IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Prevalence of Urinary Tract Infections in Term and Preterm Neonates with Prolonged Jaundice

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ABSTRACT

Background: Our objective is to find out the prevalence of urinary tract infections (UTI) among neonates with prolonged jaundice, and to review their clinical characteristics, causative microorganisms, treatment used, and underlying renal structural abnormalities.

Methods: This is a retrospective cross-sectional study of neonates with prolonged jaundice over a 5-year period at Jordan University Hospital. The study included term and preterm neonates less than 5 weeks of age with prolonged hyperbilirubinemia which was defined as persistent elevation of serum bilirubin of more than 8 mg/dl in term neonates more than two weeks of age and more than three weeks for the preterm neonates.

Results: 280 newborns had prolonged jaundice and the majority were full term. The two most common causes for prolonged jaundice were urinary tract infection and breast milk jaundice. The prevalence of urinary tract infection in our study was high, reaching 33.9 %. Escherichia coli was the most common organism in neonates with UTI. Renal anomalies were detected in 9.5%. In term neonates, the mean age of presentation and the highest bilirubin levels recorded were significantly higher in neoantes with prolonged jaundice caused by UTI compared to other cause of prolonged jaundice ($p<0.05$).

Conclusion: Our study showed a high rate of UTI in neonates with prolonged jaundice especially in preterm neonates which necessitates appropriate screening and management of UTI in prolonged jaundiced neonates.

Keywords: Hyperbilirubinemia, Prolonged Jaundice, Urinary tract infection

Introduction

Neonatal jaundice or hyperbilirubinemia is one of a spectrum of conditions occurring in newborns within the first 2 weeks of life. The most affected group of newborns are the preterm newborns with 80% of them affected versus 60% of term newborns (1, 2). The most common etiology is physiological. However, prolonged jaundice is defined as persistent elevation of bilirubin levels of more than two weeks of age in term neonates and more than three weeks in preterm neonates (3, 4). Congenital hypothyroidism, urinary tract infections (UTI) Crigler-Najjar and hemolytic disorders are the common pathological causes leading to indirect prolonged jaundice while breastfeeding is considered a benign causative factor (5, 6). It was suggested that the bacteria causing UTI produce toxins that destroy red blood cells and leads to jaundice (7).

In fact, jaundice may be the only presenting sign in neonates with UTI (8). UTI incidence varies from 0.1 to 1% among all neonates (9, 10). The prevalence of UTI across multiple studies

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Please cite this paper as:
Albaramki JH, Hammad W, Barakat T, Al-Sanouri M, Hammad A, Khdair FA. Prevalence of Urinary Tract Infections in Term and Preterm Neonates with Prolonged Jaundice. Iranian Journal of Neonatology. 2025 Jul: 16(3). DOI: 10.22038/ijn.2025.76877.2496

among jaundiced neonates is variable and ranged between 5.8% and 21% (11–14).

In a meta-analysis by Tola et al the prevalence of UTI in prolonged jaundice was variable ranging from 0.6 to 53.9% with an average overall prevalence of 11 % (15), another study in Nepal showed a UTI prevalence of 18.9% (16). Therefore, urine culture is recommended for neonates with prolonged jaundice by AAP (American academy of pediatrics) & NICE (The National Institute for Health and Care Excellence). Nevertheless, many papers have discouraged urine culture due to the low incidence of UTI in different populations (17–19).

Our aim in this study is to find out the prevalence of UTI among neonates with prolonged jaundice, and to review their clinical characteristics, significant associations, causative microorganisms, treatment used, and underlying renal structural abnormalities. Other causes of prolonged jaundice will also be reviewed.

Methods

This is a retrospective cross-sectional study of neonates with prolonged jaundice who presented to the pediatric clinics at Jordan University Hospital between June 2016 and June 2021.The study included term and preterm neonates less than 5 weeks of age with prolonged hyperbilirubinemia which was defined as persistent elevation of serum bilirubin of more than 8 mg/dl in term neonates more than two weeks of age and more than three weeks for the premature neonates (5, 6) .

Term neonates were defined as newborns with a gestational age (GA) between 37 and 42 weeks. Preterm neonates were defined as newborns with a gestational age less than 37 weeks. Preterm newborns were divided further into groups: late preterm with GA less than 37 and ≥ 34 weeks, moderate preterm with GA less than 34 weeks and ≥ to 32 weeks and very preterm with GA less than 32 weeks and ≥ to 28 weeks. Data was collected from the patients' electronic medical records.

Data included clinical demographics as gender, birth weight; mode of delivery; gestational age; birth weight, feeding pattern whether the newborn is exclusively breast milk or is on mixed formula with breast milk; age of presentation of jaundice, presenting symptoms, hospitalization, use of phototherapy and antibiotics used for treatment of urinary tract infection. Antimicrobial resistance of the causative microorganisms was also studied. The causes of prolonged jaundice were analyzed. Furthermore, neonates with prolonged hyperbilirubinemia with UTI and neonates with prolonged hyperbilirubinemia and other causes were separated into different groups and these groups were compared regarding demographical and laboratory data.

Laboratory data included serum total and direct bilirubin levels, baby and mother blood groups and Rh, hemoglobin levels; white blood cells (WBC) , C-reactive protein (CRP) and reticulocyte count; renal function tests (creatinine); free T4 and thyroid-stimulating hormone (TSH) levels; glucose-6-phosphate dehydrogenase levels (G6PD); results of ultrasound and micturating cystourethrogram (MCUG); Urine samples for cultures were collected through sterile catheterization. Urine cultures of singe growth with counts more than or equal to 10,000 cfu were considered positive for UTI. Mixed growth cultures were repeated and cultured again and mixed growths on two repetitive urine cultures were considered positive for UTI.

Antimicrobial resistance was analyzed and extended spectrum beta lactamase producing (ESBL) organisms were recorded.

Data was analyzed using SPSS (version 26). Inclusion criteria for prolonged jaundice was applied and outlier data were deleted. Descriptive analysis was used to assess study variables including means, standard deviations, percentages, ranges, and frequencies. Finally, Chi-square and independent sample T-test were used to examine the categorical and scale variables. A p-value <.05 was considered significant in this study.

Ethical Approval

The study was conducted in accordance with the ethical regulations of the Declaration of Helsinki, and the study protocol was approved by the institutional review board (IRB) at Jordan University Hospital (ID number (376/2021)).

Results

Characteristics of newborns with prolonged jaundice

Our sample consisted of 280 jaundiced newborns with prolonged jaundice. 80% (n=224) of them were full term and 20% (n=56) were preterm. We found that the prevalence of UTI in newborns with prolonged jaundice was 33.9% (n=95), other causes included: G6PD deficiency 1%, (n=3), hypothyroidism0.35%, (n=1), ABO incompatibility 2.1%,(n=6) and breast milk jaundice 31.7%, (n=89), the cause of prolonged

Table 1. demographics of term and preterm neonates with prolonged jaundice

Term(N)			Preterm(N)		
Gender	224	Male Female	136(60.7%) 88(39.3%)	56	35(62.5%) 21(37.5%)
Nutrition	211	Breast milk Formula or mixed feeding	111(52.6%) 100(47.4%)	54	27(50%) 27(50%)
Delivery	189	Vaginal delivery Cesarean Section	94(49.7%) 95(50.3%)	40	13(32.5%) 27(67.5%)
Needed NICU admission.	224	Yes No	65(29%) 159(71%)	56	45(80.4%) 11(19.6%)
Needed phototherapy	224	Yes No	27(12.1%) 197(87.9%)	56	26(46.4%) 30(53.6%)

jaundice could not be identified in 19.6% (n=55), and in 11% (n=31) a urine culture wasn't performed.

Characteristics of full-term newborns with jaundice

80% of newborns with prolonged jaundice were full term (n=224) with a mean gestational age of 38.17 ± 0.92 weeks and mean birth weight of 3.08 kg ± 0.45. Majority of newborns were males (60.7%, n=136), and the average age of presentation was 18.27 days ± 5.3. 29% of the newborns had Neonatal intensive care unit (NICU) admission (n=65), mostly due to respiratory distress (37.7%, n=26), jaundice (17.3%, n=12), transient tachypnea of the newborn (8.6%, n=6), prolonged rupture of membrane (7.2%, n=5) and others. Detailed demographics are shown in table 1.

The prevalence of UTI in full-term newborns was 32.1 %(n=72) other causes included: G6PD deficiency in 0.9% (n=2), ABO incompatibility in 2.67% (n=6), breast milk jaundice in 33% (n=74). The cause of jaundice could not be identified in 20%, (n=45), and in 11.1% (n=25) urine culture wasn't performed.

Characteristics of preterm newborns with jaundice

The remaining 20% were preterm newborns (n=56), of which 45 were late preterm, 9 were moderate, 1 very and 1 extreme preterm. They had a mean gestational age of 35.07± 1.39 weeks and a mean birth weight of 2.42±0.488 kg. Majority of newborns were males (62.5%, n=35) and the average age of presentation was 24.2 ± 5.4 days (14 to 35). 80.4% of the newborns had NICU admission (n=45), mostly due to respiratory distress (53.3%, n=24), prematurity (24.4%, n=11), and jaundice (13.3%, n=6). Detailed demographics are shown in table 1.

41.1% of preterm newborns with prolonged jaundice had UTI (n=23), other causes included: G6PD deficiency1.8%,(n=1), hypothyroidism 1.8%, (n=1), and breast milk jaundice 26.7%, (n=15), the cause of jaundice could not be identified in 17.8% (n=10), and in 10.7% (n=6) a urine culture wasn't performed.

Characteristics of neonates with UTI

On further analysis of the 280 neonates, 95 (33.9%) neonates had a positive urine culture, 71 were males and 24 were females, 72 were full term and 23 were preterm. The mean age of presentation was 19.58 ±5.27 days for full-term and 22.35 ±5.1 days for preterm with an average birth weight of 2.42 ±0.53 kg for preterm and 3.04±.41 kg for full-term. Most of the newborns had a chief complaint of yellowish discoloration (99%, n=94). Other symptoms included vomiting (4.2%, n=4), diarrhea (5.2%, n=5), irritability (1.8%, n=2), hypoactivity (1.05%, n=1) and fever (2.1%, n=2). The mean total bilirubin at admission was 11.8± 4.8 mg/dl (11.7±4.8 mg/dl for full-term and 11.3 ± 4 mg/dl for preterm). The mean highest bilirubin levels measured was 13.22 ±5 mg/dl for full-term and 13.19 ± 3.3 mg/dl for preterm. The mean direct bilirubin was 0.75 ±0.44 mg/dl for full term and 0.64 ±0.17 mg/dl for preterm. All neonates with UTI had indirect hyperbilirubinemia and there was no evidence of hemolysis in UTI patients. The mean Hemoglobin level was 14.1 ±2.6 mg/dl, hematocrit of 41.3± 8.2%, WBC of 11.8± 2.8 and CRP of 2.9.

87.3% of the newborns had a renal ultrasound done (n=83), out of them 89.1% had normal ultrasound (n=74) and 9.5% had abnormal findings (n=9); 5 patients had bilateral hydronephrosis, 4 had unilateral hydronephrosis. MCUG was done in 13 patients in which only 1

Table 2. independent t test for scale variables comparing UTI neonates with other causes of prolonged jaundice

Demographic factors(mean)		Caused by UTI	Other causes	T test	P value
Age of presentation (days)	Term	19.58 ±4.8	17.52 ±5.4	-2.7	0.017
	Preterm	22.35 ±5.5	25.18 ±5.1	1.97	0.054
Gestational age (weeks)	Term	38.2 ±0.92	38.17 ±0.94	-0.15	0.88
	Preterm	35.29 ±1.56	35 ±1.27	-0.83	0.41
Birth weight (Kg)	Term	3.04 ±0.41	3.11 ±0.46	1.02	0.31
	Preterm	2.42 ±0.54	2.46 ±0.46	0.28	0.78
highest bilirubin level (mg/dl)	Term	13.22 ±4.97	11.04 ±3.53	-3.57	0.000
	Preterm	13.19 ±3.51	10.53 ±4.1	-2.43	0.19
mean bilirubin at admission (mg/dl)	Term	11.7 ±4.99	10.8 ±3.48	-1.6	0.11
	Preterm	11.3 ±3.25	9.7 ±2.92	-1.9	0.65

showed grade 1 vesicoureteric reflux . 22.7% of newborns had received phototherapy (n=25).

Quantitative analysis between neonates with UTI and neonates with other causes of jaundice showed a statistically significant difference between the mean age of presentation and the highest bilirubin levels recorded between the two groups ($p<0.05$) in term neonates only. Preterm neonates didn't show any similar correlation in these factors ($p=0.054$, $p=0.19$ respectively). Moreover, males were statistically significant to have UTI than females in term neonates ($p<0.05$). (table 2 and 3).

Urine culture characteristics and organisms

On the analysis of the 95 positive UTI patients, 28.4% of them had mixed growth (n=27) while the remaining 68 had single growth. The single growth cultures (n=68) had the following organisms: 35.2% was Escherichia coli (n=24), 20.5% was Enterobacteria species (n=14), 20.5% was Klebsiella pneumonia (n=14) Enterococcus 4.4% (n=3), 4.4% Streptococcus agalactiae (n=3), the remaining cultures were other gram-negative bacteria.

Antimicrobial therapy

Regarding antibiotic usage, 82 newborns received antibiotic regimen (86.3%) while 13 were lost follow up (13.6%). The most common antimicrobial agents were Amikacin alone (29.2%, n=24), or Amikacin with Ampicillin (23.2%, n=19), Ampicillin (7.3%, n=6) Carbapenems (9.7%, n=7), Vancomycin (1.2%, n=1) or combination between those antibiotics (37.8%, n=31). The average duration 6.89 ± 1.37.

When antimicrobial resistance for single growth cultures were analyzed, we found the

Table 3. Chi square test comparing categorical variables in UTI neonates with other causes of prolonged jaundice

Demographic factors n(%)			Caused by UTI	Other causes	Chi square	P value
Gender	Term	Male	55(40.4%)	81(59.6%)	10.28	0.001
		Female	17(19.8%)	69(80.2%)		
	preterm	Male	16(45.7%)	19(54.3%)	0.83	0.36
		Female	7(33.3%)	14(66.7%)		
Nutrition	Term	Breast milk	31(27.9%)	80(72.1%)	1.77	0.41
		Formula or mixed feeding	35(35%)	65(65%)		
	Preterm	Breast milk	12(44.4%)	15(55.6%)	0.31	0.58
		Formula or mixed feeding	10(37%)	17(63%)		
Delivery type	term	Vaginal delivery	20(21.3%)	74(78.7%)	0.66	0.42
		Cesarean Section	25(26.3%)	70(73.7%)		
	Preterm	Vaginal delivery	2(15.4%)	11(84.6%)	1.42	0.23
		Cesarean Section	9(33.3%)	18(66.7%)		
Needed NICU admission.	term	Yes	19(29.2%)	46(70.8%)	0.356	0.55
		No	53(33.3%)	106(66.7%)		
	Preterm	Yes	17(37.8%)	28(62.2%)	1.03	0.31
		No	6(54.5%)	5(45.5%)		
Needed phototherapy	Term	Yes	7(25.9%)	20(74.1%)	0.54	0.46
		No	65(33%)	132(67%)		
	preterm	Yes	12(46.2%)	14(53.8%)	0.52	0.47
		No	11(36.7%)	19(63.3%)		

following resistance pattern : 10/41 (24.4%) were resistant to Gentamycin ; 21/28 (75%) to Cefuroxime; 9/31 (29%) to Trimethoprim/ Sulfamethoxazole ; 11/21 (52.4%) to cefotaxime ; 13/23 (56.5%) to Ceftriaxone.; 1/26 (4%) to Amikacin ; 1/8 (12.5%) to Vancomycin ; (4.3%) to 1/23 Piperacillin/ Tazobactam. There was no resistance against Imipenem and meropenem. 13 (14.8%) of the bacteria were ESBL producing bacteria.

Discussion

Jaundice is a common problem in the neonatal period. It can be physiologic or pathological and prolonged. UTI is a known cause of prolonged neonatal jaundice (20–22), also unexplained jaundice can be an early sign of UTI. A study from Iran found UTI in 12.5% of asymptomatic jaundiced newborn less than 4 weeks of age (23), a prior study about neonatal UTI in Jordan University Hospital NICU revealed that the most common presenting symptom of UTI was prolonged jaundice which was seen in 53% of that cohort study (24). Therefore, investigations for UTI should be performed in neonates with prolonged jaundice. The aim of our study was to evaluate the different causes of prolonged jaundice, especially UTI prevalence and its characteristics.

The prevalence of UTI in our study was high reaching 33.9% compared to other studies. A meta-analysis in Iran found that the prevalence of UTI in Iranian neonates with prolonged jaundice was variable ranging from 0.5 to 53.9% with an overall pooled prevalence of 11 %, the 53.9% prevalence was high in one study because the studied sample was from the NICU, all the other 8 studies included in the meta-analysis had a prevalence of below 15% (15), another meta-analysis done in the United Kingdom showed that UTI prevalence in neonates with prolonged jaundice was ranging between 0-14.9%, included studies were further classified and showed that UTI prevalence in UK was 0.21% (0.0–0.73%) and it was significantly higher than non UK studies 8.21% (4.36–13.0%) (18). An observational study in Nepal showed that 18.9% of newborns with prolonged jaundice had UTI (16). Another study from Turkey revealed that UTI was detected in 20.7% of 226 neonates with prolonged jaundice (25). This variability in UTI prevalence among different studies may be due to the different population recruited and the definition of UTIs regarding the threshold number of colonies per unit and the inclusion or exclusion of mixed cultures, different methods of obtaining the urine sample such as urine bag, bladder or suprapubic catheterization may also play a role. The inclusion of two positive mixed culture and 10000 colonies in our cross-sectional study, may explain our high UTI prevalence, excluding mixed cultures in our study would lower the UTI prevalence to 24%.

Our study revealed that the prevalence of UTI in preterm neonates was higher compared to term neonates, 41.1% versus 32.1% respectively. This result is similar to the Iranian meta-analysis (UTI prevalence of 25% in preterm versus 13% in term neonates) and to the Nepali study (UTI prevalence of 33.3% in preterm versus 13.2% in term newborns) (15, 16). It is well known that preterm neonates are at more risk for urinary tract infections as they have reduced immunity compared to term neonates (26–28).

UTI was significantly associated with male gender in prolonged jaundice term neonates ($P<0.05$), the male to female ratio was 3:1 in term neonates with UTI. Many studies have also showed the same pattern (16, 23, 24), also a study in Lebanon showed that males were 2.366 more prone to having UTI than females (confidence interval [CI]: 1.173 – 4.774; $P = 0.016$) (29).

Escherichia coli was the most common organism in neonates with UTI in our study (35.2%) which is similar to several studies (13, 15, 16, 29), while Klebsiella pneumonia was the most common in other studies (12, 14, 23). We found a high resistance rate to several antimicrobial agents such as Cefotaxime (52.4%) and Ceftriaxone (56.5%), these local biogram numbers were found in a similar study on neonatal UTI in our hospital where 64% had resistance to third generation cephalosporins (24).

ESBL isolates were seen in 13% of UTI neonates which is similar to a recent systematic review and meta-analysis that showed a 14% pooled prevalence of pediatric UTI caused by ESBL producing Enterobacteriaceae in different countries (30).

In our study term neonates with UTI were significantly associated with the highest bilirubin levels reached compared to other causes of prolonged jaundice as in a study from Lebanon which showed maximum bilirubin level was higher in UTI positive neonates (mean 16.32 ± 5.17) in comparison to UTI negative (mean 14.81 ± 4.62) (29). This study also showed higher bilirubin levels at admission in UTI neonates. In a

study by Ozcan et al UTI was also associated with higher total (p=0.005) and direct bilirubin levels (p=0.001) (14).

The main cause of prolonged jaundice in our study was UTI, whereas breast milk jaundice was the second most common cause affecting 31.7% of neonates with prolonged jaundice. In many other studies, breast milk jaundice was the most common cause of prolonged neonatal jaundice where it was seen in 15-40% of neonates with prolonged jaundice (31–33). It is diagnosed after the exclusion of other pathological causes of hyperbilirubinemia and can be explained by some enzymes activity in breast milk that lead to hyperbilirubinemia and these enzymes are not present in formula (34).

In our study ultrasound abnormalities were detected in 9.5% of neonates. In a study from Turkey Cebiyev et al reported that pathological ultrasound findings were detected in 13.6% of term newborns with UTI (25). Other studies reported a higher prevalence of abnormal ultrasound findings reaching 18.2 % (13) and 28 % (35).

There are some limitations in our study, the first one lies in its retrospective nature which may have some missing data from electronic records, and that not all neonates with prolonged jaundice had a urine culture, also the high rate of mixed growth in neonates with UTI and prolonged jaundice may be a drawback. To limit potential bias, we ensured that all available data were extracted systematically and standardized across patient records. Furthermore, we cross-checked multiple data sources to minimize discrepancies and didn't include cases with conflicting or incomplete data entries.

Conclusion

UTI is a common cause of prolonged neonatal jaundice in our country which necessitates screening for UTI in neonates with prolonged jaundice and early detection of renal anomalies and providing the appropriate treatment to prevent long term scarring and kidney damage, following the guidelines of AAP (American academy of pediatrics) & NICE (The National Institute for Health and Care Excellence).

Acknowledgments

None.

Conflicts of interest

The authors declare no conflict of interest related to this study.

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