Randomized Controlled Trial of 7-Day vs. 14-Day Antibiotics for Neonatal Sepsis

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Summary
There are no evidence-based guidelines available regarding the duration of antibiotics in neonatal septicemia. We compared the effectiveness of a 7-day intravenous antibiotic regimen with the standard 14-day regime in blood-culture-proven sepsis in neonates. This was a controlled, blinded, randomized trial with stratification (for birth weight). Blood-culture-positive septic babies ≥32 weeks and/or ≥1500 g were enrolled if meningitis and other deep-seated focal infections were ruled out. Parental consent was obtained. Randomization to either 7-day or 14-day therapy was done on day 7 of antibiotics if the baby had clinically remitted by day 5. Blood culture was repeated 24 h after antibiotic completion. Subjects were observed in the hospital for at least 72 h, and followed-up for 28 days by weekly visits and telephonic contacts. The primary outcome was treatment failure within 28 days defined as a positive blood culture, or clinical signs accompanied by either positive CRP or adjudicated to be a relapse by an expert committee. A total of 120 babies were eligible, 51 were excluded (no consent: 12; non-remission: 39), and 69 were randomized to receive either a 7-day course (n = 34) or a 14-day course (n = 35) of antibiotics. Baselines variables were comparable in the two groups. Primary outcome assessment could be done in 33 cases in either group. There was a trend to greater treatment failures in the 7-day group compared with 14-day group (5 vs. 1, respectively; P = 0.19). On subgroup analysis of subjects with Staphylococcus aureus infection, those who received 7-day therapy (n = 7) had significantly more treatment failure than 14-day therapy (n = 7) (four and zero, respectively; P = 0.022), whereas on sub-group analysis of babies with non-S. aureus infections, treatment failure rates were identical (3.8% in both groups). On comparing the organisms isolated in the group of subjects which was not randomized by virtue of being symptomatic (n = 39) vs. the group which was randomized (n = 69), it was found that S. aureus infections were significantly commoner in the former group (61.5 vs. 21.3%, respectively; P < 0.001). Neonates ≥32 weeks and/or ≥1500 g with S. aureus sepsis require 14 days of antibiotics. S. aureus infection is also associated with failure to achieve clinical remission by the 5th day of antibiotic therapy. Larger trials are required to confirm whether neonates with non-S. aureus sepsis, whose symptoms remit by 5 days, can be treated with 7 days of antibiotics.

Keywords: antibiotics, duration, neonate, septicemia, Staphylococcus aureus

Neonatal septicemia is the chief cause of morbidity and mortality in the neonatal period, particularly so in developing countries. India has a huge burden of neonatal sepsis, with septicemia contributing to half the neonatal deaths in the community setting [1] and to a quarter of all neonatal deaths in hospitals [2]. In medical literature, there are no evidence-based guidelines regarding the duration of antibiotic therapy for neonatal septicemia. Though current textbooks of neonatology recommend durations of 7–14 days for blood culture positive or clinically probable infections [3–5], the rationale and safety of these recommendations have never been evaluated.

A shorter duration antibiotic course, if proved to be as effective as the conventional course, can reduce the duration of hospital stay and the cost of therapy for neonatal septicemia. The shorter duration course would be expected to have less adverse effects, less risk of secondary infections and drug resistance.

Some researchers have studied the use of C-reactive protein (CRP) to decide about the duration of antibiotics [6–10]. They stopped antibiotics when serially measured CRP levels fell below a predetermined limit, and they were able to demonstrate no increase in mortality and morbidity during a 4-week follow-up period, when compared with conventional antibiotic regimes [8, 9]. These studies assayed quantitative CRP by nephelometry,
which is expensive and not widely available, and thus, this method cannot be generalized to all levels of neonatal care.

There have been successful trials of shorter duration antibiotic therapy in systemic infections among children and infants beyond the neonatal period [11–14], and one trial has been conducted on neonatal pneumonia [15]. One can extend the argument, to the neonatal period, that currently recommended durations of antibiotic therapy are unnecessarily prolonged, and shorter courses may be equally effective.

We hypothesized that intravenous antibiotics for culture-proven neonatal septicemia can be stopped on day 7 if the clinical signs of sepsis have remitted by day 5, without incurring a significantly greater treatment failure rate than the standard 14-day antibiotic regime. To test this hypothesis, we performed a pilot randomized controlled trial (RCT). A part of our objective was to generate data to enable a larger multi-centric trial on this issue.

Methods
This was a controlled, single-blinded, randomized trial with stratification and blocking. The study was conducted from January 2002 to August 2003 in a level III neonatal unit in Northern India. The unit has a large referral load and caters to a middle to low socio-economic population. Neonates who satisfied the enrollment criteria were prospectively enrolled after obtaining written, informed consent from the parents. This study had approval from the Institute’s Ethics Committee.

Enrollment criteria
We enrolled babies with gestational age ≥32 weeks and/or birth weight ≥1500 g, who satisfied the following criteria of bacterial septicemia:

(i) They had clinical signs of sepsis, and
(ii) Blood culture showed growth of a pathogenic bacterium from two separate, but concurrently inoculated blood culture bottles.

The ‘gestational age’ was calculated from the best estimate of a combination of Nagael’s formula and new Ballard score. Subjects were administered antibiotics according to the sensitivity report.

The following patients were not enrolled:
• Patients with central nervous system infections, based on cerebro-spinal fluid examination and culture.
• Patients with clinically evident bone/joint or localized infections.
• Patients with life-threatening congenital malformations.
• Patients whose blood cultures were interpreted as ‘contaminant or possible contaminant’.

This was defined as (a) growth of two different organisms from the two culture bottles, or (b) growth in only one culture bottle or (c) mixed growth of flora.

Data recording
Enrolled subjects were followed from the day when blood culture was reported positive and their demographic, baseline and outcome information was recorded in a standard proforma.

Randomization
Randomization was done at the end of day 7. Only those enrolled babies, who fulfilled both the following criteria, were randomized:

(i) Those who completed 7 days of antibiotic therapy to which the organism was sensitive, and
(ii) who had shown clinical remission of sepsis (i.e. become completely asymptomatic) before the end of day 5. All the presenting signs should have resolved and the subject should not have developed fresh signs from a pre-defined list of signs, to be labeled ‘completely asymptomatic’.

Eligible babies were randomly allocated to one of the two groups: (i) 7-day group: these subjects did not receive further antibiotics after a total of 7 days, or (ii) 14-day group: these subjects received 7 more days of antibiotics, i.e. a total of 14 days.

Stratification was done for birth weight, the strata being 1500–1800 g and >1800 g. Each stratum consisted of permuted blocks of randomly varying sizes. The random allocation sequence was computer generated and slips of paper bearing the intervention were kept in serially numbered, opaque, sealed envelopes. The sizes of the blocks were concealed till the end of the study. One of the investigators (S.D.) generated the allocation sequence and another (G.C.) enrolled and assigned participants.

There were no differences in the routine and supportive care provided to the patients in both arms of the study. In our unit, we use central lines very rarely. Total parenteral nutrition is used primarily for advanced necrotizing enterocolitis or gastro-intestinal surgical problems. The use of breast milk is aggressively promoted, and intra-venous fluids are stopped once milk intake crosses 100–120 ml/kg/day.

Monitoring and follow-up
The minimum period of observation was 28 days after completion of antibiotics, which included a mandatory 72-h period of direct observation in hospital. During the mandatory period, signs of clinical deterioration were actively looked for, and a
blood culture sent at 24 h after antibiotic completion. Asymptomatic subjects who were eligible for discharge were sent home only if the 48-h report of the blood culture was sterile. Meticulous steps were taken to ensure that no episode of illness was missed after discharge from hospital. Parents were asked to contact the chief investigator by telephone and to report to our unit for each episode of illness till 28 days. CRP and blood culture were done for all such episodes. In addition, all subjects were followed-up by weekly appointments for 28 days. At each visit, information regarding episode/s of illness in the previous week was recorded. If any subject did not come for follow-up, they were contacted by telephone or a home visit. An objective adjudication proforma was filled for those episodes of illness, in which CRP and blood culture were non-contributory. A three-member, blinded, adjudication committee of experienced neonatologists reviewed these pro formas along with masked laboratory data and masked X-ray films. Each member gave his/her opinion independently on whether the episode of illness represented bacterial septicemia or not, and the majority opinion was accepted.

Primary outcome variables
The primary outcome was treatment failure. It was defined by the occurrence of any one of the following within 28 days after antibiotic completion.

(i) The same organism grown on blood culture either at 24 h after antibiotic completion or during any episode of illness.
(ii) An episode of illness in which CRP was positive by a semi-quantitative latex agglutination-based commercially available kit (Beacon Diagnostics, Kabilpore, Navsari, India), provided that the concurrent blood culture was either sterile or it was not growing a different organism. As per the kit, a level greater than 12 mg/l was taken as ‘positive’.
(iii) Episode diagnosed to be clinical relapse of sepsis, as per the decision of the adjudication committee.

Subjects with treatment failure were given additional antibiotics for 7 days.

Secondary outcome variables
Common adverse effects of antibiotic usage, such as skin rashes, deranged liver and renal functions were evaluated on the 7th and 14th day of antibiotics.

Blinding
Personnel, who performed the CRP and blood culture were blinded, as was the adjudication committee.

Sample size
There are no published data regarding failure rates of a 14-day regime. Hence we recruited a convenience sample of 70 subjects. We also decided a priori that the study would be stopped if any subject in the 7-day group died during the 28-day follow-up period.

Statistical Analysis
The baseline variables were described. As all outcome variables were categorical, \( \chi^2 \) test with Yates correction, Fisher’s exact test or Mantel Haentzel test, as applicable, were used. A \( P \)-value <0.05 was taken as significant. Sub-groups for analysis were decided before hand: patients ≤1800 g, those infected with any gram-positive organism, those infected with \textit{Staphylococcus aureus}, and those with early onset sepsis. We analyzed subjects as per intention to treat. Losses to follow-up were analyzed by sensitivity analysis (assuming worst case scenarios). Analysis was done using SPSS version 10.0 and Microsoft Excel 2000.

Results
From January 2002 to August 2003, 120 babies were enrolled and observed till day 7 of antibiotic therapy. Parents of 12 subjects did not give consent and 39 were excluded because they had not achieved clinical remission by day 5 (Fig. 1). Of the 69 babies eligible for randomization, 34 were randomized to receive the 7-day antibiotic regime and 35 the 14-day regime. The mean gestational age of babies in this study was 35.38 ± 2.81 weeks and mean birth weight was 1947 ± 669 g. There were 43 males and 26 females. 44.9% had early onset sepsis, and median age of randomization was 12 days.

Prognostic baseline variables related to patient demography, maternal characteristics, the nature of the organism and features of the septic episode were comparable between the two study groups (Table 1). All cases randomized to either group completed their respective courses of appropriate antibiotics with full compliance. One case was lost to follow-up in 7-day therapy group; two were lost in the other group. Thus, we had 33 cases left in each group to assess the primary outcome.

Treatment failure (Table 2)
Five babies in the 7-day group had treatment failure as opposed to only one in 14-day group. This difference did not achieve statistical significance (\( P = 0.19 \)). A sensitivity analysis was also performed, by assuming a worst case scenario, i.e. the baby lost to follow-up in the 7-day group was assumed to have treatment failure and two babies lost in the 14-day group were assumed to
Blood culture positive sepsis among babies ≥32 weeks and/or ≥1500 grams

\[ n = 229 \]

- Died = 73
- Meningitis = 26*
- Other deep-seated infections = 10*
- Life threatening malformation –1
*One baby had both

Enrolled
\[ n = 120 \]

Not asymptomatic = 39
No consent for randomization=–12

Randomized
\[ n = 69 \]

- Excluded

7-day antibiotic group
\[ n = 34 \]

14-day antibiotic group
\[ n = 35 \]

Follow-up
\[ n = 33 \]

Follow-up
\[ n = 33 \]

**Fig. 1. Flow chart of patient movement.**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of baseline variables</th>
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<tr>
<td>Baseline variables</td>
<td>7-day group</td>
</tr>
<tr>
<td>Gestation in weeks (mean ± SD)</td>
<td>35.76 ± 2.82</td>
</tr>
<tr>
<td>Birth weight in grams (mean ± SD)</td>
<td>2015 ± 732</td>
</tr>
<tr>
<td>Sex ratio – M:F</td>
<td>23:11</td>
</tr>
<tr>
<td>Age at randomization in days [median (range)]</td>
<td>12 (7–41)</td>
</tr>
<tr>
<td>Weight at randomization in grams (mean ± SD)</td>
<td>2020 ± 698</td>
</tr>
<tr>
<td>Early onset sepsis</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>7 (20.6)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages, unless otherwise specified.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of treatment failure between the two groups</th>
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<tbody>
<tr>
<td>Outcome variables</td>
<td>7-day group</td>
</tr>
<tr>
<td>Treatment failure among those who completed follow-up</td>
<td>5/33 (15.2)</td>
</tr>
<tr>
<td>Treatment failure among all randomized subjects*</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Bacteria in treatment failure</td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>4/5</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>1/5</td>
</tr>
</tbody>
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Figures in parentheses are percentages.
*Sensitivity analysis.
have successful treatment. Sensitivity analysis did not augment the difference in failure rates to the level of statistical significance ($P = 0.055$).

Of the six treatment failures there were two who relapsed with blood cultures growing the same organism (both in 7-day group, grew $S. aureus$) and four had a positive CRP with sterile cultures (three in group 1 and one in group 2). Three subjects in the 7-day group, whose post-treatment CRP was positive, received antibiotics for 7 more days, following which CRP became negative and they remained asymptomatic on follow-up for a month.

There were four more babies with symptomatic episodes that were neither positive for CRP nor blood culture. They were diagnosed by the adjudication committee as having ‘no sepsis’.

Among the treatment failures, four had $S. aureus$ as the causative organism and all were in the 7-day group. The remaining two babies who had treatment failure (one in each group) had Klebsiella pneumonia as the infecting organism.

**Sub-group analysis**

We performed a sub-group analysis on those infected with $S. aureus$. Out of a total of 14 cases of $S. aureus$ sepsis, equal numbers received 7-day and 14-day antibiotic therapy, respectively. In the 7-day group, 4 (57.14%) had treatment failure, whereas all the babies in 14-day group had successful treatment. This difference was statistically significant ($P = 0.02$). When a similar sub-group analysis was performed on the subjects who were infected with organisms other than $S. aureus$, there was no difference between the 7-day and 14-day groups (3.8% in both groups, $P = 1.0$).

Subgroup analysis was also done for patients $\leq 1800$ g, with gram positive sepsis, those with early onset sepsis and for babies who received antibiotics backed by *in vitro* sensitivity. None of these analyses yielded statistically significant results (all $P > 0.05$).

**Post hoc comparison with subjects who were ineligible for randomization**

Thirty-nine subjects were excluded prior to randomization because they were still symptomatic on days 6 and 7 of antibiotic therapy. To determine the predictors of lack of complete clinical response, we compared this group of 39 subjects with the 69 who became asymptomatic.

On comparison of the cultured organisms, it was found $S. aureus$ constituted 61.5% of culture isolates in babies who were still symptomatic on day 6 and 7 of antibiotic therapy as compared with only 21.3% of isolates in babies who became asymptomatic. This difference was statistically significant ($P = 0.0001$). These groups were comparable as far as demographic variables like sex ratio, gestation age and birth weight were concerned.

**Secondary outcomes**

There were no subjects with skin rash, deranged liver functions or renal functions in either group.

**Discussion**

Our study showed that neonates infected with $S. aureus$ require 14 days of antibiotics. The study also generates the possibility that those infected with *non-S. aureus* organisms may be treated with 7 days of antibiotics, provided they clinically remit by day 5 of treatment.

We did not include clinically suspected sepsis, because babies without true sepsis would show a spuriously favorable response irrespective of duration of antibiotics. In contrast, none of the patients in Engle’s study had a positive blood culture [15]. Previous studies that evaluated CRP-based decisions to stop antibiotics had one or other of the following drawbacks: sepsis was not necessarily confirmed by positive blood cultures, outcome variables were often subjective and assessment of outcomes was non-blinded [6–10].

In our study, randomization was done at the end of day 7 of the treatment only if the baby was completely asymptomatic for at least 48 h, because among babies who were still symptomatic it was impossible to exclude persisting infection with reasonable certainty. Secondly, in our study we wanted to replicate the clinical dilemma that exists whenever a patient becomes asymptomatic after a few days of antibiotics. Engle, *et al.* [15] in their RCT on neonatal pneumonia randomized cases on day 4 of antibiotic therapy only if they were completely asymptomatic for at least 48 h.

We did not limit ‘treatment failure’ to blood culture positive relapses, since blood culture reports may be falsely negative due to exposure to antibiotics in hospital and administration of antibiotics by primary physicians or parents. Since we compared a shorter (and potentially riskier) regime with a standard antibiotic regime, we erred on the side of assuming that all episodes of sickness could potentially be relapses. Unlike our study, Engle, *et al.* [15], followed-up patients for only 2–3 days.

In our study, sensitivity analysis suggested a trend towards increased treatment failures in the 7-day group as opposed to the 14-day group. Sub-group analysis showed that this trend could be explained by the sub-group with $S. aureus$ infection, which had significantly higher number of treatment failures in 7-day group. This suggests that it is more difficult to eradicate $S. aureus$ as compared with other bacteria. Importantly, none of the Staphylococcal treatment failures had any signs of focal infection during treatment, which was in fact an exclusion criterion. In the study by Engle, *et al.* [15] on neonatal pneumonia, 6% infants in the 4-day group and 0% in the 7-day group became
symptomatic within 24 h of stopping therapy. The difference of 6 vs. 0% was considered non-significant by the authors. As all subjects had sterile blood cultures, there were no data about S. aureus.

On comparing the bacteriological profile of randomized vs. non-randomized groups it was found that the percentage of babies infected with S. aureus was significantly higher in babies who were still symptomatic on day 7 of therapy. S. aureus is known to have a propensity to lodge in various organs and cause micro-abscesses. While there are recommendations to treat focal and deep-seated S. aureus infections for about 4–6 weeks, there were no evidence-based recommendations till date regarding the antibiotic duration for neonates with uncomplicated S. aureus septicemia with no obvious localization. Hence, on the basis of our study, we recommend that all neonates with uncomplicated S. aureus septicemia must be treated for 14 days.

In our study, if we exclude cases with S. aureus sepsis, we are left with identical treatment failure rates in the two groups. Unfortunately, the number of subjects with non-S. aureus sepsis was small, and there was inadequate power to conclude that there was indeed no difference between the two groups. We have used the data generated from the current study to perform a sample size calculation for a larger, adequately powered trial on babies with non-S. aureus septicemia. We are currently engaged in such a trial.

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