

## The Frequency and Role of Urinary Tract Infection in Prolonged Jaundice in Neonates

### Yenidoğanlarda Uzamış Sarılıktaki İdrar Yolu Enfeksiyonunun Sıklığı ve Rolü

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#### ABSTRACT

**Objective:** The study aims to investigate the frequency and role of urinary tract infection (UTI) in prolonged jaundice in preterm and term neonates.

**Materials and Methods:** This retrospective study occurred at Zeynep Kamil Maternity and Children's Hospital in İstanbul between January 2014 and April 2018. The study involved 391 neonates who presented to our outpatient clinics with prolonged jaundice. UTI was defined as urine culture growth of at least 10.000 colony-forming units per millilitre (CFU/ml) in samples obtained via urethral catheterization. Birth weight, sex, gestational age, chronological age, laboratory results, hospital courses of patients, ultrasound findings and phototherapy history were recorded.

**Results:** UTI frequency was found to be 2.8% in 391 neonates with prolonged jaundice. Nine of them were male (81.8%), and 2 were female (18.2%). Eight patients with UTI (72.7%) were term and 3 (29.3%) were preterm. History of phototherapy, presence of leukocyturia or nitrituria, white blood cell count, and thrombocyte counts were significantly higher in the UTI group.

**Conclusions:** Prolonged jaundice may be the first sign of UTI in neonates. Routine urine culture in neonates with prolonged jaundice may be useful, especially in those with a history of phototherapy and high white blood cell and thrombocyte counts.

**Keywords:** Phototherapy history, prolonged jaundice, urinary tract infection

#### ÖZ

**Amaç:** Bu çalışma preterm ve term yenidoğanlarda uzamış sarılıktaki idrar yolu enfeksiyonunun (İYE) sıklığını ve rolünü belirlemeyi amaçlar.

**Materyal ve Metot:** Retrospektif tipteki bu çalışma, Ocak 2014-Nisan 2018 zaman aralığında İstanbul Zeynep Kamil Kadın Doğum ve Çocuk Hastanesi'nde yapıldı. Uzamış sarılık nedeni başvuran 391 yenidoğan incelendi. İYE, üretral kateterizasyonla elde edilen idrar kültürünün en az 10.000 koloni oluşturan ünite/ml pozitifliği olarak tanımlandı. Başvuru yapan hastaların doğum ağırlığı, cinsiyeti, gebelik haftası, yaşı, laboratuvar değerlendirmeleri, hastane seyri, ultrason bulguları ve fototerapi öyküsü kaydedildi.

**Bulgular:** Uzamış sarılığı olan 391 yenidoğanda İYE sıklığı %2,8 olarak bulundu. Dokuzu (%81,8) erkek, 2'si (%18,2) kız idi. Sekizi (%72,7) term, 3'ü (%29,3) preterm idi. Fototerapi öyküsü, lökositüri veya nitritüri varlığı, beyaz küre sayısı ve trombosit sayısı İYE grubunda anlamlı olarak yüksekti.

**Sonuç:** Uzamış sarılık yenidoğanlarda idrar yolu enfeksiyonunun ilk belirtisi olabilir. Bu nedenle uzamış sarılığı olan, özellikle fototerapi öyküsü olan, lökosit ve trombosit sayısı yüksek olan yenidoğanlarda rutin idrar kültürü yapılması faydalı olabilir.

**Anahtar Kelimeler:** Fototerapi öyküsü, idrar yolu enfeksiyonu, uzamış sarılık

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## INTRODUCTION

Serum total bilirubin (STB) level  $\geq 10$  mg/dl lasting  $\geq 14$  days in term neonates, and  $\geq 21$  days in preterm neonates is considered a prolonged jaundice. Breast milk jaundice constitutes a significant portion of prolonged jaundice; however, it is a diagnosis of exclusion, and other pathological causes must be ruled out.<sup>1</sup> Major pathological causes of prolonged jaundice are infections, e.g. urinary tract infection (UTI), hypothyroidism, inborn errors of metabolism, congenital liver diseases and hemolytic disorders.<sup>2</sup>

Urinary tract infection is one of the important causes of prolonged jaundice in neonates. The frequency of UTI varies in studies conducted in newborns with prolonged jaundice. Reported frequencies were between 0.3% and 11% in the literature.<sup>3-4</sup> UTI causes jaundice by inducing erythrocyte hemolysis, reducing liver conjugation and impeding bilirubin excretion.<sup>5</sup> The consequences of a UTI are typically mild; however, in early infancy, there is a possibility of progression to renal scarring, particularly if there is a febrile UTI. Hypertension, proteinuria, renal damage, and even chronic renal failure in many adults are delayed sequela associated with renal scarring.<sup>6</sup> In the present study, we aimed to investigate the frequency and role of UTI as an etiology of prolonged jaundice in preterm and term neonates, and to define the characteristics of patients with UTI in our prolonged jaundice cohort.

## MATERIALS AND METHODS

**Ethical Status:** The ethical approval was obtained from the Clinical Research Ethics Committee of Zeynep Kamil Maternity and Children's Hospital (Date: 02/12/2020, decision no: 2020-176). The study was carried out in compliance with the Declaration of Helsinki.

**Patients:** This retrospective study occurred at Zeynep Kamil Maternity and Children's Hospital, Istanbul, between January 2014 and April 2018. The study involved 391 neonates who presented to our outpatient clinics with prolonged jaundice during the study period. Prolonged jaundice was defined as a STB level  $\geq 10$  mg/dl detected at  $\geq 14$  days of life in full-term neonates or at  $\geq 21$  days

of life in preterm neonates. UTI was defined as urine culture growth of at least 10.000 colony-forming units per millilitre (CFU/ml) in samples obtained via urethral catheterization. Birth weight, sex, gestational age, chronological age, phototherapy history and hospital course of patients were recorded. Collected laboratory values were direct Coombs test, serum total and direct bilirubin, complete blood count, c-reactive protein (CRP), blood culture, urine analysis and urine culture. If available, renal ultrasound findings of patients with UTI were also recorded.

**Statistical Analysis:** Statistical Package for Social Sciences for Windows 22.0 program (IBM Corporation, USA SPSS) was used for statistical analysis. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistical tests were used to present baseline demographic and clinical data. Numbers and percentages were used to present categorical variables. The mean and standard deviation were reported for normally distributed continuous variables. The median and minimum-maximum values were presented for non-normally distributed continuous variables. The Mann-Whitney U test was used for binary comparisons of non-normally distributed continuous variables. The comparison of categorical variables between groups was carried out using the Pearson Chi-Square or the Fischer Exact test. A p-value of less than 0.05 was considered as the threshold for determining statistical significance.

## RESULTS

In this study, 391 neonates with prolonged jaundice were admitted to our outpatient clinics during the study period: 246 (62.9%) male and 145 (37.1%) female. Of 391 neonates, 315 (80.6%) were term and 76 (19.4%) were preterm. Phototherapy history was found to be in 129 (33.0%) neonates. Urine cultures were sent from all 391 neonates with prolonged jaundice. Complete urine analysis was obtained from 313 neonates. Leukocyturia ( $\geq 5$  cells/area) was detected in 34 (10.9%) neonates. Nitrituria was found to be in 6 (1.9%) neonates (Table 1).

**Table 1.** Characteristics and baseline laboratory values of study cohort (n: 391).

Characteristics	Data
Age at presentation, days, median (Min-Max)	22 (14-52)
Birth weight, gram, median (Min-Max)	3180 (1750-4650)
Total bilirubin, mg/dl, median (Min-Max)	12.6 (10.0-20.8)
Direct bilirubin, mg/dl, median (Min-Max)	0.52 (0.24-1.44)
Hemoglobin, g/dl, median (Min-Max)	13.8 (7.4-20.2)
White blood cell, count/microL, median (Min-Max)	7,400 (3,900-16,800)
Thrombocyte, count/microL, median (Min-Max)	310,000 (140,000-690,000)

Table 1. Continue.

<b>Gestational age, n (%)</b>	Term	315 (80.6)
	Preterm	76 (19.4)
<b>Gender, n (%)</b>	Male	246 (62.9)
	Female	145 (37.1)
<b>Phototherapy history, n (%)</b>	Yes	129 (33.0)
	No	262 (67.0)
<b>Direct Coombs, n (%)</b>	Positive	12 (3.1)
	Negative	379 (96.9)
<b>Leukocyturia <math>\geq 5</math> Cells/Area*, n (%)</b>	Yes	34 (10.9)
	No	279 (89.1)
<b>Nitrituria*, n (%)</b>	Yes	6 (1.9)
	No	307 (98.1)

\*: Complete urine analysis was obtained from 313 of the newborns.

Eleven neonates with prolonged jaundice had urine culture growth consistent with UTI; 9 were males (81.8%), and 2 (18.2%) were female. Eight patients with UTI (72.7%) were term and 3 (29.3%) were preterm. A history of phototherapy was found in 8 (72.7%) newborns with UTI. All direct Coombs tests were negative in patients with UTI. Median STB level was 11.8 (min-max 10.1-16.4) mg/dl. The median hemoglobin, white blood cell and thrombocyte counts were 14.7 g/dl (min-max=11.5-17.6), 10.600 count/microL (min-max=6.780-14.200) and 407.000 count/microL (min-max=246.000-566.000), respectively. Ten of the newborns with UTI had a complete urinalysis. Leukocyturia and nitrituria were found in 6 (60%) and 3 (30%) newborns with UTI, respectively. There were statistically significant differ-

ences between UTI and no-UTI groups regarding urine analysis results. Leukocyturia (60% vs 9%) and nitrituria (30% vs. 1%) were significantly more common in the UTI group compared to the no-UTI group (both  $p < 0.001$ ). The median white blood cell 10.600 count/microL (min-max=6.800-14.200), vs 7.400 count/microL (min-max=3.900-16.800) and thrombocyte 407.000 count/microL (246.000-566.000), vs 296.000 count/microL (min-max=140.000-690.000) were also significantly higher in UTI group compared to non-UTI group ( $p = 0.001$  and  $p = 0.006$ , respectively). A history of phototherapy was found in 8 (72.7%) of 11 newborns with UTI and 121 (31.8%) of 380 newborns without UTI ( $p = 0.007$ ) (Table 2). Pelvicalyceal ectasia was found in 3 (27%) of 11 newborns with UTI on urinary ultrasonography.

Table 2. Comparison of study characteristics and laboratory values between UTI and No-UTI groups.

Parameters	UTI (n=11)	No-UTI (n=380)	p-value
<b>Total bilirubin, mg/dl, median (Min-Max)</b>	11.8 (10.1-16.4)	12.7 (10.0-20.8)	0.3
<b>Hemoglobin, g/dl, median (Min-Max)</b>	14.7 (11.5-17.6)	13.6 (10.4-20.2)	0.1
<b>White blood cell, count/microL, median (Min-Max)</b>	10.600 (6.800-14,200)	7.400 (3.900-16.800)	0.001
<b>Thrombocyte, count/microL, median (Min-Max)</b>	407.000 (246.000-566.000)	296.000 (140.000-690.000)	0.006
<b>Gestational age, n (%)</b>	Term	8 (72.7)	307 (80.8)
	Preterm	3 (29.3)	73 (19.2)
<b>Gender, n (%)</b>	Male	9 (81.8)	237 (62.4)
	Female	2 (18.2)	143 (37.6)
<b>Phototherapy history, n (%)</b>	Yes	8 (72.7)	121 (31.8)
	No	3 (29.3)	259 (68.2)
<b>Direct Coombs, n (%)</b>	Positive	0 (0)	12 (3.2)
	Negative	11 (100.0)	368 (96.8)
<b>Leukocyturia <math>\geq 5</math> Cells/Area*, n(%)</b>	Yes	28 (9.2)	6 (60.0)
	No	275 (90.8)	4 (40.0)
<b>Nitrituria*, n (%)</b>	Yes	3 (30.0)	3 (1.0)
	No	7 (70.0)	300 (99.0)

\*: Complete urine analysis was obtained from 313 of the newborns.

None of the neonates with UTI had high CRP values (>1 mg/dL). Blood culture growth was not detected in any of the patients with UTI. Pathogens detected in urine cultures were *Escherichia coli* (n=4, 36%), *Enterobacter* spp. (n=3, 27%), *Klebsiella* spp. (n=2, 18%), group b *Streptococcus* (n=1, 9%) and *Enterococcus* spp (n=1, 9%). Treatment regimens were ampicillin-gentamicin

in 6 patients, ampicillin-amikacin in 3 patients, ampicillin-cefotaxime in 1 patient and meropenem in 1 patient. The median length of hospital stay in newborns with UTI was 7 (min-max 7-10) days (Table 3).

**Table 3.** Ultrasound findings, some laboratory values, treatments and length of hospital stay in newborns with UTI (n=11).

Characteristics	UTI	
<b>Ultrasound findings, n (%)</b>	Normal	8 (73)
	Pelvicalyseal ectasia	3 (27)
<b>High c-reactive protein (CRP) value (&gt;1 mg/dL), n (%)</b>	Yes	0 (0)
	No	11 (100)
<b>Blood culture growth, n (%)</b>	Yes	0 (0)
	No	11 (100)
<b>Pathogens, n (%)</b>	<i>Escherichia coli</i>	4 (36)
	<i>Enterobacter</i> spp.	3 (27)
	<i>Klebsiella</i> spp.	2 (18)
	Group B <i>Streptococcus</i>	1 (9)
	<i>Enterococcus</i> spp.	1 (9)
<b>Treatment, n (%)</b>	Ampicillin-gentamicin	6 (55)
	Ampicillin-amikacin	3 (27)
	Ampicillin-cefotaxime	1 (9)
	Meropenem	1 (9)
<b>Length of hospital stay, day, median (Min-Max)</b>	7 (7-10)	

## DISCUSSION AND CONCLUSION

Urinary tract infection is one of the significant factors of prolonged jaundice in neonates. The frequency of UTI varies in studies conducted on neonates with prolonged jaundice. In a systematic review and meta-analysis study involving 1750 Iranian infants with prolonged jaundice, the total prevalence of UTI was found to be 11%.<sup>4</sup> In a study conducted in Türkiye in 2020, UTI was detected in 8% of all infants with prolonged jaundice.<sup>5</sup> Eleven (2.8 %) neonates had urine culture growth consistent with UTI in our neonate cohort with prolonged jaundice. This significant difference in UTI rates was likely related to the definition of jaundice (STB levels  $\geq 10$  mg/dl in our study vs 5 mg/dl in those studies). UTI may cause mild jaundice (STB levels between 5 mg/dl and 10 mg/dl) rather than more severe jaundice ( $\geq 10$  mg/dl). Although not statistically significant, the incidence of UTI in male newborns with prolonged jaundice was higher in our study, similar to a study conducted by Tola, et al.<sup>4</sup> In a study by Chowdhury T et al. with 319 infants with prolonged jaundice, only 1 infant had UTI confirmed by recurrent culture.<sup>3</sup> In this study, urine samples were collected using a urine pad, not urethral catheterization.<sup>3</sup> In our study, UTI was defined as a positive urine culture with at least 10.000 colony-forming units/ml in urine samples obtained by

urethral catheterization under sterile conditions. According to our study, this difference may be due to racial variations or alterations in obtaining the urine sample.

Neonates with UTI with prolonged jaundice are more frequently accompanied by a history of previous phototherapy.<sup>7</sup> In a study by Ozcan et al. in Türkiye, 155 newborns who received phototherapy for jaundice in the first 10 days of their lives were evaluated for UTI.<sup>7</sup> In this study, UTI was detected in 16.7% of neonates who received phototherapy for jaundice in the first 10 days of life.<sup>7</sup> In another study conducted by Bilgin et al. in Türkiye, it was found that 51% of infants with prolonged jaundice had a previous history of phototherapy.<sup>8</sup> In our study, the history of phototherapy rates in neonates with prolonged jaundice was 33%. When we compared the proportions of phototherapy history between UTI and no-UTI groups, a statistically significant difference was found (p=0.007). Considering the high rate of UTI in neonates with jaundice in the first 10 days of life in a study conducted by Ozcan et al., we speculate that UTI was the undiagnosed reason for phototherapy in patients who had both UTI and a history of phototherapy in our study.<sup>7</sup> In another study in Taiwan in 2018 by Weng et al., a history of phototherapy was found in 67% of those with prolonged jaundice and 42% of those

without prolonged jaundice.<sup>9</sup> Similar to our study result, previous jaundice and a history of phototherapy are significant risk factors for prolonged jaundice in a study conducted by Weng et al.<sup>9</sup>

Total serum bilirubin levels, white blood cell counts, hemoglobin levels and thrombocyte counts may differ in newborns with and without UTI.<sup>10</sup> In a study conducted by Nickavar et al. in 2015, a significant difference was found between the mean levels of STB (mg/dl) between those with and without urine culture growth.<sup>10</sup> In our study, no significant difference in the median levels of STB was found between those with and without UTI. In this study by Nickavar et al., patients with UTI had lower mean hemoglobin levels than those without UTI.<sup>10</sup> However, in our study, no significant difference was found in median hemoglobin level (g/dl) between those with and without UTI (14.7 vs 13.6,  $p=0.1$ ). We found a statistically significant difference in white blood cell count between UTI and no-UTI groups (10.600 vs 7.400 count/microL,  $p=0.001$ ). In the study by Nickavar et al., white blood cell counts were significantly different between those with and without UTI (10.970 vs 9.292 count/microL,  $p=0.014$ ).<sup>10</sup> A high white blood cell count can be a warning sign of a UTI in neonates with prolonged jaundice. In the study by Nickavar et al., no significant difference was found in thrombocyte counts between those with and without UTI (333.215 vs 298.580 count/microL,  $p=0.2$ ).<sup>10</sup> We found a statistically significant difference in thrombocyte count. In the study by Nickavar et al., no significant difference was found regarding thrombocyte between those with and without UTI (407.000 vs 296.500 count/microL,  $p=0.006$ ). In another study by Kahraman et al., the white blood cell count and the platelet count were significantly higher in patients with a positive urine culture ( $p=0.004$  and  $p=0.015$ , respectively).<sup>11</sup> High platelet counts may be an indicator of infections such as UTI in prolonged jaundice since thrombocytes, like white blood cells, are acute phase reactants. None of the newborns in our cohort had increased CRP or blood culture growth; however, CRP value was found to be high in 17% of infants with UTI, and no culture growth was detected in the study by Nickavar et al.<sup>10</sup> This difference in proportions of increased CRP may be related to timing of sample collection (early vs late in disease course) or severity of the clinical disease.

In the study by Ünsal et al., leukocyturia was found to be positive with a frequency of 75% and nitrite at 30% in pediatric patients with UTI.<sup>12</sup> In our study, leukocyturia and nitrituria were found in 6 (60%) and 3 (30%) newborns with UTI, re-

spectively. When the presence of leukocyturia or nitrituria in the complete urine analysis was compared according to the presence of growth in the urine culture, it was found that there was a statistically significant difference between the groups ( $p<0.001$  and  $p<0.001$ , respectively). Leukocyturia or nitrituria may be significant findings of a UTI.

Abnormal findings in the urinary system may contribute to a UTI. In the study by Bahat Özdoğan et al., all jaundiced infants with UTI were evaluated with urinary ultrasonography; abnormal findings such as pelvicalyceal ectasia and increased echogenicity in the renal parenchyma were detected in 28.1% of infants.<sup>13</sup> In terms of urinary ultrasonography findings, pelvicalyceal ectasia was found in 3 (27%) of the 11 infants with prolonged jaundice and UTI in our study. UTI detection for prolonged jaundice evaluation may be an opportunity to detect congenital urinary anomalies.

In conclusion, our study had important limitations with its retrospective design, such as missing important variables. We could not extract potentially impactful parameters like weight loss, nutritional status (breastfeed vs formula) and maternal blood group. Our study was single-centered and had a low event (UTI) number, which makes its statistical power and generalizability low. In the present study, we reported 391 newborns with prolonged jaundice. UTI was detected in 2.8% as a presumed etiology of prolonged jaundice. Although not statistically significant, likely because of the small sample size, the proportion of UTIs in males and preterm newborns was higher. History of phototherapy, presence of leukocyturia or nitrituria, white blood cell count, and thrombocyte count were significantly higher in the UTI group. Although we reported a low incidence of UTI in newborns with prolonged jaundice, UTI should be considered a potentially treatable etiology in newborns with prolonged jaundice.

**Ethics Committee Approval:** Ethical approval was obtained from the Clinical Research Ethics Committee of Zeynep Kamil Maternity and Children's Hospital (Date: 02/12/2020, decision no: 2020-176).

**Conflict of Interest:** No conflict of interest was declared by the authors.

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