Duration of Antibiotic Therapy in Neonatal Gram-negative Bacterial Sepsis—10 Days Versus 14 Days

A Randomized Controlled Trial

Anurag Fursule, DNB, Anup Thakur, MD, DNB, Pankaj Garg, MD, and Neelam Kler, MD

Background: Optimal duration of antibiotic therapy in Gram-negative bacterial (GNB) sepsis in non-VLBW infants has not been specifically evaluated in previous studies.

Methods: This was an open labeled noninferiority randomized controlled trial. Non-VLBW infants with GNB sepsis without meningitis whose blood culture were sterile after day 7 of treatment and who were in clinical remission on day 9 of appropriate antibiotic were randomized to short duration (SDR) group and long duration (LDR) group. Infants in SDR group and LDR group received antibiotic therapy for 10 days and 14 days respectively. Primary objective was to compare treatment failure. Secondary objectives were to compare duration of hospitalization, complications of intravenous (IV) therapy and its duration, episodes of new-onset sepsis and all-cause mortality.

Results: Of 222 infants with GNB sepsis, 58 eligible infants were randomized in each group and 113 of these were analyzed. There was no difference in proportion of infants with multidrug-resistant (MDR) organism in SDR versus LDR group [33(60%) versus 32(55.1%) (P=0.84)]. There were no treatment failures in either group. Median (IQR) duration of hospital stay was higher in LDR group as compared with SDR group: 20(18, 23) versus 16(13, 20) days (P<0.001). Infants in LDR group required IV therapy for a longer duration as compared with SDR group mean (SD): 15.2(1.2) versus 10.9(0.8) days (P<0.001). Median (IQR) episodes of extravasation were higher in LDR group: 5(4.7) versus 3(2.3) (P<0.001). There was no difference in episodes of phlebitis and hematoma. No infants had died on follow up.

Conclusion: In suitably selected non-VLBW infants with Gram-negative sepsis, 10 days therapy is noninferior to 14 days therapy.

Key Words: short duration therapy, long duration therapy, treatment failure

(*Pediatr Infect Dis J* 2022;41:156–160)

Neonatal sepsis is a systemic inflammatory response syndrome that is secondary to infection and remains a significant cause of morbidity and mortality in neonates. Neonatal sepsis is categorized according to the infant's postnatal age at onset of disease. Although the definitions for early-onset and late-onset sepsis vary, most clinicians define early-onset sepsis as that occurring at or before 72 hours of life and late-onset sepsis as those occurring after 72 hours of life.[1]

Overall, neonatal sepsis caused by Gram-negative bacteria (GNB) is responsible for 18%–78% of cases.[2–6] In India, this proportion ranges from 55.8% to 64%.[7,8] Antibiotics remain the mainstay of treatment for neonatal sepsis but the duration of appropriate antibiotic therapy for neonatal sepsis is not based on strong clinical evidence. Various standard textbooks differ in recommending the optimum duration of therapy.[1,9,10] National Neonatology Forum of India's (NNFI) evidence-based clinical practice guidelines recommend administration of appropriate antibiotics for a total duration of 10–14 days in blood culture positive sepsis.[11] A shorter duration of antibiotic therapy may lead to undertreatment and resurgence of infection with resultant increased morbidity and mortality.[12] On the other hand, 14-day course may carry the risk of unnecessary antibiotic exposure, increased cost of care, unnecessary intravenous cannulation, prolonged hospitalization and risk of colonization with pathogenic organisms leading to the emergence of drug-resistant strains. Rising antibiotic resistance is a major concern, especially in developing countries.[13] A recent study in India (DeNIS) showed alarming trends of increase in multidrug-resistant organisms (54%) across 3 large public hospitals in Delhi.[8]

There is a paucity of randomized controlled trials that have systematically evaluated the optimum duration of antibiotics in culture positive sepsis in neonates.[14–16] There are no studies that have specifically evaluated the optimal duration of antibiotic therapy in GNB sepsis. Therefore, we conducted a randomized controlled trial to determine whether 10 days (short duration, SDR) of antibiotic therapy in GNB sepsis is noninferior to 14 days (long duration, LDR) therapy for treatment failure.

MATERIALS AND METHODS

This parallel open-label, noninferiority randomized controlled trial with 1:1 allocation was conducted in the NICU of a tertiary center in northern India from July 2017 till May 2020. Infants with birth weight ≥ 1500 g [nonvery low birth weight infants (VLBW)] with GNB sepsis on blood culture without meningitis were eligible. Infants were enrolled if repeat blood culture after 7 days of appropriate antibiotic therapy was sterile and clinical remission, defined as being on full feeds, not on mechanical ventilation or on inotropes, was achieved. Infants born with major congenital malformations, those with severe birth asphyxia (defined as APGAR score ≤3 at 5 minutes), meningitis, ventriculitis, osteomyelitis, septic arthritis, other deep-seated infections, or requiring surgery or unlikely to follow up for 28 days were excluded. An informed written consent was obtained from the parents. The trial was approved by the institutional ethics committee and registered with Clinical Trial Registry of India.

Accepted for publication August 1, 2021
From the Department of Neonatology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India.
CTRI No: CTRI/2018/01/011453
The authors have no funding or conflicts of interest to disclose.
Ethically cleared—July 11, 2017, Ethics committee, Sir Ganga Ram Hospital (EC/07/17/1193).
P.G., A.T., and N.K. conceptualized the project and wrote the protocol. A.F. had primary responsibility of patient screening, enrollment, and data collection. A.T. and A.F. performed the statistical analysis and wrote the article. N.K. and P.G. supervised during enrolment, outcome assessment and article writing. All authors approved the final article.
Address for correspondence: Neelam Kler, MD, Department of Neonatology, Institute of Child Health, Sir Ganga Ram Hospital Marg, Old Rajinder Nagar, New Delhi 110060 India. E-mail: drneelamkler@gmail.com.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com)

ISSN: 0891-3668/22/4102-0156
DOI: 10.1097/INF.0000000000003314

All non-VLBW infants with clinical signs of sepsis based on NEOKISS criteria[17] were evaluated by obtaining a complete blood count, C-reactive protein, immature to the total neutrophil ratio, blood culture, urine, and CSF analysis. NEOKISS criterion was met if any 2 of the following were present (without other recognized cause): fever (>38°C) or temperature instability or hypothermia (<36.5° C), tachycardia (>200/min), or new/ more frequent bradycardia (<80/min), capillary refill time >2 seconds, new or more frequent apnea (>20 seconds), unexplained metabolic acidosis, new-onset hyperglycemia (>140mg/dl), or other signs/ symptoms of sepsis: (1 or more; skin color (pale/mottled, lethargy, poor feeding, unexplained respiratory distress, increased oxygen requirements or requiring intubation, unstable condition, apathy, or laboratory evidence (CRP).

Empirical antibiotics were started as per institutional guidelines, pending culture, and sensitivity reports. Infants showing growth of a pathogenic organism in blood culture were treated with antibiotics as per sensitivity. After completion of 7 days of appropriate antibiotic therapy, a repeat blood culture was sent to document sterility. Infants with GNB sepsis, who were documented to have sterile blood culture after day 7 of treatment and were in clinical remission (defined by being on full feeds and not on mechanical ventilation or on inotropes) on day 9 of appropriate antibiotic were eligible for enrollment.

Randomization and Blinding

Eligible infants were randomly allocated to 1 of the 2 groups—SDR group or LDR group—by computer-generated randomization sequence with variable block sizes of 4 and 6 generated by an independent researcher. This allocation sequence was concealed in sealed opaque envelopes. The opaque envelopes were sequentially numbered by another independent staff member and were kept in the Neonatal Intensive Care Unit (NICU). The NICU nurse in charge opened the sealed opaque envelope and disclosed the intervention (SDR/LDR). The nature of the intervention prevented us from blinding.

Intervention

Infants assigned to SDR group received 10 days of appropriate antibiotic therapy and those in LDR group received 14 days of appropriate antibiotic therapy.

Monitoring and follow up

All infants received similar standard supportive care in the NICU except for the duration of antibiotic therapy and subsequent to that, were observed in-house for at least 24 hours. Infants were discharged as per unit criteria and were followed at 48–72 hours of discharge and then weekly till 28 days. At each visit, assessment for general well-being and evaluation for signs/symptoms of sepsis was done. In addition to these visits, parents were asked to report to the NICU for any signs/symptoms they perceive as abnormal. Those infants suspected to have sepsis were admitted and treated as per institutional guidelines. In cases where parents could not come for follow up, telephonic consultation was done by the principal investigator.

Outcome Measures

The primary outcome measure of our study was "treatment failure" defined as the reappearance of signs and symptoms suggestive of sepsis within 28 days after completion of the antibiotic course and confirmed by positive blood culture for the same organism. Secondary outcomes were duration of hospital stay, complications of IV therapy such as extravasation injuries, phlebitis or hematoma, duration of IV therapy, episodes of new-onset sepsis (blood culture positive) by a different organism and all-cause mortality within 4 weeks of completion of antibiotic therapy.

Sample size calculation

In a study by Gathwala et al,[14] the success rate of antibiotic therapy in 10 days group was 96.7%. For a success rate of 96.7% in both the groups, with a power of 90%, α error of 0.05, 10% noninferiority limit, a total of 110 infants, 55 in each group was required. Assuming an attrition rate of 10%, the final sample size was calculated to be 122 infants.

Statistical Methods

Analysis of data was done by using SPSS software version 17. Mean and standard deviation were calculated for normally distributed data while for skewed data, median, and interquartile range were calculated. Quantitative data with normal distribution was compared using student t-test and in those with skewed distribution, Mann-Whitney *U* test was used. Categorical data were compared using Chi-square test or Fisher exact test. Two-sided *P* value of <0.05 was considered significant.

RESULTS

A total of 2964 infants were admitted to the NICU during the study period, of which 2848 infants were excluded due to various reasons (Fig. 1). A total of 116 infants underwent definite inclusion and 58 infants were randomized to each group. Three infants in LDR group did not complete allotted intervention and 113 infants were analyzed at the end of the study.

Maternal and neonatal characteristics, clinical manifestation, and laboratory parameters at admission were similar in both the groups (Tables 1 and 2). The antibiotic regimen used and sensitivity pattern is depicted in Supplemental Digital Contents 1 and 2, http://links.lww.com/INF/E521. Fifty percent (29/58) of cases in SDR group and 60% (33/55) of cases in LDR required a change in antibiotic therapy based on susceptibility, ($P=0.34$). Overall, *Klebsiella pneumoniae* was the commonest isolate [57/113 (50.4%)] followed by *Acinetobacter baumannii* [20/113 (17.6%)] (Table 3). Multidrug-resistant organisms formed 57.5% (65/113) of all isolates; 66.67% (38/57) of *Klebsiella pneumoniae*, 55% (11/20) of *Acinetobacter baumannii*, 42.8% (6/14) *of Burkholderia cepacia* were multidrug resistant. The proportion of infants with multidrug-resistant organism in LDR and SDR group were similar (Table 3). Proportion of infants with MDR organism was significantly higher in extramural as compared with intramural admissions [77.6% (59/76) versus 18.9% (7/37), $P<0.001$]. Infants in LDR and SDR group had similar requirement for intensive care including ventilation, need for inotropes, and transfusion (Table 4).

Of 113 infants followed for up to 4 weeks, there was no treatment failure in either group. However, 2 infants were readmitted with clinical features of sepsis, 1 from each group. Blood culture from infant in SDR group was sterile whereas that from infant in LDR group showed growth of *Staphylococcus aureus*. None of the infants died on follow up.

Of the secondary outcomes analyzed, the median (IQR) duration of hospital stay was significantly higher in LDR group as compared with SDR group [20 (18, 23) versus 16 days (13, 20) ($P<0.001$)]. Infants in the LDR group required IV therapy for a longer duration [mean (SD)] as compared with SDR group [15.2 (1.2) versus 10.9 (0.8) days ($P<0.001$)]. Similarly, episodes of extravasation median (IQR) were higher in the LDR group [5 (4.7) versus 2 (2.3) ($P<0.001$)]. There was no difference in episodes of phlebitis and hematoma (Table 5).

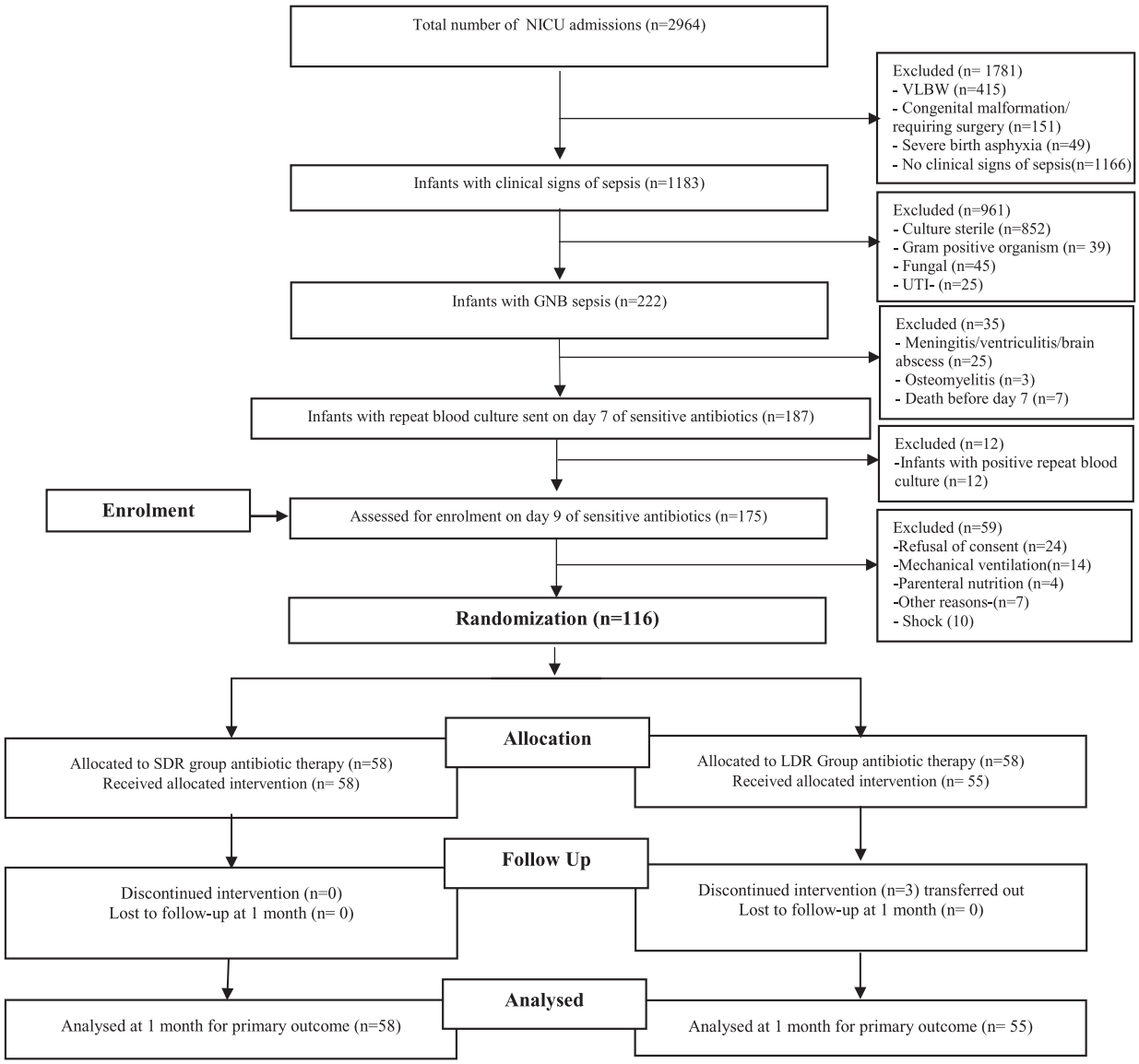

FIGURE 1. Consort flow diagram.

DISCUSSION

Duration of antibiotic therapy in GNB sepsis has not been systematically evaluated. We conducted a randomized controlled trial to determine whether 10 days of antibiotic therapy in GNB sepsis is noninferior to 14 days for treatment failure. We found that a 10-day duration of treatment was not inferior to 14 days of treatment.

In our study, none of the infants in either group developed treatment failure on follow up till 4 weeks of discharge. Our findings are consistent with other studies[14–16] that compared the different duration of antimicrobial therapy in neonatal sepsis caused by both Gram-negative and Gram-positive organisms. In a pilot randomized controlled trial, Chowdhary et al compared the effectiveness of a 7-day intravenous antibiotic regimen with a 14-day regimen for neonatal sepsis.[15] The investigators recruited a total of 69 non-VLBW infants to receive either a 7-day course (n=34) or a 14-day course (n=35) of antibiotics and found no difference in treatment failure in the 2 groups [15.2% (5/33) versus 3% (1/33) (P=0.19)]. In another randomized controlled trial, Gathwala et al enrolled 60 infants ≥32 weeks gestation and ≥1500 g birth weight on day 7 of therapy if the infants were in clinical remission and CRP was negative.[14] The authors compared the effectiveness of a 10-day course of antibiotic therapy with a 14-day course in culture-proven sepsis in terms of treatment failure within 28 days defined as either positive CRP or positive blood culture or clinical relapse. Although, it was not a noninferiority design and sample size was not estimated a priori, the authors reported that 10-day course of antibiotic therapy was as effective as 14-day therapy with 1 infant failing treatment in each group. In a recent RCT, Rohatgi et al[16] enrolled infants of gestational age ≥32 weeks, birth weight ≥1500 g and compared the efficacy of 7 versus 10 days duration of intravenous antibiotics in culture positive sepsis. One hundred and thirty-two infants who were in clinical remission, tolerating feeds, not requiring >40% FiO_2 or inotropic support were randomized on day 5 of antimicrobial therapy to receive either 7 or 10 days duration of intravenous antibiotics. The authors reported similar rates of treatment failure

TABLE 1. Maternal and Neonatal Characteristics

Parameter	LDR Group (n = 55)	SDR Group (n = 58)	*P*
Maternal age (yrs)*	30.5 (4.0)	30.2 (4.2)	0.70
Preterm labor	6 (10.9)	13 (22.4)	0.13
PPROM	8 (14.5)	13 (22.4)	0.33
LSCS	50 (90.9)	45 (77.6)	0.07
Inborn	16 (29.1)	21 (36.2)	0.43
Gestational age (wks)*	35.6 (3.1)	35.6 (2.5)	0.94
Birth weight (g)*	2350 (706)	2328 (568)	0.85
Male	44 (80)	42 (72.4)	0.38
SGA	8 (14.5)	9 (15.5)	0.90

Data expressed as n (%) unless specified.
*Mean (SD).
LSCS indicates lower section cesarean section; PPROM, preterm premature rupture of membrane; SGA, small for gestational age.

TABLE 2. Clinical Characteristics and Laboratory Parameters at Presentation

Characteristics	LDR Group (n = 55)	SDR Group (n = 58)	*P*
Onset of symptoms in days*	4 (1, 11)	3 (1, 6)	0.19
EONS	23 (41.8)	31 (53.4)	0.26
Fever	13 (23.6)	9 (15.5)	0.27
Hypothermia	2 (3.6)	3 (5.2)	0.69
Tachycardia	17 (30.9)	12 (20.7)	0.28
Hyperglycemia	11 (20)	7 (12.1)	0.30
Hypoglycemia	5 (9.1)	2 (3.4)	0.26
Apneas	23 (41.8)	25 (43.1)	1.0
Poor feeding	28 (50.9)	27 (46.6)	0.70
Feed intolerance	18 (32.7)	16 (27.6)	0.68
Lethargy	34 (61.8)	39 (67.2)	0.56
Respiratory distress	35 (63.6)	37 (63.8)	1.0
Central line in situ	9 (16.4)	13 (22.4)	0.48
Invasive ventilation	25 (45.5)	24 (41.4)	0.66
Noninvasive ventilation	22 (40)	23 (39.6)	0.97
Septic shock	13 (23.6)	11 (19)	0.64
Metabolic acidosis	20 (36.4)	14 (24.1)	0.21
TLC*	9600 (6130, 15,900)	10,520 (5475, 15,940)	0.95
ANC*	4853 (2967, 9396)	5655 (2418, 8735)	0.71
CRP*	51.9 (11.4, 99.1)	47 (11.3, 99.8)	0.52
I:T ratio*	0.14 (0.09, 0.35)	0.12 (0.06, 0.20)	0.34
Time to culture positivity (hours)*	11.2 (8.7, 13.6)	12 (10.4, 15.8)	0.11

Data expressed as n (%) unless specified.
*Median (IQR).
ANC indicates absolute neutrophil count: cells/cu.mm; CRP, C-reactive protein: mg/l; EONS, early-onset neonatal sepsis; I:T ratio, immature to the total neutrophil ratio; LDR, long duration; SDR, short duration; TLC, total leucocyte count: cells/cu.mm.

TABLE 3. Spectrum of Isolated Organisms

Organism	LDR Group (n = 55)	SDR Group (n = 58)	*P*
Klebsiella pneumoniae	33 (60)	24 (41.4)	
Acinetobacter baumannii	9 (16.4)	11 (19)	
Burkholderia cepacia	4 (7.3)	10 (17.2)	
Escherichia coli	4 (7.3)	5 (8.6)	
Stenotrophomonas maltophilia	2 (3.6)	0 (0)	
Pseudomonas aeruginosa	1 (1.8)	2 (3.6)	
Pseudomonas stutzgeri	0 (0)	1 (1.7)	
Enterobacter cloacae	1 (1.8)	2 (3.6)	
Serratia marcescens	1 (1.8)	1 (1.7)	
Ralstonia mannitolytica	0 (0)	1 (1.7)	
Acinetobacter junii	0 (0)	1 (1.7)	
MDR organisms	33 (60)	32 (55.1)	0.84

Data expressed as n (%). MDR definition for *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp: The isolate is nonsusceptible to at least 1 agent in ≥ 3 antimicrobial categories.[18]
LDR indicates long duration; MDR, multidrug resistant; SDR, short duration.

TABLE 4. Intensive Care Required During NICU Stay

Outcomes	LDR group (n = 55)	SDR group (n = 58)	*P*
Invasive ventilation	23 (41.8)	27 (46.6)	0.70
Noninvasive ventilation	37 (67.3)	40 (69)	1.0
Inotropes	16 (29.1)	12 (20.7)	0.38
Parenteral nutrition	35 (63.6)	38 (65.5)	0.84
Need for blood products	24 (43.6)	18 (31)	0.17
Packed red blood cells	6 (10.9)	11 (19)	0.29
Platelet concentrate	21 (38.2)	13 (22.4)	0.10
Fresh frozen plasma	5 (9.1)	6 (10.3)	1.0
Duration in hours*			
• Noninvasive ventilation	48 (0, 96)	42 (0, 72)	0.38
• Invasive ventilation	0 (0, 96)	0 (0, 63)	0.59
• Parenteral Nutrition	48 (0, 96)	36 (0, 96)	0.91
• Inotropes	0 (0, 48)	0 (0, 0)	0.25

Data expressed as n (%) unless specified.
*Median (IQR).
IQR indicates interquartile range; LDR, long duration; SDR, short duration.

in the 7-day group [2/64 (3%)] as compared with a 10-day group [2/64 (3%)]. Despite treatment failure being defined variably in these studies, no difference in the rates of treatment failure in long duration or short duration groups has been reported. In our study, none of the infants had treatment failure which could be due to more stringent inclusion criteria. We enrolled infants with GNB sepsis, whereas all 3 mentioned studies included infants with both Gram-negative and positive sepsis. In addition, we documented a sterile blood culture on day 7 before randomization.

Another important finding in our study was that treatment failure was independent of infection being caused by MDR organism, provided appropriate antibiotic was given for stipulated duration. We found that *Klebsiella pneumoniae* was the most common organism isolated (50.4%), followed by *Acinetobacter baumannii* (17.6%), and *Burkholderia cepacia* (12.3%). A total of 57.5% of isolated organisms were multidrug-resistant. Rohatgi et al also reported *Klebsiella* being the common isolate (40.9%), while Gathwala et al found *Pseudomonas* to be the most common isolate (51.6%). These studies did not report the burden of MDR organism. A recent study from New Delhi reported 82% of *Klebsiella* isolates and 54% of *Acinetobacter* to be MDR.[8]

On evaluating our secondary outcomes, we found decreased duration of hospital stay, duration of IV therapy and episodes of extravasations in short duration group. In our study, the median difference in hospital stay in the 2 groups was 4 days. Two studies have reported the duration of hospital stay as a secondary outcome and found similar results. Gathwala et al reported duration of 13 days versus 17.5 days in a short duration and long duration group while Rohatgi et al observed duration of 17 days and 19.4 days respectively.[14,16] The decreased duration in our study is probably due to earlier discharge in SDR group who would otherwise be hospitalized for IV therapy despite other discharge criterion being fulfilled. Similarly, days on IV therapy was less in SDR group due to study design per se. This decrease in duration of hospital stay and IV therapy may translate into lower cost of care which is more relevant in lower and middle-income countries with limited resources.[19–22] In addition, since extravasation is associated with IV cannulation, infants in the SDR group had lesser episodes of

TABLE 5. Outcome Measures

Outcome Measures	LDR Group (n = 55)	SDR Group (n = 58)	*P*
Primary outcome Treatment failure*	0	0	-
Secondary outcomes			
Duration of hospital stay	20 (18, 23)	16 (13, 20)	<0.001
Duration of IV antimicrobial therapy*	15.2 (1.2)	10.9 (0.8)	<0.001
Episodes of extravasation	5 (4, 7)	3 (2, 3)	<0.001
Episodes of phlebitis	3 (2, 3)	2 (2, 4)	0.76
Hematoma	1 (0, 2)	1 (0, 1)	0.35
Any organism isolated on follow up†	1	0	-
All-cause mortality within 4 weeks†	0	0	-

Data expressed as median (IQR) unless specified.

*Mean (SD).

†SPSS software did not compute the *P* value as an outcome in LDR group and SDR group was zero.

IQR indicates interquartile range; IV, intravenous; LDR, long duration; SDR, short duration.

extravasation. Other secondary outcomes such as all-cause mortality after 28 days of completion of therapy were not observed in any infant. One infant from LDR group had new-onset sepsis by *Staphylococcus aureus*.

The strength of our study includes its noninferiority design, exclusive inclusion of GNB neonatal sepsis, carefully defined cohort randomized only after clinical remission and documented microbiologic sterility and meticulous follow up. Our study has certain limitations. The findings of our study cannot be broadly extrapolated to all infants with neonatal sepsis and this limits the generalizability of our study. We adopted an extremely cautious approach and our cohort was carefully selected. Only non-VLBW infants were included in our study as VLBW infants being immune-compromised are more likely to have treatment failure if the duration of antibiotics is curtailed. Secondly, we randomized infants after completion of 7 days of appropriate antibiotics with documented sterile blood culture on day 9 and only if they were in complete clinical remission, that is, off inotropes, on room air or noninvasive mode of ventilation and on full enteral feeds. In addition, those with deep-seated infections like meningitis, hepatic abscess, osteomyelitis, septic arthritis were excluded. The choice of noninferiority margin may seem high but given the anticipated advantages such as decreased duration of NICU stay, reduction in IV antimicrobial therapy days and decrease in complications related to IV therapy, delta of 10% is justified and abides by the rules of noninferiority design.[23,24] Finally, we could not account for the effect on the administration of intrapartum antibiotics on treatment failure since the majority of infants in our study were extramural admission in whom the history of intrapartum antibiotics was not available.

CONCLUSIONS

In suitably selected non-VLBW infants with Gram-negative sepsis, 10 days therapy is noninferior to 14 days therapy, in terms of treatment failure. In addition, a short duration antibiotic decreases the length of hospital stay, duration of IV therapy and episodes of extravasation.

REFERENCES

1. Leronard G, Dobbs K. Neonatal perinatal medicine. In: Martin R, Fanaroff A, Walsh M, eds. *Neonatal Perinatal Medicine*. 10th ed. Saunders; 2017:734–750.
2. Couto RC, Carvalho EA, Pedrosa TM, et al. A 10-year prospective surveillance of nosocomial infections in neonatal intensive care units. *Am J Infect Control*. 2007;35:183–189.
3. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2 pt 1):285–291.
4. Kamath S, Mallaya S, Shenoy S. Nosocomial infections in neonatal intensive care units: profile, risk factor assessment and antibiogram. *Indian J Pediatr*. 2010;77:37–39.
5. Tseng YC, Chiu YC, Wang JH, et al. Nosocomial bloodstream infection in a neonatal intensive care unit of a medical center: a three-year review. *J Microbiol Immunol Infect*. 2002;35:168–172.
6. Macharashvili N, Kourbatova E, Butsashvili M, et al. Etiology of neonatal blood stream infections in Tbilisi, Republic of Georgia. *Int J Infect Dis*. 2009;13:499–505.
7. Deorari A, Agrawal R, Paul VK, et al. *National Neonatal-Perinatal Database*. NNPD Nodal Center AIIMS Delhi. 2005.
8. Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *Lancet Glob Heal*. 2016;4:e752–e760.
9. Ferrieri P, Wallen D. Newborn sepsis and meningitis. In: Gleason A, Juul E, eds. *Avery's Diseases of the Newborn*. 10th ed. Elsevier; 2018:564.
10. Issacs A, Russell A. Infections in newborns. In: Rennie M, ed. *Rennie and Roberton's Textbook of Neonatology*. 5th ed. Elsevier; 2012:1026.
11. Kadam S, Saini SS, Venkataseshan S. Management of neonatal sepsis. In: Kumar P, Jain N, Thakre R, Murki S, eds. *Evidence Based Clinical Practice Guideline*. 1st ed. National Neonatology Forum; 2010:155–172.
12. Low DE, Scheld WM. Strategies for stemming the tide of antimicrobial resistance. *JAMA*. 1998;279:394–395.
13. Chaurasia S, Sivanandan S, Agarwal R, et al. Neonatal sepsis in South Asia: huge burden and spiralling antimicrobial resistance. *BMJ*. 2019;364:k5314.
14. Gathwala G, Sindwani A, Singh J, et al. Ten days vs. 14 days antibiotic therapy in culture-proven neonatal sepsis. *J Trop Pediatr*. 2010;56:433–435.
15. Chowdhary G, Dutta S, Narang A. Randomized controlled trial of 7-day vs. 14-day antibiotics for neonatal sepsis. *J Trop Pediatr*. 2006;52:427–432.
16. Rohatgi S, Dewan P, Faridi MMA, et al. Seven versus 10 days antibiotic therapy for culture-proven neonatal sepsis: a randomised controlled trial. *J Paediatr Child Health*. 2017;53:556–562.
17. Gastmeier P, Geffers C, Schwab F, et al. Development of a surveillance system for nosocomial infections: the component for neonatal intensive care units in Germany. *J Hosp Infect*. 2004;57:126–131.
18. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18:268–281.
19. Cheah IGS. Economic assessment of neonatal intensive care. *Transl Pediatr*. 2019;8:246–256.
20. Garg P, Krishak R, Shukla DK. NICU in a community level hospital. *Indian J Pediatr*. 2005;72:27–30.
21. Prinja S, Manchanda N, Mohan P, et al. Cost of neonatal intensive care delivered through district level public hospitals in India. *Indian Pediatr*. 2013;50:839–846.
22. Karambelkar G, Malwade S, Karambelkar R. Cost analysis of healthcare in a private sector neonatal intensive care unit in India. *Indian Pediatr*. 2016;53:793–795.
23. Committee for Medicinal Products for Human Use; Efficacy Working Party; Committee for Release for Consultation. Committee for Medicinal Products for Human Use (CHMP) guideline on the choice of the non-inferiority margin. *Stat Med*. 2006;25:1628–1638.
24. Hahn S. Understanding noninferiority trials. *Korean J Pediatr*. 2012;55:403–407.