# Role of urinary tract infection in development of neonatal pathological unconjugated hyperbilirubinemia

**Ajay Kumar*, Mohammed Uvaise Batcha**

*From Departments of Neonatology and Paediatrics*, Maulana Azad Medical College, New Delhi, India*

**Correspondence to:** Dr. Ajay Kumar, Department of Neonatology, Maulana Azad Medical College, New Delhi - 110 002, India. E-mail: ajayneonatology@gmail.com

Received - 27 February 2018 Initial Review - 22 March 2018 Published Online - 23 May 2018

## ABSTRACT

**Introduction:** American Academy of Pediatrics recommends investigating for urinary tract infection (UTI) in neonates with conjugated hyperbilirubinemia, but UTI may be associated with unconjugated hyperbilirubinemia also. **Objective:** The objective of this study was to evaluate the frequency of UTI in initial 4 weeks of life in pathological unconjugated hyperbilirubinemia and to study the effect of treatment of UTI on the course of hyperbilirubinemia in these neonates. **Methods:** This hospital-based prospective cohort study included 100 consecutive neonates with a gestational age more than or equal to 35 weeks and <42 weeks with unconjugated hyperbilirubinemia in pathological range. Babies were treated with phototherapy (and exchange transfusion), and neonates with UTI were treated with antibiotics also. The primary outcome was the frequency of UTI, confirmed by a positive urine culture and secondary outcomes included positive leukocyte esterase (LE) and nitrite reactions, significant pyuria, and rate of fall of bilirubin levels. **Results:** Seven neonates had a positive urine culture growth (UTI group) while remaining 93 babies constituted non-UTI group. In the UTI group, six and five babies had positive LE and nitrite reactions, respectively, and four babies had significant pyuria also. Exchange transfusion was done in 23 neonates in the non-UTI group. The median (range) duration of phototherapy in the remaining 70 neonates in the non-UTI group was 39 (15–117) h and in the UTI group, it was 36 (21–100) h (p=0.943) with a median (range) rate of fall of bilirubin of 0.17 (0.01–0.5) and 0.27 (0.05–0.42) mg/dL/h, respectively (p=0.172). **Conclusion:** Neonates with non-hemolytic pathological unconjugated hyperbilirubinemia should be screened for UTI with urine multi dipsticks and, microscopy, and urine culture if any of these parameters are positive.

**Key words:** *Culture, Jaundice, Neonate, Unconjugated, Urine*

American Academy of Pediatrics (AAP) recommends investigating for urinary tract infection (UTI) in neonates with conjugated hyperbilirubinemia,[1] but UTI may be associated with unconjugated hyperbilirubinemia also.[2,3] There are studies regarding the relationship of idiopathic hyperbilirubinemia and bacterial infections such as UTI.[2] Direct hyperbilirubinemia associated with UTI may be due to cholestasis as a result of microcirculatory disorders in the liver, direct bacterial products, or endotoxin-induced mediators[4] while indirect hyperbilirubinemia may be due to hemolysis caused by *Escherichia coli* and other Gram-negative microorganisms.[5,6] Lee *et al.*[3] observed that infants with UTI may present with unconjugated hyperbilirubinemia in the early stage but after 6 weeks, it is always conjugated hyperbilirubinemia. Therefore, the present study was conducted to evaluate the frequency of UTI in initial 4 weeks of life in pathological unconjugated hyperbilirubinemia and to study the effect of the treatment of UTI on the course of hyperbilirubinemia in these neonates.

## MATERIALS AND METHODS

The prospective cohort study was conducted in referral neonatal unit of a teaching hospital over 12-month period starting from March 2014 to February 2015. The study was approved by the institutional ethical committee in November 2013. Informed written consent was obtained from parents of all subjects before enrollment in the study.

Neonates (gestational age ≥35 weeks and <42 weeks) with unconjugated hyperbilirubinemia in pathological range were included in the study.[1] Neonates treated with exchange transfusion before admission were excluded from the study. Based on the past 12-month admission rate in the referral neonatal unit with requisite inclusion and exclusion criteria, a convenient sample size of 100 consecutive neonates was included in the study.

### Outcome Variable

Primary: The presence of UTI confirmed by a positive urine culture with more than 10,000 CFUs/mL of a single pathogen.[7]

Secondary: Positive leukocyte esterase (LE) and nitrite reactions, significant pyuria (defined as more than 10 pus cells per high power field of an uncentrifuged urine sample), and rate of fall of bilirubin levels.

Baseline characteristics included sex, age, and weight at enrollment, and gestational age was collected in a predesigned pro forma. History was elicited from mother or from a reliable informant and recorded. Antenatal history included booking status of pregnancy, gestational diabetes, pregnancy-induced hypertension, risk factors for early-onset sepsis, oxytocin usage, duration of labor, and drug intake. Birth history regarding birth order, multiple pregnancy, mode, and place of delivery, asphyxia, and resuscitation required were recorded. Sibling history included jaundice in the previous sibling, neonatal death due to jaundice, and unexplained death. Feeding history included initiation, duration, and frequency of breastfeeding. Details of top feeds such as type, frequency, and dilution were also asked. History of previous nursery admissions, intravenous fluid therapy, duration, dosage and name of antibiotics received, and details of urinary catheterization were also included. Age at onset of jaundice, presence of acute bilirubin encephalopathy, and treatment of hyperbilirubinemia including type and duration of phototherapy and history of neonatal UTI such as fever, refusal to feed, vomiting, and blood in urine were recorded.

Clinical assessment was done at enrollment and the heart rate, respiratory rate, temperature, pallor, icterus, and its extent on the body were recorded. Clinical features of the acute bilirubin encephalopathy, namely mental state, muscle tone, and cry were observed daily and scored as per clinical bilirubin-induced neurologic dysfunction score.[8] Total and direct serum bilirubin was measured by direct spectrophotometry method.[9] Bilirubin measurement was repeated as per clinical condition and unit protocol until jaundice returned to physiological levels.

Urine collection and testing were done at enrollment by bladder catheterization under aseptic precautions, and catheter was removed immediately after urine collection. In neonates who were started on antibiotics, the urine sample was obtained before the first dose of antibiotic. Urine sample was divided into three parts and processed as detailed: One part was used for urine culture (semi-quantitative method with calibrated loop using MacConkey agar medium) within 4 h of collection or refrigerated at 4°C in case of delay, the second part was analyzed using Multistix 10 (Bayer, Germany) dipsticks for LE and nitrite tests,[10] and the third part was analyzed by microscope for the presence of pus cells.

Treatment protocols included the following: Total serum bilirubin (TSB) levels that require intervention (phototherapy or exchange transfusion) were considered as unconjugated pathological hyperbilirubinemia or pathological jaundice as per the AAP guidelines,[1] and neonates with positive urine culture growth or UTI were treated with antibiotics.[11,12]

### Statistical Analysis

Data were entered into MS Excel programme and statistical analysis was done using Statistical Package for the Social Sciences (SPSS 16.0). Fischer's exact test or the Chi-square test was applied for comparison of qualitative variables between two groups. For comparison of quantitative variables, Student's *t*-test or Mann–Whitney U-test was applied based on the normality of the data. Normality of data was determined using Shapiro–Wilk test. $p<0.05$ was statistically significant. An intention to treat method of analysis was used.

## RESULTS

During the 12-month study period, 1281 babies were admitted to the neonatal unit. 100 consecutive neonates satisfying inclusion criteria were enrolled in the study. Seven neonates had a positive urine culture growth fulfilling the primary outcome criteria (UTI group) while rest of the 93 babies without any bacterial growth in their urine constituted the non-UTI group (Table 1). Majority of the babies (80 of 93 babies in the non-UTI group and all the seven babies in the UTI group) were enrolled between 2 and 7 days of life (Fig. 1). Of 93 babies in the non-UTI group, 20 babies were preterm, two babies were very low birth weight (VLBW), and 63 babies were low birth weight (LBW) while in the UTI group, only one baby was preterm and four babies were LBW. All the 100 study subjects were singleton births. In the non-UTI group, three neonates died during the study period and four neonates left against medical advice, while in the UTI group one neonate was taken against medical advice (study compliance more than 85%).

The most common symptom among study subjects was the refusal of feeds (30.1% in the non-UTI group and 28.6% in the UTI group) followed by lethargy (18.2% in the non-UTI group and 28.6% in the UTI group). Fever was present in only one of the seven neonates in the UTI group (14.3%) (Table 2). In the non-UTI group, 21 neonates had acute bilirubin encephalopathy (ABE) at enrollment and four developed bilirubin encephalopathy during the hospital stay.

Total and direct serum bilirubin concentration was estimated at enrollment in all subjects. Fig. 1 depicts median TSB level in both non-UTI and UTI groups at the different age of enrollment. The median (range) TSB at enrollment (TSB-E) in the non-UTI group was 20.70 (11–53) mg/dL and in the UTI group, it was 23.20 (17–26) mg/dL ($p=0.665$). The median (range) peak bilirubin value reached during the hospital stay in the non-UTI group was 21.60 (12–53) mg/dL, and in the UTI group, it was 23.20 (17–26) mg/dL (Table 3).

17 subjects in the study group had evidence of hemolysis in the peripheral blood smear out of whom 11 neonates in the non-UTI group and none in the UTI group had a positive Coombs test. Five neonates in the non-UTI group and one baby in the UTI group had non-isoimmune cause for hemolysis.

Urine dipstick analysis using *Multistix 10* (Bayer, Germany) revealed positive LE reaction in six of the seven neonates (85.7%) with positive urine culture growth while none of the neonates in the non-UTI group had a positive reaction (Table 4). Five (71.4%) neonates had a positive nitrite reaction in the UTI group. Microscopic analysis of urine revealed pyuria in four of the seven

**Table 1: Baseline characteristics of study subjects**

| Characteristics | Non-UTI group (n=93) | UTI group (n=7) |
|---|---|---|
| Age at enrollment (hours) mean (SD) | 102.3 (60) | 79.4 (17) |
| Sex female n (%) | 24 (25.8) | 1 (14.3) |
| Gestational age (weeks) mean (SD) | 37.8 (1.6) | 38.7 (1.9) |
| Enrollment weight (grams) Mean (SD) | 2296 (453) | 2565 (411) |
| Primi mother n (%) | 37 (39.8) | 5 (71.4) |
| Booked pregnancy n (%) | 71 (76.3) | 7 (100) |
| Gestational diabetes mellitus, Pregnancy-induced hypertension n (%) | 7 (7.6) | 0 |
| Prolonged leaking *Per vaginum* n (%) | 11 (11.8) | 2 (28.5) |
| Induction of labor with oxytocin n (%) | 11 (11.8) | 2 (28.5) |
| Neonatal jaundice in sibling n (%) | 11 (11.8) | 0 |
| Home delivery n (%) | 28 (30.1) | 1 (14.3) |
| Vaginal delivery n (%) | 84 (90.3) | 5 (71.4) |
| Resuscitation at birth n (%) | 12 (12.9) | 0 |
| Exclusive breastfeeding n (%) | 46 (49) | 6 (85.7) |
| Study compliance n (%) | 86 (92.5) | 6 (85.7) |

**UTI: Urinary tract infection, SD: Standard deviation**

**Table 2: Clinical features of study subjects**

| Clinical features | Non-UTI group (n=93) (%) | UTI group (n=7) (%) |
|---|---|---|
| Refusal of feeds | 28 (30.1) | 2 (28.6) |
| Lethargy | 17 (18.2) | 2 (28.6) |
| Fever | 3 (3.2) | 1 (14.3) |
| Arching of neck and trunk on stimulation | 4 (4.3) | 0 |
| High pitched cry when aroused | 3 (3.2) | 1 (14.3) |
| Shrill cry, difficult to console | 2 (2.1) | 0 |
| Apnea | 1 (1.1) | 0 |
| Asymptomatic | 62 (66) | 5 (71.4) |

**UTI: Urinary tract infection**

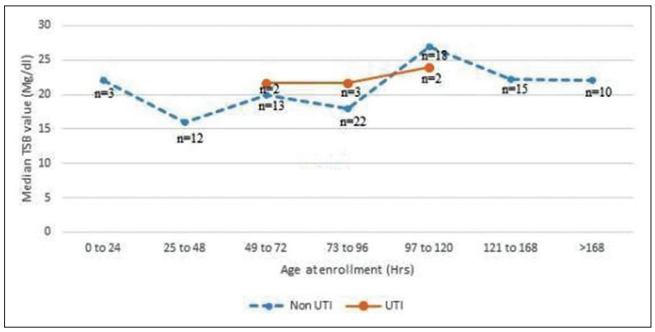


**Figure 1: Severity of jaundice in study subjects at enrollment**

neonates (57.1%) in the UTI group. Urine culture revealed the growth of *E. coli* in six neonates and *Pseudomonas species* in one neonate.

19 neonates had received intravenous antibiotics and had a negative urine culture at enrollment. 18 neonates received two antibiotics each and mean (SD) antibiotic duration per baby was 2.15 (0.3) days. None of the neonates in the UTI group were catheterized elsewhere before arrival to the hospital and had not received antibiotic before enrollment in the study.

All the study subjects were started on phototherapy at enrollment according to AAP guidelines.[1] In addition, exchange transfusion for hyperbilirubinemia was done in 23 neonates in the non-UTI group. The median duration of phototherapy in the remaining 70 neonates in the non-UTI group and seven neonates in the UTI group was comparable (p=0.943) (Table 5) with a comparable median rate of fall of bilirubin in the two groups (p=0.172). Further, on subgroup analysis of these babies without exchange transfusion and without evidence of hemolysis in the peripheral blood smear, the median (range) duration of phototherapy in 64 babies in the non-UTI group was 38 (15–117) h and in six babies in the UTI group was 38 (21–100) h, with a median (range) rate of fall of bilirubin of 0.16 (0.03–0.50) and 0.22 (0.05–0.34) mg/dL/h, respectively.

Antibiotics were started after dipstick and microscopic analysis and urine culture. Intravenous antibiotics were given for 10–14 days. A second sample of urine for culture sent after completion of a course of sensitive antibiotics was sterile in all the treated neonates. Subsequently, neonates were started on oral cephalexin prophylaxis until structural anomalies of the urinary tract were ruled out. Ultrasound scanning of the kidney urinary bladder region was normal in all neonates except one in whom there was thickening of the urinary bladder which normalized on follow-up scan after 1 month. A voiding micturating

**Table 3: Biochemical profile of jaundice in study subjects**

| Parameter | Range | Non-UTI group (n=93) (%) | UTI group (n=7) (%) |
|---|---|---|---|
| TSB at enrollment (mg/dL) | 0–11 | 0 | 0 |
| | 11.1–15 | 7 (7.5) | 0 |
| | 15.1–25 | 63 (67.7) | 5 (71.4) |
| | More than 25 | 23 (24.7) | 2 (28.6) |
| Maximum TSB (mg/dL) | 0–11 | 0 | 0 |
| | 11.1–15 | 6 (6.5) | 0 |
| | 15.1–25 | 61 (65.6) | 5 (71.4) |
| | More than 25 | 26 (28) | 2 (28.6) |
| Development of conjugated bilirubinemia | | 3 (3.2) | 0 |

**UTI: Urinary tract infection, TSB: Total serum bilirubin**

**Table 4: Result of urine analysis and culture**

| Case No. | LE reaction | Nitrite reaction | Pyuria | Organism (CFU/mL) | Sensitive to antibiotics |
|---|---|---|---|---|---|
| 6 | Positive | Positive | Present | *E. coli* ($10^5$) | NFT, Cipro |
| 9 | Positive | Positive | Present | *E. coli* ($10^6$) | Ceph, Amox |
| 17 | Positive | Positive | Absent | *E. coli* ($10^5$) | Genta, NFT |
| 18 | Positive | Negative | Present | *E. coli* ($10^5$) | Genta, Cipro |
| 32 | Negative | Negative | Absent | *Pseudomonas species* ($10^6$) | Cipro, Ceft, Amika |
| 81 | Positive | Positive | Present | *E. coli* ($10^6$) | Cipro, Genta |
| 87 | Positive | Positive | Absent | *E. coli* ($10^6$) | Ceftr, Ceph |

**Amika: Amikacin, Amox: Amoxicillin, Ceftr: Ceftriaxone, Ceft: Ceftazidime, Ceph: Cephalexin, Cipro: Ciprofloxacin, Genta: Gentamycin, NFT: Nitrofurantoin, LE reaction: Leukocyte esterase reaction, CFU: Colony-forming unit, *E. coli: Escherichia coli***

**Table 5: Effect of treatment of UTI on hyperbilirubinemia**

| Parameters | Non-UTI group without ET (n=70) | UTI group (n=7) |
|---|---|---|
| TSB-E (mg/dL) median (range) | 19.40 (11–29) | 23.20 (17–26) |
| TSB-P (mg/dL) median (range) | 12.75 (6.2–20.9) | 11.40 (7.6–18.2) |
| Duration of PT (hours) median (range) | 39 (15–117) | 36 (21–100) |
| Bilirubin fall (mg/dL/h) median (range)* | 0.17 (0.01–0.5) | 0.27 (0.05–0.42) |

**TSB-E: Total serum bilirubin at enrollment, TSB-P: Total serum bilirubin at stop of phototherapy, PT: Phototherapy, ET: Exchange transfusion, *p=0.1720, UTI: Urinary tract infection**

cysto-urethrogram done in all the seven neonates with a positive urine growth was normal.

## DISCUSSION

The incidence of the UTI in general population in the neonatal age group is 0.1–1%.[13] In the present study, the incidence of the UTI in neonates with pathological unconjugated hyperbilirubinemia was 7% (seven out of 100 babies). In a study by Garcia *et al.* in 160 asymptomatic jaundiced infants younger than 8 weeks, UTI was found in 7.5% of cases out of whom two cases had direct hyperbilirubinemia.[14] In another study by Bilgen *et al.,*[15] the incidence of UTI in clinically well, <2-week-old jaundiced infants with a TSB level above 15 mg/dl were 7.8% (8 out of 102 neonates). However, in a study by Mutlu *et al.,*[16] neonates aged 4–14 days of life with jaundice above phototherapy limits set by AAP guidelines, UTI was diagnosed in 19 of the enrolled 104 neonates (18%). This higher incidence of UTI might be due to the exclusion of neonates in whom an apparent cause for the jaundice was present (blood group incompatibility, hemolysis in peripheral smear, or positive direct Coombs test) and thus there was a higher possibility of other causes such as UTI for jaundice in the included neonates. Further, in the study by Nejad *et al., the* incidence of UTI in neonates with clinical icterus was 18% (16 out of 90 neonates) and in this study also neonates with an apparent cause for jaundice was not included in the study.[17] In the present study, on subgroup analysis of babies without evidence of hemolysis in the peripheral blood smear, six out of 83 babies (7%) had associated UTI. Further, 19 out of 100 study subjects had received antibiotic therapy before enrollment and had a negative urine culture. This could also be considered as a reason for the relatively low incidence of UTI in the present study when compared with those of Mutlu *et al.* and Nejad *et al.*

Antibiotic treatment of UTI was started in all the seven neonates with a positive urine culture. All the study subjects were started on phototherapy at enrollment. None of the seven neonates in the UTI group developed ABE during the study period and did not require exchange transfusion for treatment of hyperbilirubinemia while in the non-UTI group 25 neonates developed ABE and 23 out of 93 (24.7%) neonates required exchange transfusion (p=0.1974). The median duration of phototherapy in the non-UTI group who did not require exchange

transfusion was comparable to the neonates in the UTI group (p=0.943), again with a comparable rate of fall of bilirubin in the two groups (p=0.172). However, in the study by Mutlu *et al.*,[16] the duration of phototherapy was longer in those with UTI (42.9 h) than those without UTI (32.6 h).

There are some limitations in the present study. The study was done in the referral neonatal unit involving outborn neonates in whom onset and progression of jaundice and clinical features of UTI could not be followed from birth; 19 neonates had received antibiotics before urine culture, and this could have affected the culture positivity rate in these study subjects. Therefore, to evaluate cause and effect relationship between UTI and unconjugated hyperbilirubinemia, a study in an inborn nursery setting is suggested for future research.

## CONCLUSION

UTI in the newborn period can present with indirect hyperbilirubinemia. Evaluation for neonatal UTI as a cause of non-hemolytic pathological unconjugated hyperbilirubinemia with urine multi dipsticks and microscopy, and urine culture should be recommended, even in the 1st week of life as in the present study, the incidence of UTI in jaundiced neonates was 7% (higher than normal population) and the mean age at enrollment of neonates with UTI was 79.4 h.

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*Funding: None; Conflict of Interest: None Stated.*

**How to cite this article:** Kumar A, Batcha MU. Role of urinary tract infection in development of neonatal pathological unconjugated hyperbilirubinemia. Indian J Child Health. 2018; 5(4):262-266.

Doi: 10.32677/IJCH.2018.v05.i04.008