   | 431.3 ±84.33 | 0.1269  |
| C-reaction protein > 8 mg/l                 | 77 (64.17%)                      | 9 (34.62%)                 | 0.0055  | 14 (77.78%)    | 5 (26.32%)   | 0.0162  |
| Procalcitonin > 0.5 ng/ml                   | 73 (62.39%)                      | 9 (31.03%)                 | 0.0023  | 12 (70.59%)    | 2 (18.18%)   | 0.0068  |

Defined by using clinical status or abnormal neuroimaging examination on hospital discharge and the GOS. We found that shorter hospital stay was associated with unfavorable outcome in 33 prenatal infection infants in our study. This indicates that prenatal infected infants may need longer...
treatment. Two retrospective studies showed that high CSF protein and low CSF glucose concentration were important prognostic factors of complications in neonatal meningitis [37, 38]. Our study was concordant with this result. Additionally, we found the CSF cell count was associated with unfavorable outcome in term infant meningitis. Though a previous study showed that thrombocytopenia was a main factor of the poor prognostic, the platelet counts in the unfavorable outcome group were not reduced in our study. We advocate rigorous application of ongoing empirical antibiotic treatment and prompt discontinuation of therapy if blood cultures are negative and clinical laboratory measurements indicate a low risk of sepsis. Clinical trials where ceftriaxone has been evaluated in neonates are few. A limitation of this study is the inability to take into account all factors that indicate the severity of illness, although we sought to compare different antibiotic combinations from trials to observe the optimal duration of empirical antibiotic therapy. Additionally, limitations of neonates who developed early sepsis limited the utility of early leukocyte indices and acute phase reactants in identifying culture-negative infants who might benefit from a prolonged duration of antibiotics.

Our study indicated that longer than 21 days of treatment with third generation cephalosporin has no impact on clinical prognosis in term neonates with bacterial meningitis in the negative cerebrospinal fluid culture, and in whom the clinical condition is stable.

In conclusion, we concluded that longer than 3 weeks' administration of third generation cephalosporin has no impact on the infant's prognosis. Because the NICU is kind of sanctuary form antimicrobial stewardship, though many antibiotics are used in the NICU, which is the beginning point of this retrospective study. Owing to increasing resistance and the very limited arsenal of new agents, especially against Gram-negative pathogens, carefully designed antibiotic regimens are obligatory for the particular patient neonates. Also it is recommended to minimize antibiotic use and its contingent collateral damage.

Conflict of interest

The authors declare no conflict of interest.

References

1. Furyk JS, Swann Q, Molynieux E. Systematic review: neonatal meningitis in the developing world. Trop Med Int Health 2011; 16: 672-9.
2. Gaschignard J, Levy C, Romain O, et al. Neonatal bacterial meningitis: 444 cases in 7 years. Pediatr Infect Dis J 2011; 30: 212-7.
3. Okike IO, Ribeiro S, Ramsay ME, Heath PT, Sharland M, Ladhan I. Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004-11: an observational study. Lancet Infect Dis 2014; 14: 301-7.
4. Okike I, Johnson AP, Henderson KL, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged < 90 days in the United Kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Clin Infect Dis 2014; 59: e150-7.
5. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed 2015; 100: F257-63.
6. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med 2011; 364: 2016-25.
7. Sivanandan S, Soraisham AS, Swarnak M. Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. Int J Pediatr 2011; 2011: 712150.
8. Tzialla C, Borghesi A, Perotti GE, Garofoli F, Manzoni P, Stranger M. Use and misuse of antibiotics in the neonatal intensive care unit. J Matern Fetal Neonatal Med 2012; 25 Suppl 4: 35-7.
9. Huang FK, Chen HL, Yang PH, Lin HC. Bird's eye view of a neonatologist: clinical approach to emergency neonatal infection. Pediatr Neonatol 2016; 57: 167-73.
10. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr 2015; 61: 1-13.
11. Martin E, Koup JR, Paravicini U, Stoeckel K. Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. J Pediatr 1984; 105: 475-81.
12. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Paediatr Drugs 2013; 15: 93-117.
13. Pacifici GM. Pharmacokinetics of cephalosporins in the neonate: a review. Clinics (Sao Paulo) 2011; 66: 1276-74.
14. Radetsky M. Duration of treatment in bacterial meningitis: a historical inquiry. Pediatr Infect Dis J 1990; 9: 2-9.
15. Riordan A. Preventing meningitis and septicaemia: are we nearly there yet? Lancet Infect Dis 2014; 14: 363-4.
16. Molynieux E, Nizami SQ, Saha S, et al. 5 versus 10 days of treatment with ceftriaxone or cefotaxime, or both, as treatment for meningitis in children: a double-blind randomised equivalence study. Lancet 2011; 377: 1837-45.
17. Duke T, Michael A, Mokela D, Wal T, Reeder J. Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries? Arch Dis Child Fetal Neonatal Ed 2015; 100: F257-63.
18. Sudarsanam TD, Rupali P, Tharyan P, Abraham OC, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease. Cochrane Database Syst Rev 2013; 8: CD005437.
19. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed 2003; 88: F173-8.
20. Cohen-Wolkowiez M, Moran C, Benjamin DK, et al. Early and late onset sepsis in late preterm infants. Pediatr Infect Dis J 2009; 28: 1052-6.
21. Manan MM, Ibrahim NA, Aziz NA, Zulkiifly HH, Al-Worafi YM, Long CM. Empirical use of antibiotic therapy in the prevention of early onset sepsis in neonates: a pilot study. Arch Med Sci 2016; 12: 603-13.
22. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed 2005; 90: F220-4.
23. Koster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. J Infect 2008; 57: 449-54.
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24. Shlaes DM, Gerdin DN, John JF Jr, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis 1997; 25: 584-99.

25. Cotten CM, Taylor S, Stoll B, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009; 123: 58-66.

26. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr 2011; 159: 720-5.

27. Afjeh SA, Sabzehei MK, Fahimzad SA, Shiva E Shamshiri AR, Esmaili F. Antibiotic therapy for very low birth weight newborns in NICU. Iran J Pediatr 2016; 26: e2612.

28. Mathur NB, Kharod P, Kumar S. Evaluation of duration of antibiotic therapy in neonatal bacterial meningitis: a randomized controlled trial. J Trop Pediatr 2015; 61: 119-25.

29. Bentlin MR, Ferreira GL, Rugolo LM, Silva GH, Mondelli AL, Rugolo A Jr. Neonatal meningitis according to the microbiological diagnosis: a decade of experience in a tertiary center. Arq Neuropsiquiatr 2010; 68: 882-7.

30. Garges HP, Moody MA, Cotten CM, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics 2006; 117: 1094-100.

31. Rajesh NT, Dutta S, Prasad R, Narang A. Effect of delay in analysis on neonatal cerebrospinal fluid parameters. Arch Dis Child Fetal Neonatal Ed 2010; 95: F25-9.

32. Gowin E, Wysocki J, Avonts D, et al. Usefulness of inflammatory biomarkers in discriminating between bacterial and aseptic meningitis in hospitalized children from a population with low vaccination coverage. Arch Med Sci 2016; 12: 408-14.

33. Lin TY, Chrane DF, Nelson JD, McCracken GH Jr. Seven days of ceftriaxone therapy is as effective as ten days’ treatment for bacterial meningitis. JAMA 1985; 253: 3559-63.

34. Singhi P, Kaushal M, Singhi S, Ray P. Seven days vs. 10 days ceftriaxone therapy in bacterial meningitis. J Trop Pediatr 2002; 48: 273-9.

35. Karageorgopoulos DE, Valkimadi PE, Kapaskelis A, Rafailidis PI, Falagas ME. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. Arch Dis Child 2009; 94: 607-14.

36. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004; 39: 1267-84.

37. Klinger, G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. Pediatrics 2000; 106: 477-82.

38. Anderson SG, Gilbert GL. Neonatal gram negative meningitis: a 10-year review, with reference to outcome and relapse of infection. J Paediatr Child Health 1990; 26: 212-6.