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Original article

The consequences of prolonged duration of antibiotics in premature infants with suspected sepsis in a large tertiary referral hospital: a retrospective cohort study

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ABSTRACT

Objective: To assess whether there is any association between prolonged duration of the first course of empirical antibiotic treatment for suspected neonatal sepsis and other factors including comorbidities, interventions, and adverse outcomes.**Background:** Neonatal sepsis is one of the main reasons of mortality among premature infants in Neonatal Intensive Care Unit (NICU). Therefore, commencing antibiotics treatment on admission plays a crucial role in reducing the complications of neonatal sepsis, however the arbitrary use of antibiotics holds many serious complications. In our study we investigated the complications of prolonged use of antibiotics in treating suspected early onset of sepsis.**Study design:** This is a retrospective cohort study of infants of gestational age 32 weeks or less and with birth weight of 1500 g or less along with suspected neonatal sepsis admitted to our neonatal intensive care unit from July 2015 to June 2017. The study outcome measures were the association between the antibiotic treatment duration and maternal factors, gender, adverse outcomes, developmental factors, comorbid conditions, early-onset sepsis, and late-onset sepsis.**Results:** Of 295 premature infants, late-onset sepsis was associated with the duration of early empiric antibiotic use ($n = 54/295$), where 50 (92.6%) infants with LOS received the antibiotic treatment for more than 5 days ($P < .001$). Approximately 91.2% of those receiving the prolonged treatment had a positive blood culture result. Necrotizing enterocolitis was more prevalent in those with long duration of antibiotic treatment (95.1%). Among patients with the comorbid conditions patent ductus arteriosus ($n = 123/295$), intraventricular hemorrhage ($n = 73/295$), and periventricular leukomalacia ($n = 25/295$), 100 (81.3%), 60 (82.2%), and 21 (84%) of them, respectively, received prolonged treatment.**Conclusion:** Prolonged administration of empiric antibiotics to infants with very low birth weight along with sterile cultures is associated with the adverse outcomes late-onset sepsis and necrotizing enterocolitis. However, no association with other adverse outcomes, namely, candidiasis or maternal factors, was found.© 2018 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Sepsis is one of the main causes of mortality among neonates

worldwide. The incidence of neonatal sepsis in the United States is approximately two per 1000 live births [10]. The aim of a study conducted in Saudi Arabia was to determine the overall incidence

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of neonatal sepsis in very low birth weight (VLBW) infants born in one of the university hospitals in Riyadh during 1999–2007. The rate of neonatal sepsis in VLBW infants was 48%. Neonatal sepsis is a very complex type of neonatal infection that affects newborns, where infants suffer from bloodstream infections (BSIs). The percentage of neonatal deaths due to life-threatening BSIs in developing countries has reached 99%, with a total of 1 million annual deaths [1]. In 2014, neonatal sepsis prevalence reached 48% in Saudi Arabia [2]. Neonatal sepsis is categorized as early-onset sepsis (EOS) and late-onset sepsis (LOS) according to age [3,4]. EOS is a maternal vertical transmission of bacterial pathogens to the infant occurring in the first 3 days of the infant's life [3], whereas LOS is the horizontal transmission of pathogens from the environment occurring after 7 days of an infant's life [4–6]. In neonatal intensive care units (NICUs), antibiotics are the most commonly prescribed treatment. For treatment, empiric antibiotics are administered in the first postnatal days to infants with extremely low birth weight. The duration of the initial empiric antibiotic treatment course plays an important factor in neonatal sepsis therapy [5]. In case of suspected LOS, rapid initiation of treatment with empiric antibiotics is important; however, prolonged and unnecessary antibiotic use may lead to adverse outcomes in neonates. In some cases, owing to previous treatment with antibiotics or small blood volume, the result of blood cultures is negative and the decision to continue or discontinue antibiotic treatment depends on the case. Nevertheless, prolonged treatment with broad-spectrum antibiotics in case of a negative culture result can be associated with increased risks of necrotizing enterocolitis (NEC) or death [6–9]. The aim of this study was to assess any association between the duration of antibiotic treatment for neonatal sepsis and other factors including comorbidities, interventions, and adverse outcomes.

2. Methods

2.1. Study design

This was a retrospective cohort study in which infants with suspected EOS were admitted in the NICU of King Saud Medical City from July 2015 to June 2017. This study followed the principles of the Declaration of Helsinki, in accordance with the Medical Research Involving Human Subjects Act (WMO) and was approved by the medical ethical review committee of our institution.

We conducted the study on 323 neonates with suspected EOS; the infants received empiric antibiotic treatment, and a standardized questionnaire was used to collect information about maternal and neonatal parameters. We classified the dataset according to the duration of the antibiotics administered: premature neonates who received antibiotic treatment for 5 days or less and those who received antibiotic treatment for more than 5 days.

All neonates were inborn, with age less than or equal to 180 days; were admitted to our NICU; and received antibiotic treatment. Outborn neonates, those who did not receive antibiotics, those with postpartum age of more than 180 days, and those with major congenital anomalies were excluded from the study. We followed up all neonates until their discharge, transfer, or death.

The primary outcome measures were the association between the antibiotic treatment duration and maternal factors, gender, adverse outcomes, developmental factors, comorbid conditions, EOS, and LOS.

We conducted all statistical tests at a confidence level of 95%. We used SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc., Chicago, IL, USA) for statistical analyses, and we represented numerical data as mean and standard deviation or median and interquartile range and categorical data as frequency (count) and relative frequency (percentage).

To compare categorical data, we performed a chi-square test or Phi–Cramer test and used the exact test instead when the expected frequency was less than 5. We made comparisons between quantitative variables using the Student t-test and the nonparametric Mann–Whitney test when needed, and we considered *P* values less than 0.05 as statistically significant.

Univariate analysis comparing different characteristics between survivors and nonsurvivors was conducted using an independent *t*-test for normally distributed data and the Mann–Whitney *U* test for skewed data. We used a χ^2 test to compare differences in survival for categorical variables. Variables with a *P* value < .05 in the univariate analysis were entered into a multiple stepwise logistic regression model to establish predictors of mortality.

3. Results

The number of infants included in the dataset was 323; as we were unable to retrieve records for 28 infants, the study included 295 infants; 28 neonates were excluded. Of the 28 infants excluded, 16 of them were outborn, six did not receive antibiotic treatment, five had major congenital anomalies, and one was outborn and had major congenital anomalies, thus leaving 295 cases included in the analysis. The number of infants with antibiotic treatment duration of 5 days or less was 104 and that of infants with duration of more than 5 days was 191.

3.1. Baseline characteristics

Out of 295 infants, 153 (51.9%) of them were males and 142 (48.1%) were females. Fifty-three mothers (18%) went for a follow-up at the perinatology clinic before delivery. One hundred thirty-six infants (46.1%) were delivered by spontaneous vaginal delivery (SVD), whereas the others (159; 53.9%) were delivered by cesarean section (CS). Additionally, 27 (9.2%) infants had intrauterine growth restriction (IUGR; Table 1).

3.2. Antibiotic duration

Gender, developmental factors, and maternal factors:

The duration of antibiotic treatment was not associated with gender, IUGR, or extreme prematurity. The number of males who received antibiotic treatment for 5 days or less and for more than 5 days were 54 (35.3%) and 99 (64.7%), respectively, and for females, it was 50 (35.2%) and 92 (64.8%), respectively. Differences among these groups were, however, not statistically significant (*P* = .988). For premature neonates who had IUGR, five (18.5%) of them received antibiotic treatment for 5 days or less and 22 (81.5%) of them received the treatment for more than 5 days (*P* = .056) (Table 2).

3.3. Comorbid conditions

Among the comorbidities, the percentage of infants with respiratory distress syndrome (95.30%) and pulmonary hemorrhage (90.80%) was high. There was an association between the presence of patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) and the duration of antibiotic treatment. Twenty-three (18.7%) out of 295 infants with PDA received the antibiotic treatment for 5 days or less and 100 (81.3%) of them received the treatment for more than 5 days (*P* < .001). Among the 73 infants who had IVH, there was statistically significant difference (*P* < .001) between those who received the treatment for 5 days or less (13; 17.8%) and those who received the treatment for more than 5 days (60; 82.2%). The total number of infants with PVL was 25, where four (16%) of them received

Table 1
Baseline characteristics.

	Valid	Missed	Number of infants with the condition (%)	
			n	% of total
Follow up by the perinatology clinic before delivery	295	0		
Yes			53	18.00
No			242	82.00
Mode of delivery	295	0		
SVD			136	46.10
CS			159	53.90
Gender	295	0		
Male			153	51.90
Female			142	48.10
Intrauterine growth restriction (IUGR)	295	0		
Yes			27	9.20
No			268	90.80
Extreme prematurity	295	0		
Yes			99	33.70
No			195	66.30
Respiratory distress syndrome	295	0		
Yes			281	95.30
No			14	4.70
Pneumothorax	295	0		
Yes			16	5.40
No			279	94.60
Pulmonary hemorrhage	295	0		
Yes			268	90.80
No			27	9.20
Patent ductus arteriosus	295	0		
Yes			123	41.70
No			172	58.30
Intraventricular hemorrhage	295	0		
Yes			73	24.70
No			222	75.30
Periventricular leukomalacia	295	0		
Yes			25	8.50
No			270	91.50
Umbilical arterial catheter	295	0		
Yes			107	36.30
No			188	63.70
Central line: UVC	295	0		
Yes			224	75.90
No			71	24.10
Central line: CVC	295	0		
Yes			6	2.00
No			289	98.00
Central line: PICC	295	0		
Yes			53	18.00
No			242	82.00
Type of sepsis	295	0		
EOS			5	1.70
LOS			54	18.30
Positive blood culture	295	0		
Yes			57	19.30
No			238	80.70
Bacterial resistance	65	0		
Yes			32	49.20
No			33	50.80
Candidiasis	295	0		
Yes			2	0.70
No			293	99.30
Necrotizing enterocolitis	295	0		
Yes			102	34.60
No			193	65.40
Mortality	295	0		
Yes			64	21.70
No			231	78.30

Table 2

Gender, developmental factors and maternal factors.

	Valid	Missed	Duration of antibiotics				P value
			Five days		More than		
			or less		five days		
			n	%	n	%	
Gender	295	0					
Male			54	35.3	99	64.7	.988
Female			50	35.2	92	64.8	
Intrauterine growth restriction (IUGR)	295	0					.056
Yes			5	18.5	22	81.5	
No			99	36.9	169	63.1	
Extreme prematurity	295	0					.391
Yes			38	38.4	61	61.6	
No			65	33.3	130	66.7	
Follow up by the perinatology clinic before delivery	295	0					.293
Yes			22	41.5	31	58.5	
No			82	33.9	160	66.1	
Mode of delivery	295	0					.217
SVD			53	39.0	83	61.0	
CS			51	32.1	108	67.9	

Table 3

Comorbid conditions and duration of antibiotics.

	Valid	Missed	Duration of antibiotics				P value
			Five days		More than		
			or less		five days		
			n	%	n	%	
Respiratory distress syndrome	295	0					.588
Yes			99	35.2	182	64.8	
No			5	35.7	9	64.3	
Pneumothorax	295	0					.73
Yes			5	31.3	11	68.8	
No			99	35.5	180	64.5	
Pulmonary hemorrhage	295	0					.827
Yes			95	35.4	173	64.6	
No			9	33.3	18	66.7	
Patent ductus arteriosus	295	0					<.001
Yes			23	18.7	100	81.3	
No			81	47.1	91	52.9	
Intraventricular hemorrhage	295	0					<.001
Yes			13	17.8	60	82.2	
No			91	41.0	131	59.0	
Periventricular leukomalacia	295	0					.035
Yes			4	16.0	21	84.0	
No			100	37.0	170	63.0	

antibiotic treatment for 5 days or less and 21 (84%) of them were treated for more than 5 days ($P=.035$) (Tables 1 and 3).

3.4. Interventional factors

Umbilical vein catheter (UVC) and peripherally inserted central catheter (PICC) were associated with the duration of antibiotic treatment. Among the infants who underwent UVC ($n = 224/295$, 75.9%), a significant difference ($P=.047$) was observed between the percentage of those who received the treatment for 5 days or less (72; 32.1%) and who received the treatment for more than 5 days (152; 67.9%). Infants who underwent PICC were 53, among which three (5.7%) received the treatment for 5 days or less and 50 (94.3%) received the treatment for more than 5 days ($P < .001$). It was observed that the use of PICC and UVC was not associated with the duration of antibiotic treatment ($P=.944$).

3.5. Adverse outcomes

LOS was associated with the duration of early empiric antibiotic use. Among infants with LOS ($n = 54/295$), four (7.4%) of them received antibiotic treatment for 5 days or less and 50 (92.6%) of them received antibiotic treatment for more than 5 days ($P < .001$). In addition, both positive blood culture result ($P < .001$) and bacterial resistance ($P=.013$) were associated with the duration of antibiotic treatment. Approximately 91.2% of those receiving treatment for prolonged duration had positive blood culture result, and all the infants with bacterial resistance were receiving prolonged therapy. NEC was more prevalent in those with a long duration of antibiotic treatment (95.1%) than in those with a short duration of treatment ($P < .001$). Candidiasis was insignificantly ($P > .05$) more prevalent in those with a long duration of antibiotic treatment (Table 4) than in those with a short duration of treatment. The survival percentage reached 78.3%, among which 70% had a prolonged duration of antibiotic therapy.

Table 4
Adverse outcomes.

	Valid	Missed	Duration of antibiotics				P value
			Five days or less		More than five days		
			n	%	n	%	
Type of sepsis	295	0					
EOS			1	20.0	4	80.0	.66
LOS			4	7.4	50	92.6	< .001
Positive blood culture	295	0					< .001
Yes			5	8.8	52	91.2	
No			99	41.6	139	58.4	
Bacterial resistance	65	0					.013
Yes			0	0.0	32	100.0	
No			6	18.2	27	81.8	
Candidiasis	295	0					.418
Yes			0	0.0	2	100.0	
No			104	35.5	189	64.5	
Necrotizing enterocolitis	295	0					< .001
Yes			5	4.9	97	95.1	
No			99	51.3	94	48.7	
Mortality	295	0					< .001
Yes			36	56.3	28	43.7	
No			68	29.4	163	70.6	

Table 5
Other factors.

	Valid	Missed	Five days or less		More than five days		P value
			Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
			Gestational age in weeks	277	18	28.9 (3.6)	
Birth weight	277	18	1133.7 (337.2)	1170 (585)	1130.1 (266.2)	1137.5 (419)	.864
Hospital stay in days	277	18	11.5 (14)	4 (16)	46.5 (29.3)	43 (42.5)	< .001
Temperature	277	18	36.1 (0.9)	36.4 (0.6)	36.1 (2.8)	36.3 (0.7)	.379
Blood loss at week 1 per Kg body weight	277	18	1.9 (5.3)	0 (0)	6 (12)	0 (8.94)	.003
Packed RBCs transfusion	277	18	0.5 (0.9)	0 (1)	3.1 (3.7)	2 (5)	< .001
Platelets transfusion	277	18	0 (0.2)	0 (0)	1.2 (3.1)	0 (1)	< .001
Fresh frozen plasma transfusion	277	18	0.2 (0.5)	0 (0)	0.7 (1.7)	0 (1)	.007

3.6. Other factors

Data of premature neonates who received antibiotics for 5 days or less and those who received antibiotics for more than 5 days with regard to hospital stay in days were mean (SD) 2811.5 (14) and median (IQR) 4 (16). There was also a significant difference between those who received antibiotics for 5 days or less and those who received antibiotics for more than 5 days with regard to blood loss ($P = .003$), packed RBC transfusion ($P < .001$), platelet transfusion ($P < .001$), or fresh frozen plasma transfusion ($P = .007$; Table 5).

4. Discussion

The main objective of the study was to assess the association between the duration of early empiric antibiotic treatment for suspected neonatal sepsis and other factors including comorbidities, interventions, and adverse outcomes. Prolonged treatment with empiric antibiotics is associated with adverse outcomes including invasive candidiasis, increased antimicrobial resistance, NEC, LOS, and death. However, the choice of antibiotic or duration of empiric antibiotic treatment is often not associated with risk factors for sepsis [8]. Our study was conducted for a period of 24 months. The total number of the population with suspected neonatal sepsis admitted to the NICU was 323.

Throughout the study, a higher percentage of infants with PDA, IVH, and PVL received antibiotic treatment for more than 5 days. Our data showed that prolonged treatment with antibiotics is

associated with increased risk of NEC and death. Results showed that prevalence of infants with NEC reached 95.1% within the study population. The study conducted by Michael Cotten et al. [5] assessed the association between the duration of the initial antibiotic course and subsequent NEC or death among 5693 ELBW infants across 19 centers. They reported that 4039 infants survived (71%), 2147 of which (53%) had received prolonged (>5 days) empiric antibiotic treatment [5]. On the other hand, our study showed that 70% of premature infants who survived were on prolonged treatment of antibiotics.

In the multicenter study by Ying Dong [4], 5693 ELBW infants with sterile cultures started empiric antibiotic treatment within the first 3 days postdelivery; the initial median duration of empiric antibiotic treatment was 5 (3–9.5) days. Additionally, the study revealed that each additional day of antibiotic treatment was accompanied by increased risk of NEC or death, which accounts to an increase by 7% in NEC and by 16% in death [4]. A multicenter retrospective cohort study examined 790 ELBW infants with regard to the duration of empiric antibiotic therapy for EOS. The dataset was classified into two groups: infants who received ≤ 3 days of empiric antibiotic therapy and those who received ≥ 7 days. Out of the total population, 695 infants had negative culture results, among which 40% received ≤ 3 days of therapy and 34% received ≥ 7 days of therapy [7].

In a retrospective cohort study conducted by Venkata S. kuppala et al., of the 365 infants who survived 7 days free from NEC or sepsis, 36% had received prolonged initial empiric antibiotic

treatment. Approximately 17 infants (4.6%) were diagnosed with NEC and 20 (5.5%) died. Moreover, they found that 76 (21%) infants in the study population had LOS. LOS, NEC, or death occurred more frequently in the group that received prolonged antibiotic treatment than in the limited antibiotic treatment group [9]. In our study, LOS was also associated with prolonged antibiotics therapy (>5 days); among LOS infants, 50 (92.6%) received antibiotic treatment for more than 5 days. In another study by Sobaih et al. [2], the rate of neonatal sepsis in VLBW infants was found to be high (48%) with high rates of both EOS and LOS. This necessitates highly prioritizing the prevention and control of sepsis [2].

To conclude, both positive blood culture result and bacterial resistance were associated with the duration of early empiric antibiotic treatment. There was also an association between prolonged antibiotic treatment (>5 days) and comorbid conditions (PDA, IVH, and PVL). However, no association with other adverse outcomes such as candidiasis or maternal factors was found.

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Conflicts of interest

None declared.

Consent for publication

Not applicable.

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