Antibiotic Therapy for Very Low Birth Weigh Newborns in NICU

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Abstract

Background: Prolonged empiric antibiotics therapy in neonates results in several adverse consequences including widespread antibiotic resistance, late onset sepsis (LOS), necrotizing enterocolitis (NEC), prolonged hospital course (HC) and increase in mortality rates.

Objectives: To assess the risk factors and the outcome of prolonged empiric antibiotic therapy in very low birth weight (VLBW) newborns.

Materials and Methods: Prospective study in VLBW neonates admitted to NICU and survived > 2 W, from July 2011 - June 2012. All relevant perinatal and postnatal data including duration of antibiotics therapy (Group I < 2W vs Group II > 2W) and outcome up to the time of discharge or death were documented and compared.

Results: Out of 145 newborns included in the study, 62 were in group I, and 83 in Group II. Average duration of antibiotic therapy was 14 days (range 3 - 62 days); duration in Group I and Group II was 10 ± 2.3 vs 25.5 ± 10.5 days. Hospital stay was 22.3 ± 11.5 vs 44.3 ± 14.7 days, respectively. Multiple regression analysis revealed following risk factors as significant for prolonged empiric antibiotic therapy: VLBW especially < 1000 g, (P < 0.001), maternal Illness (P = 0.003), chorioamnionitis (P = 0.048), multiple pregnancy (P = 0.03), non-invasive ventilation (P < 0.001) and mechanical ventilation (P < 0.001). Seventy (48.3%) infants developed LOS; 5 with NEC > stage II, 12 (8.3%) newborns died. Infant mortality alone and with LOS/NEC was higher in group II as compared to group I (P < 0.002 and < 0.001 respectively).

Conclusions: Prolonged empiric antibiotic therapy caused increasing rates of LOS, NEC, HC and infant mortality.

Keywords: VLBW, Newborns, Antibiotics

1. Background

Antibiotics are the most common medications prescribed in a neonatal intensive care unit (NICU) (1). Pioneering efforts of fleming, florey and chain led to the introduction of Penicillin, the first antibiotic (AB) and truly a 'wonder drug' for treatment of infections that would normally have resulted in certain death (2). It was Luis Pasteur who in 1889, first coined the term 'antibiotic' derived from 'antibiosis', meaning an 'association between organisms that is harmful to one of them'. Later observations have shown that not only antibiotics kill microorganisms, but these drugs may be potentially dangerous for human beings, (especially newborns) as well (3).

One of the challenges faced by the neonatologists is how to deal with prolonged utilization of antibiotics in the NICU. Studies have revealed that 95% of newborns in NICUs (4), 65% of extremely low birth weight infants (ELBW), and 50% of low birth weight neonates (LBW) receive parenteral antibiotics for more than 3 - 5 days despite negative culture results (5). This practice leads to an increase in antibiotic resistance, late onset sepsis, development of fungal infections, outbreaks of various infections in the NICU, prolonged hospital stay, escalating costs and finally infant mortality (3, 6, 7). On the other hand, not giving antibiotics when needed in neonatal sepsis, may increase infant mortality rate up to 20% in LBW infants (8). It is a fact that the mortality rate in neonates with systemic infection is up to 3 times higher than in non-infected babies (9).

Although all experts agree about the necessity of starting antibiotics in sick neonates with positive cultures; there is a great diversity in opinion and practices in different neonatal centers regarding the initiation and duration of antibiotics in newborns with suspected sepsis or negative cultures. This diversity may be partly accounted for the presence of various risk factors, like pre-eclampsia, chorioamnionnitis, Apgar score < 6, baby's gender, LBW, low gestational age, infant feeding, need for inotropes, mechanical ventilation (MV) and/or surfactant (surf) (3).

2. Objectives

This study was done to assess the risk factors for prolonged empiric antibiotic therapy in VLBW newborns and to compare the outcome in patients receiving less than 2 weeks of anti-bacterials with those given > 2 weeks, in the tertiary level NICU in Tehran.

3. Materials and Methods

This was a prospective study in which all VLBW neonates hospitalized in the Mahdieh hospital between July 2011 and June 2012 were included. Mahdieh is a tertiary level perinatal center in Tehran, capital of Iran, affiliated with Shahid Beheshti University of Medical Sciences (SBUMS), with a 39-bed NICU and 5000 deliveries per year. Criteria for inclusion were: admission within 24 hours after birth, surviving more than 14 days, no major congenital anomaly or chromosomal disorder. This study was approved by committee of medical ethics at SBUMS. Parental consent for the study on babies was obtained.

Demographic and other relevant information regarding the mothers and neonates was documented on a pre-designed questionnaire. Neonatal data included birth weight, gender, gestational age, details of early and late onset sepsis, (EOS and LOS), need for mechanical ventilation, type and duration of the administered antibiotics, clinical course, development of complications including necrotizing enterocolitis (NEC), duration of hospital course and the final outcome.

Sepsis was diagnosed on the basis of CDC criteria (3); EOS as positive cultures from a normally sterile site during the first 3 days of life and LOS as positive cultures between day 4 and day 120. Classification of sepsis as possible, if only clinical manifestations were present, probable; clinical signs plus a positive CBC score; WBC < 4,000 or > 20,000, immature to total neutrophil ratio I/T > 0.2, or positive C-reactive protein (CRP $\geq$ 2$^+$) and definite, clinical signs plus positive cultures (3, 7). NEC was graded according to Bell et al. criteria (10), Intra ventricular hemorrhage (IVH) as Papilla staging (11) and retinopathy of prematurity (ROP) on the basis of international classification (12).

Sepsis work-up was done on all neonates. Ampicillin and gentamicin (Cefotaxime and Amikacin in those with MV $\pm$ SURF) was started on admission. If the culture results were positive after 72 hours, antibiotics were continued for 10 days; in babies with negative cultures, decision to discontinue antibiotics was made on the basis of clinical and para-clinical (chest X-ray, CBC, CRP, etc.) findings. Neonates were then categorized in two groups I and II (GI and GII) according to the duration of antibiotic therapy. GI received antibiotics for < 14 days and GII for > 14 days. Risk factors for prolonged antibiotic therapy as well as the final outcome were compared between the two groups.

Course of antibiotics was defined according to the frequency antibiotics were changed, for example if a patient was first put on ampicillin and gentamicin, then changed to amikacin + cefotaxime, and later vancomycin was added, this patient would be regarded as having received 3 courses of antibiotics.

3.1. Statistical Methods

Predictor variables of prolonged antibiotic prescription were evaluated by logistic regression analysis. For detecting potential confounding factors bivariate analyses (simple logistic regression) were performed and those with at least P value < 0.20 selected for multiple logistic regression analysis with forward stepwise method. The statistical level of significance was set at less than 0.05.

4. Results

Of 754 newborns admitted to NICU during the study period (July 2011 - June 2012), 184 were VLBW infants. One baby was discharged against medical advice, and 38 infants died before 14 days of age; data of 145 neonates were included in the final analysis. 104 were inborn, 117 had been delivered by cesarean section and 48.9% were male.

Mean gestational age was 31.26 $\pm$ 2.47 vs 29.1 $\pm$ 2.2 weeks and mean birth weight was 1287.88 $\pm$ 173.76 vs 1136.75 $\pm$ 212.37 g respectively in GI and GII.

Group I, consisted of 62 neonates with < 2 weeks of antibiotic therapy and GII; 83 neonates, which administered antibiotics for > 2 weeks (62 infants for 2 - 4 weeks and 21 babies for > 4 weeks).

Antibiotic courses were prescribed in different combinations; 50 neonates had received 1 course, 34 were given 2 courses; 30 were administered 3 courses, and 31 had been treated with $\geq$ 4 antibiotic courses (Tables 1 - 3).

Antibiotics were discontinued after a negative sepsis work-up in asymptomatic newborns, Duration of antibiotics free treatment in 51 infants was < 2 weeks, 63 newborns received it for > 2 weeks, and 13 for > 4 weeks, In 18 (12.4%) newborns AB had to be restarted 3 - 26 days after its discontinuion.

Antibiotics were restarted or changed during the hospital stay of 70 (48.2%) newborns with a diagnosis of LOS, (possible sepsis: 29, probable sepsis: 6, definite sepsis: 8, meningitis: 2, pneumonia: 20 and 5 with NEC). Only 5 of these neonates belong to GI and other 65 were in GII.

During 4901 hospital days, newborns received antibiotics for 2738 days (AD = antibiotic days = 55.9%) while 2163

Table 1. Patients' Characteristics (Part 1)[a]

Characteristics	Duration[b]		Total (n = 145)
	≤ 2 (n = 62)	> 2 (n = 83)	
Birth weight, g			
≤ 1000	2 (7.14)	26 (92.86)	28 (19.31)
1001 - 1250	22 (41.51)	31 (58.49)	53 (36.55)
1251 - 1500	38 (59.38)	26 (40.63)	64 (44.14)
Gestational age, w			
≤ 28	8 (18.18)	36 (81.82)	44 (30.34)
29 - 32	36 (46.75)	41 (53.25)	77 (53.1)
> 32	18 (75)	6 (25)	24 (16.55)
Sex (Female)	28 (37.84)	46 (62.16)	74 (51.03)
Birthplace (inborn)	45 (43.27)	59 (56.73)	104 (71.72)
Delivery type (NVD)	9 (32.14)	19 (67.86)	28 (19.31)
Gravidity			
Single	35 (42.17)	48 (57.83)	83 (57.24)
Twins	15 (34.09)	29 (65.91)	44 (30.34)
Triplet and more	12 (66.67)	6 (33.33)	18 (12.41)
Maternal disease	33 (50)	33 (50)	66 (45.52)
PROM ± Chorioamnionitis	7 (33.33)	14 (66.67)	21 (14.48)
Maternal antibiotic	51 (46.79)	58 (53.21)	109 (75.17)
Antenatal steroids	62 (42.76)	83 (57.24)	145 (100)
Apgar/1' (≤ 6)	15 (31.25)	33 (68.75)	48 (33.1)
Apgar/5' (≤ 6)	0	5 (100)	5 (3.45)

Abbreviations: NVD, normal vaginal delivery; PROM, premature rupture of membrane.
[a]Values are expressed as No. (%) or mean ± SD.
[b]Duration of antibiotic therapy, wk.

Table 2. Patients' Characteristics (Part 2)[a]

Characteristics	Duration[b]		Total (n = 145)
	≤ 2 (n = 62)	> 2 (n = 83)	
CPR	11 (23.91)	35 (76.09)	46 (31.72)
RDS	33 (34.38)	63 (65.63)	96 (66.21)
NCPAP/ NIV	18 (20)	72 (80)	90 (62.07)
INSURE	5 (21.74)	18 (78.26)	23 (15.86)
MV ± SURF	7 (12.07)	51 (87.93)	58 (40)
LOS (Late onset sepsis)	5 (7.14)	65 (92.86)	70 (48.28)
Age at late onset sepsis (During 1st 14 days)	5 (10.64)	42 (89.36)	47 (32.41)
NEC (Stage ≥ 2)	1 (20)	4 (80)	5 (3.45)
IVH (>GII)	0	6 (100)	6 (4.14)
ROP (Stage ≥ 1)	2 (5.88)	32 (94.12)	34 (23.45)
TPN day			
mean ± SD	11.47 ± 4.74	24.12 ± 9.5	18.83 ± 9.97
Range	4 - 27	7 - 48	NA
IV day			
mean ± SD	13.76 ± 5.32	28.67 ± 10.05	22.52 ± 10.98
Range	3 - 29	15 - 62	NA
Free AB day	14.90 ± 8.79	14.89 ± 10.49	14.9 ± 9.77
Total AB day			
mean ± SD	9.96 ± 2.28	25.52 ± 10.59	18.88 ± 11.2
Range	3 - 14	15 - 62	NA

Abbreviations: CPR, cardio pulmonary resuscitation; NA, not available; RDS, respiratory diseases syndrome.
[a]Values are expressed as No. (%) or mean ± SD.
[b]Duration of antibiotic therapy, wk.

days were antibiotic free (AF). This set in relatiion to duration of hospital course (HC) renders: AD: HC = 0.5, AF: AD = 0.8 and AB/1000 PD (patient days) = 547 (13).

In patients with LOS, 61 infants had abnormal white blood cell counts (WBC), either < 4000 μL or > 20,000 μL, CRP ≥ 2[+] in 21 cases, blood culture positive for Staphylococcus. sapprophyticus in 8 and cerebro-spinal fluid (CSF) positive for Acinetobacter in 2 infants.

The 5 patients with NEC had been born with birth weight ranging between 840 - 1149 g and gestational age of 27 - 31 weeks and enteral feeding had been started in all except a 840 g baby who did not survive. NEC was graded as stage II in 2 infants and as stage III in 3 newborns 4 of whom were in GII.

Twelve of 145 (8.3%) infants died; 5 with ventilator associated pneumonia (VAP), 3 with sepsis, meningitis, 1 with

NEC, 1 severe RDS, and 1 with cardio-pulmonary arrest during central venous line (CVL) insertion. Birth weight of these patients was 570 - 1320 g with gestational age of 25 - 31 weeks, and duration of antibiotic therapy between 15 - 39 days (all in GII).

RDS developed in 96 (66.2%) neonates, nasal continuous positive airway pressure (NCPAP)/non-invasive ventilation (NIV) was used for respiratory support in 90, INSURE (INtubation, SURFactant administration, Extubation) in 23, MV ± SURF in 58 patients. MV duration was < 24 hours in 21 cases, 2 - 7 days in 19 neonates, 7 - 14 days in 7 and > 2 weeks in 11 infants; 87.9% of infants in the MV group belonged to G II (Tables 1 - 3).

Statistical analysis revealed that in children with LOS, mortality was significantly higher in GII as compared to GI, (P < 0.001). This difference was seen both in mortality and LOS per se and also in mortality with LOS/NEC (Table 4).

Table 3. Patients' Characteristics (Part 3)[a]

Characteristics	Duration[b]		Total (n = 145)
	≤ 2 (n = 62)	> 2 (n = 83)	
Death after 14th day of life (DOL14)	0	12 (100)	12 (8.28)
Death/NEC (≥ 2) after 14th day of life (DOL14)	1 (6.25)	15 (93.75)	16 (11.03)
Death/NEC (≥ 2)/LOS after 14th day of life (DOL14)	3 (4.41)	65 (95.59)	68 (46.9)
Ampicilin + Gentamycin	39 (62.9)	23 (37.1)	62 (42.76)
Cefotaxim + Amikacin	22 (25.58)	64 (74.42)	86 (59.31)
Cefotaxim + Vancomycin	3 (11.54)	23 (88.46)	26 (17.93)
Ceftazidim + Vancomycin	0	25 (100)	25 (17.24)
Meropenem + Vancomycin	0	10 (100)	10 (6.9)
Hospital Course, w			
< 2	10 (100)	0	10 (6.9)
3 - 4	29 (61.7)	18 (38.3)	47 (32.41)
> 5	23 (26.14)	65 (73.36)	88 (60.69)

[a] Values are expressed as No. (%) or mean ± SD.
[b] Duration of antibiotic therapy, wk.

Table 4. Association of Different Neonatal Outcomes With Duration of Antibiotic Therapy[a]

Characteristics	Duration, w		P Value
	≤ 2 (n = 62)	> 2 (n = 83)	
Death after 14th day of life (DOL14)	0	12 (14.46)	0.002
Death/NEC (≥ 2) after 14th day of life (DOL14)	1 (1.61)	15 (18.07)	0.002
Death/NEC (≥ 2)/LOS after 14th day of life (DOL14)	3 (4.84)	65 (78.31)	< 0.001
NEC (≥ stage 2)	1 (1.61)	4 (4.82)	0.39
LOS (Late onset sepsis)	5 (8.06)	65 (78.31)	< 0.001
Age at late onset sepsis (> 10 day)	0	38 (45.78)	< 0.001

[a] Values are expressed as No. (%).

Simple regression analysis revealed that multiple pregnancy, low gestational age, (especially < 28 weeks), VLBW (especially < 1000 g), low one-minute Apgar score (< 6), need for resuscitation at birth, RDS, NCPAP/NIV and MV had a positive association with prolonged antibiotic therapy (Table 5).

Table 5. Simple Logistic Regression

Characteristics	Adjusted OR	95% CI for OR	P Value
Birth weight, g			
1001 - 1250 vs. ≤ 1000	0.05	0.01 - 0.24	< 0.001
1251 - 1500 vs. ≤ 1000	0.11	0.02 - 0.50	0.005
Gestational age, w			
29 - 32 vs ≤ 28	0.25	0.10 - 0.61	0.002
> 32 vs ≤ 28	0.07	0.02 - 0.25	< 0.001
Sex (female)	1.51	0.78 - 2.93	0.22
Maternal disease	0.58	0.30 - 1.13	0.11
PROM ± Chorioamnionitis	0.63	0.24 - 1.66	0.35
Delivery type (C/S)	0.57	0.24 - 1.37	0.21
Multiple Pregnancy			
Twins vs single	1.41	0.66 - 3.02	0.38
Triplet and more vs single	0.36	0.12 - 1.07	0.07
Apgar 1 (≤ 6)	2.07	1.00 - 4.29	0.05
CPR	3.38	1.54 - 7.40	0.002
RDS	2.77	1.36 - 5.62	0.005
NCPAP/NIV	16.00	6.92 - 37.01	< 0.001
INSURE	3.16	1.10 - 9.05	0.03
Mechanical ventilation	5.84	2.84 - 12.03	< 0.001
NEC (≥ stage II)	3.09	0.34 - 28.34	0.32

In multiple regression analysis the following variables showed a significant association with prolonged antibiotic therapy: VLBW (especially < 1000 g): OR = 0.02, CI = 0.001 - 0.16, P < 0.001; NCPAP/NIV: OR = 13.93, CI = 3.97 - 48.88, P < 0.001 and MV with/without surfactant administration: OR = 57.65, CI = 15.44 - 296.52, P < 0.001. In addition maternal illnesses, prolonged rupture of membranes ± chorioamnionitis and multiple pregnancy were found to be positively related to prolonged antibiotic therapy (Table 6).

Figure 1 shows the positive association between duration of antibiotic therapy and prolonged stay in the hospital, (Pearson correlation coefficient = 0.75, P value < 0.001).

5. Discussion

Neonatal sepsis leads to an increase in infant mortality (14). In industrial countries the incidence of EOS is 11/1000 in VLBW newborns and 21% develop LOS (15) amounting 246,000 episodes per year. This figure is 3 millions per year in the developing countries! Studies about neonatal mortality have revealed that 99% of neonatal mortality reports are from the developing countries (5) and 25% of newborn

Table 6. Multiple Logistic Regression With Forward Stepwise Method

Characteristics	Adjusted OR	95% CI for OR	P Value
Birth weight, g			
1001 - 1250 vs ≤ 1000	0.02	0.001 - 0.16	< 0.001
1251 - 1500 vs ≤ 1000	0.04	0.004 - 0.38	0.005
NCPAP/ NIV vs none	13.93	3.97 - 48.88	< 0.001
MV ± Surf + NCPAP/NIV vs none	67.65	15.44 - 296.52	< 0.001
Maternal disease	0.15	0.05 - 0.52	0.003
PROM ± Chorioamnionitis	5.72	1.02 - 32.15	0.048
Multiple. Pregnancy			
Twins vs single	1.23	0.39 - 3.87	0.72
Triplet and more vs single	0.16	0.03 - 0.82	0.03
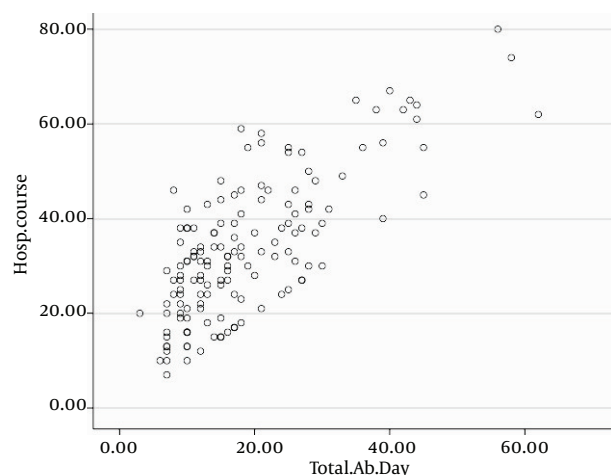
Figure 1. Antibiotic Duration and Hospital Course in Our Study

deaths occur due to infections (16). These figures underscore the necessity of early empiric antibiotic therapy in VLBW infants as they are prone to serious infections because of an immature immune system and various invasive procedures (7, 8). However, if culture results are negative and the infant remains asymptomatic, it is recommended to discontinue antibiotics after 3 - 7 days, and the baby should not be administered prolonged empiric antibiotics (3, 4, 6, 7, 14, 17-19).

The fact remains that in several neonatal centers antibiotics are continued for long periods with frequent changes (17, 20). Reasons given for this practice include: prematurity (5), admission to NICU (4), intravenous line (21), difficulties in diagnosis of definite sepsis (22), high rate of negative cultures despite positive clinical manifes-

tations (3-5, 13), abnormal results on CBC score/CRP (3, 18, 23), diagnosis of LOS on the basis of clinical manifestations (24), and the presence of risk factors for systemic infections like the birth weight (BW), MV etc. (6).

Several studies have shown that the most important factor governing the duration of empiric antibiotic therapy is the prescribing practices adopted in different centers (3, 4, 6, 16, 18, 25, 26).

Cotton et al. report that in 27% - 85% of neonatal centers empiric antibiotics have been administered for > 5 (up to 36) days to neonates with negative cultures (6). In Stark et al. study done in 2 different hospitals, duration of antibiotic therapy in one center was twice that of the other center (27). The main challenge is not starting AB, but its continuation without any evidence (17, 20).

Keeping in mind the adverse effects of prolonged empiric antibiotic therapy (2) we performed this prospective study. We informed all health care staffs in our center about meeting the necessary criteria before diagnosing systemic neonatal infections (5, 23) also the type of antibiotics (4) and the optimal duration of treatment (19). Next we introduced the policy of discontinuing antibiotic therapy in asymptomatic VLBW newborns with normal paraclinics results and negative cultures. Because of the delay in getting test results and also relative lack of the nursing personnel and limited resources, we admitted > 2 weeks of antibiotic treatment (vs 3 - 7 days as described by authors in developed countries) (3) as marker of prolonged empiric antibiotic therapy. This paper gives the results regarding the hospital course, duration and course of antibiotics, the reduction in antibiotic consumption, hospital stay and infant mortality during the first year after adopting this policy.

In this study only 10 (6.9%) infants had positive cultures but 83 (57.2 %) neonates received antibiotics for > 2 weeks. In all other cases (135 neonates), antibiotics were started and continued on the basis of clinical and para-clinical findings.

In different studies the risk factors cited for continuation of prolonged empiric antibiotics have been categorized into 2 groups: perinatal (maternal complications, especially PROM, multiple pregnancy, cesarean delivery) and neonatal (low gestational age, LBW, Apgar score < 6 at 1 or 5 minutes, neonatal resuscitation, RDS, mechanical and/or non-invasive ventilation, use of surfactant, LOS, total parenteral nutrition, surgery, etc.) (1, 2, 6, 7, 9, 25, 28, 29).

Similar to other researches, VLBW, especially < 1000 g was recognized as a significant risk factor for prolonged continuation or repeated changes in empiric antibiotics in our study (1, 3, 9). As regards NIV and MV ± SURF, our results are similar to those found by Clark et al. (1), Cotton et al. (6), Kuppala et al. (3) and Bizzarro et al. (29) and as regards ma-

ternal illnesses, multiple pregnancy and chorioamnionitis, our risk factors are similar to those of Cotten et al. (6) and Abdel Ghany and Ali (25).

Two major risk factors leading to prolonged antibiotic therapy were MV (40%), and LOS (48.28%). In the 58 children receiving MV ± SURF. Antibiotics were continued for 7 - 62 days with a mean duration of 24.01 days. In addition, 20 of them developed ventilator associated pneumonia (VAP) (30) and 5 died.

Looking at these figures it seems that intubation and ventilation are the most salient risk factors leading to prolongation of antibiotic treatment and adverse outcomes. It can be concluded that avoidance of mechanical ventilation unless absolutely necessary, utilizing non-invasive ventilation (31) as much as possible, and quality improving care (QIC) for infection-controlling measures should be the foremost strategy in order to prevent adverse outcomes in NICU (21).

In different neonatal centers prevalence of LOS has been estimated to be between 7 and 24% (8, 9, 22, 32), in VLBW newborns these figures have been recorded as 20% from the United States in 2007 (33) and Stoll et al. (9) quote a figure of 21%. On the other hand, Vain et al. report the prevalence of LOS in developing countries as multiple as that of industrial countries (34). So, prevalence of 48% in our study is of concern and demands revising existing infection-control policies in our center in order to decrease the rate of hospital acquired infection. The mean age of acquiring LOS in our patients was 13 days in contrast to 17 days reported by Wynn et al. (32). The rate of LOS in GI was 67% and in GII 92.8%, which is similar to the results of Cotten et al. (6).

In our study, mortality after 14 days of age was seen only in GII, which may be due to various risk factors including underlying illness, systemic infection or from complications of prolonged empiric antibiotics therapy. In the studies performed by Cotten et al. (6) and Abdel Ghany and Ali (25) prolonged antibiotic therapy was associated with increase in mortality rates, and Hornik et al. (26) reported twice as much mortality in neonates with LOS.

It is important that for making rational decisions about initiating and discontinuing antibiotics, modern diagnostic tests like automated blood cultures, leukocyte indices, leukocyte cell surface markers and certain pro inflammatory cytokines, serum acute phase reactants are urgently needed to diagnose the presence or absence of systemic infections (3). In the meantime a lot can be achieved by introducing an effective antibiotic stewardship program (ASP) (35-37).

In summary, as far as we know, this was the first trial to stop AB in VLBW of NICU in our country, that was fairly successful (AB/1000 pd = 547). We hope by this experiment and QIC, to report better results in future.

Limitations in our study were quality of laboratory tests especially high rate of negative blood cultures (Bactec was not available) and limited positive CBC scores.

Our study indicates that prolonged empiric antibiotic therapy leads to an increase in the prevalence of LOS, NEC, hospital course and mortality in VLBW neonates, so it is desirable to discontinue empiric antibiotics as soon as it is feasible; however, a decision on optimal duration of empiric antibiotics can only be made if and when the many faceted problems of diagnosing and managing neonatal infections (Conundrum) have been solved (38).

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Footnote

Authors' Contribution: Study concept and design: Seyyed-Abolfazl Afjeh, Mohammad Kazem Sabzehei; acquisition of data: Fatemeh Esmaili, and Ahmad Reza Shamshiri; analysis and interpretation of data: Seyyed-Abolfazl Afjeh, and Ahmad Reza Shamshiri; drafting of the manuscript: Seyyed Abolfazl Afjeh , Mohammad Kazem Sabzehei, and Farideh Shiva; critical revision of the manuscript for important intellectual content: Seyyed Abolfazl Afjeh, Mohammad Kazem Sabzehei , and Seyyed Ali Reza Fahimzad; statistical analysis: Ahmad Reza Shamshiri; administrative, technical, and material support: Seyyed Abolfazl Afjeh, Mohammad Kazem Sabzehei, and Seyyed Ali Reza Fahimzad; study supervision: Seyyed Abolfazl Afjeh.

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