



Prediction of Urinary Tract Infection in Neonates with Unexplained Indirect Hyperbilirubinemia

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Abstract

BACKGROUND: Neonates with urinary tract infection (UTI) are susceptible to higher rates of morbidity and mortality, specifically when presented with hyperbilirubinemia. Screening for UTIs in jaundiced neonates is a cost-effective strategy.

AIM: The aims of this study were to investigate the pattern of UTI (prevalence, etiology, and susceptible antimicrobial agents) in neonates admitted to the NICU with unexplained indirect hyperbilirubinemia, as well as to identify early predictors of UTI to reduce the present morbidity and long-term consequences in NICU patients.

METHODS: A cross-sectional hospital-based study that included 140 neonates diagnosed with unexplained indirect hyperbilirubinemia in the first 4 weeks of life. A questionnaire was applied to obtain demographic and clinical data. A number of laboratory parameters were assessed with clinical examination. Bacterial growth of 1×10^5 colony-forming units/mL of a single uropathogen was used to identify the existence of UTI. Multivariate analysis was used to identify the predicting factors of UTIs.

RESULTS: In the NICU group investigated, 25.7% of subjects had a culture-proved UTI. The most frequently isolated organism was *Escherichia coli*. Amikacin was the most common antibiotic that the isolates were susceptible to. In multivariable logistic regression analysis, a positive urine culture was statistically associated with an increase in WBCs (OR = 6.90, $p = 0.001$), pyuria (OR = 5.55, $p = 0.001$), small for gestational age (OR = 4.07, $p = 0.021$), prolonged phototherapy duration (OR = 3.50, $p = 0.034$), and the presence of obstetric complications (OR = 2.92, $p = 0.001$).

CONCLUSION: UTI is substantially prevalent among neonates admitted to the NICU with unexplained indirect hyperbilirubinemia. The importance of routine UTI screening (urine culture) as part of the clinical assessment of unexplained hyperbilirubinemia was highlighted in this study, particularly in neonates with leukocytosis, pyuria, small for gestational age, prolonged phototherapy, and those born from mothers with a history of obstetric complications.

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Background

Bacterial infections are frequently encountered disorders in early neonates, one-third of them affecting the urinary tract [1]. Increased susceptibility to urinary tract infection (UTI) was allied to poor uroepithelial bactericidal activity, low levels of local immunoglobulins, limited urine acidification capacity, and high periurethral colonization during the neonatal period [2]. However, the diagnosis of UTI is challenging in this period, UTI has a distinct range of clinical manifestations, including specific and non-specific manifestations. Jaundice has been thought to be one of the common nonspecific signs of UTI in young neonates. The indirect bilirubin levels rise because of UTIs [3].

Hyperbilirubinemia is an ailment defined as elevated serum bilirubin levels above the laboratory's reference range according to neonatal age when the

total bilirubin rises above the 95th percentile for age during the first 7 days of life [4]. In term and late preterm neonates, the rate of UTI associated with indirect hyperbilirubinemia ranges from 3% to 21% [5].

Neonates with UTIs are susceptible to higher rates of mortalities, particularly when presented with hyperbilirubinemia. Higher levels of bilirubin seem to be linked with increased heme oxygenase-1 enzyme activity caused by bacterial endotoxins, cytokines, and other infection-related factors [2].

Although UTI screening is recommended in the management of any neonate with unexplained indirect hyperbilirubinemia [2], [3], [5], the actual screening is mainly limited to neonates with prolonged hyperbilirubinemia and those with direct bilirubinemia [6]. Screening for UTIs in jaundiced neonates is a cost-effective strategy as early detection may help in complete recovery rather than being threatened in terms of complications. And a proper

care is crucial in minimizing neonatal mortalities in such cases [2], [7], [8]. As the exact prognostic significance of UTI in neonates with unexplained indirect hyperbilirubinemia remains controversial, more studies appear to be needed to better understand the relationship between indirect hyperbilirubinemia and UTIs in neonates [5]. Most of the previous studies considered mainly the prevalence of UTI in jaundiced neonates [2], [5], [6]. To the best of our knowledge, UTI has never been investigated in jaundiced neonates in Aswan.

Findings from this study may help to improve hospital care for NICU patients. As well as it may potentially help NICU authorities to consider the study findings in reallocation of health care resources to reduce infant mortality through setting up more effective early intervention measures in a neonate's clinic [9]. Providing the NICU staff with clear insights in the light of current proper clinical and epidemiological studies could help them to identify jaundiced neonates who are needed early urine culture with rapid treatment approaches [10].

As a result, the aims of this study were to investigate the pattern of UTI (prevalence, etiology, and susceptible antimicrobial agents) in neonates admitted to the NICU with significant unexplained indirect hyperbilirubinemia, as well as to identify early predictors of UTI to reduce the present morbidity and long-term consequences in NICU patients.

Methods

Study design, settings, and study population

A cross-sectional hospital-based study was carried out in the neonatal intensive care unit (NICU) of the Aswan University Hospital which is located in Upper Egypt from July 2019 to January 2020.

The study was conducted on full terms (≥ 37 weeks of gestational age) and late pre-terms (≥ 35 weeks of gestational age) who were diagnosed with unexplained indirect hyperbilirubinemia in the neonatal unit. The inclusion criteria were age less than 4 weeks and obtaining parental consent for the participation of their neonate in this study. Neonatal hyperbilirubinemia is diagnosed according to a curve representing the bilirubin level trends at a certain age in days. Early hyperbilirubinemia was defined after 24 h of life up to 2 weeks, and prolonged hyperbilirubinemia was defined after 2 weeks. Management of hyperbilirubinemia was based on American Academy of Pediatrics (AAP) guidelines, and serum bilirubin was measured using the spectrophotometric method [11].

The exclusion chart was created using the term "unexplained hyperbilirubinemia" as a

guide. Excluded subjects were those with hemolytic diseases (isoimmunization, ABO, Rh, or subgroup incompatibilities), direct Coombs test positivity, hemolysis on a blood smear (anisocytosis, spherocytosis, polychromasia, and poikilocytosis), anemia, polycythemia, reticulocytosis, and/or glucose-6-phosphate dehydrogenase deficiency. The study also excluded all neonates with congenital malformations, septic conditions, direct hyperbilirubinemia, hypothyroidism, metabolic illnesses, and instances with any comorbidities causing indirect hyperbilirubinemia, as well as those who had a UTI that did not coincide with the development of jaundice. All study samples with multiple growths (contaminations) were also excluded from the study findings.

Sampling

Sample size determination

Using the Epi Info™ program version 7 (CDC recommends this program), a sample size of 127 neonates was required sample when considering a prevalence of 13.6% for UTI among jaundiced neonates [12], at a confidence level of 90%, and a precision degree of 5%. The number of neonates in the sample was raised to include 140 neonates.

Sampling technique

The eligible neonates were selected using a convenience sampling method. All neonates admitted to the department of pediatrics' neonatal unit at Aswan University Hospital were screened for eligibility and sequentially chosen for the study until the required sample size of 140 subjects was obtained.

Data collection

Data were collected prospectively. All recruited neonates were subjected to the following:

1. A structured interviewer-administered questionnaire was completed by the neonates' parents. Parents were questioned in detail regarding demographic, perinatal, natal, and postnatal events, including jaundice-related data, feeding patterns, and UTI-specific symptoms and non-specific symptoms.
2. Full general and systemic clinical examination was done to assess the state of each neonate.
3. Laboratory tests to demonstrate etiology included full blood count (CBC), reticulocyte index and peripheral blood smear, coomb's test (direct), C reactive protein (CRP), urea and creatinine, liver enzymes, G6PD enzyme

assay, thyroid function (TSH and free T4), serum bilirubin level (total and direct bilirubin). In addition to urine analysis, and urine culture and sensitivity.

Clinical specimen collection that includes blood and urine

5 ml of peripheral blood was taken under aseptic conditions and divided into two parts: The first 3 ml was taken in an EDTA vacutainer for CBC with reticulocytes percent, blood group, RH, and Coombs test. The remaining 2 ml was tested for serum bilirubin, liver enzymes, and C-reactive protein (CRP) in a standard vacutainer. A hematological analyzer was used to perform the CBC. The findings of the CRP quantitative assay were interpreted in such a way that a value of <3 mg/dl was regarded normal, whereas a high value (>3 mg/dl) indicated inflammation.

Under ideal aseptic conditions, a urine sample was taken from each study participant using a urinary catheterization the basic technique for diagnosis of UTI [13]. The urine specimen was collected in two sample containers; one for urinalysis using the dipstick method and the other for culture and sensitivity. To avoid further growth of organisms in the urine specimen, both were stored in an ice pack carrier and transported in closed and secure containers to the studied hospital lab for processing immediately. Urinalysis was done using urine strips dipstick (Multistix 10 for standard urinalysis). Interpretation of the urine dipstick test was based on the manufacturer's instructions for a urine analyzer [14].

The morphology of pus cells, WBCs, and RBCs was studied microscopically under HPF on the centrifuged urine samples. Pyuria is defined as the presence of more than 5 WBCs per HPF, whereas hematuria is defined as the presence of more than 5 RBCs per HPF. Bacteriuria was defined as the presence of at least one bacterium per HPF in an unspun urine sample. Quantitative unspun-urine microscopy confirmed by oil-immersion method [15].

All subjects had a urine culture. A positive urine culture confirmed the presence of a UTI. Urine was inoculated and aerobically cultured. After 24–72 h of incubation, use the quantitative loop method to subculture on sheep blood agar and MacConkey agar. A positive urine culture was defined as the growth of $\geq 1 \times 10^3$ CFU (colony-forming unit)/mL of a single uropathogen [16].

According to the Clinical Laboratory Standard Institute (CLSI) [17], the antibiotic sensitivity of isolated bacteria was assessed using the Kirby–Bauer diffusion method for *in vitro* drug susceptibility [18]. Drug sensitivity plates were used to test the sensitivity of bacteria isolates in the positive culture sample. The plates were incubated for 24 h at 37°C, and the

areas of growth inhibition were measured. A positive inhibition zone was defined as one that was greater than 15 mL. Gram-positive uropathogens were treated with ampicillin, whereas Gram-negative uropathogens were treated with gentamycin, ceftriaxone, amoxicillin-clavulanate, clindamycin, erythromycin, nitrofurantoin, ciprofloxacin, meropenem, and amikacin. Quality control in all lab stages was assured.

Renal ultrasonography was used on neonates with a proven urinary tract infection to rule out urinary tract abnormalities such as vesicoureteral reflux and to detect any positive ultrasonography findings including hydronephrosis, stones, and pelviectasis. The Sonolay 250 convex probe with a 3.75 and 5 MHz convex linear transducer was utilized as a high-resolution real-time scanner because it provides excellent quality resolution in screening for kidney problems in newborns [19]. Longitudinal scans of the kidney were obtained, and the following points were considered: renal length and width, and comparison of the sizes of both kidneys for detection of any inconsistency, such as in cases of unilateral atrophy or hypoplasia of one side; renal parenchymal echogenicity; any abdominal masses and their relationship to the kidney; and evaluation of the urinary bladder. Voiding cystourethrography (after obtaining a sterile urine culture, approximately 1 month after the diagnosis) was performed on those with any abnormality on renal ultrasonography.

Statistical analysis

SPSS Statistics for Windows, Version 26.0 software program (IBM Corporation, Armonk, NY, USA) was used to collect, tabulate, and statistically analyze our study data. All subsequently tested variables were assessed for the normality of their distribution using the Shapiro–Wilkes test. Mean and standard deviation (SD) were used to describe quantitative data, while frequencies and percentages were used to describe qualitative variables. The differences between the two groups were tested using the independent sample t-test for the quantitative variables. The Chi-square χ^2 -test and, where applicable, the Monte Carlo exact test were applied to examine the associations between categorical variables. A logistic regression analysis was performed to determine the independent predictors of UTIs in neonates with unexplained indirect hyperbilirubinemia. The significance of the obtained results was considered when $p < 0.05$.

Ethical consideration

The study was carried out following the principles of the Declaration of Helsinki and was approved by the Ethical Review Committee of Aswan Faculty of Medicine. The subjects' parents addressed the steps of the study until they were clear. All parents signed written informed consent forms before their

children were recruited for the study. If the parents are unable to read, an impartial witness must be present to explain the contents of the informed consent and sign it on their behalf. Confidentiality and anonymity of the data were maintained throughout the study, and the right to refuse to participate or withdraw from the study at any time was emphasized.

Results

One hundred and forty neonates diagnosed with unexplained indirect hyperbilirubinemia were investigated during the study period. The mean age of NICU patients was 5.61 ± 2.4 days and the male-to-female ratio 0.64. The mean gestational age was 37.4 ± 1.5 weeks with a birth weight of 3002 ± 505 grams. Sixty percent of the pregnant women in the study were delivered through cesarean section (58.6%). Nearly half of the participated neonates (48.6%) were exclusively fed breast milk, 38.5% were exclusively fed formula, and 12.9% were fed both breast milk and formula.

Urine culture was done for all the studied neonates, positive urine culture was found in 36 out of 140 neonates (25.7%). The main causative organisms isolated were *Gram-Negative Bacilli Escherichia coli*; which was isolated in 66.7% of the positive specimens (24/36), followed by *Klebsiella pneumoniae*; which was isolated in 22.2% (8/36) then *Enterobacter spp.* which isolated in 11.1% (4/36). Table 1 illustrates the susceptibility pattern of each isolate, the highest susceptibility rates were shown for amikacin, ciprofloxacin, nitrofurantoin, and meropenem. They were sensitive to *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter spp.* whereas other commonly used drugs such as ampicillin, gentamycin, and ceftriaxone were 100% resistant to the isolated organisms.

Table 1: Isolated organisms in urine cultures, antibiotics sensitivity patterns among neonates with urinary tract infection

Drugs tested	Isolated bacteria N = 36		
	Gram Negative Bacilli <i>E. coli</i> : 24 n (%)	<i>Klebsiella pneumoniae</i> : 8 n (%)	<i>Enterobacter spp.</i> : 4 n (%)
Ciprofloxacin	8 (33.3)	5 (62.5)	2 (50.0)
Meropenem	6 (25.0)	5 (62.5)	1 (25.0)
Amikacin	16 (66.7)	6 (75.0)	3 (75.0)
Gentamycin	0 (0.0)	0 (0.0)	0 (0.0)
Ampicillin	0 (0.0)	0 (0.0)	0 (0.0)
Ceftriaxone	0 (0.0)	0 (0.0)	0 (0.0)
Ampicillin-sulbactam	1 (4.2)	0 (0.0)	1 (25.0)
Amoxicillin-clavulanic acid	2 (8.3)	0 (0.0)	1 (25.0)
Clindamycin	0 (0.0)	1 (12.5)	0 (0.0)
Erythromycin	0 (0.0)	2 (25.0)	0 (0.0)
Nitrofurantoin	2 (8.3)	4 (50.0)	1 (25.0)

The demographic and clinical data of positive UTI neonates compared to negative UTI neonates are illustrated in Table 2. Around three-quarters of positive UTI, neonates were males (72.2%). Neonates with UTI had a significantly smaller gestational age compared to those without UTI (36.89 ± 1.1 and 38.21 ± 1.6 ,

Table 2: Demographic and clinical characteristics of the studied neonates

Variable	Neonates with UTI (No = 36)	Neonates without UTI (No = 104)	p-value
Gestational age in weeks (Mean \pm SD)	36.89 ± 1.1	38.21 ± 1.6	0.040*
Gender			0.001 ^f
Male	26 (72.2%)	68 (65.4%)	
Female	10 (27.8%)	36 (34.6%)	
Birth weight (gram) (Mean \pm SD)	2592 ± 504	3011 ± 405	0.094*
The onset of jaundice (day)	2.61 ± 0.2	4.10 ± 0.3	0.031*
Age at presentation (day)	2.63 ± 2.0	3.51 ± 1.5	0.022*
Hospitalization period (day)	6.21 ± 1.2	4.61 ± 1.5	0.042*
Duration of conventional phototherapy (h)	75.91 ± 19.8	63.33 ± 21.0	0.033*
Mode of delivery			0.091 ^f
Vaginal delivery	16 (44.5%)	42 (40.1%)	
Caesarian section	20 (55.5%)	62 (59.9%)	
Feeding type			0.053 ^f
Breastfeeding	16 (44.4%)	52 (50%)	
Formula bottle feeding	14 (38.8%)	42 (40.4%)	
Mixed feeding	6 (16.8%)	10 (9.6%)	
Obstetric complications			0.001*
Gestational diabetes mellitus	4 (11.1%)	4 (3.8%)	
Preeclampsia	2 (5.5%)	0 (0.0%)	
Hypothyroidism	2 (5.5%)	0 (0.0%)	
Oligohydramnios	2 (5.5%)	0 (0.0%)	
Premature rupture of membrane \geq 18 h	8 (22.2%)	0 (0.0%)	
No complications	18 (50.2%)	100 (96.2%)	
Clinical finding			0.111*
Fever	0 (0.0%)	0 (0.0%)	
Hypothermia	1 (2.7%)	0 (0.0%)	
Vomiting	2 (5.5%)	0 (0.0%)	
Pallor	1 (2.7%)	2 (1.8%)	
Irritability	0 (0.0%)	1 (0.9%)	
Lethargy	0 (0.0%)	1 (0.9%)	
Poor suckling	3 (8.3%)	8 (7.6%)	
Poor Moro reflex	1 (2.7%)	2 (1.8%)	

Conventional phototherapy is using light irradiance of 25–30 microW/cm²/nm in the 430–490 nm band. Data are presented as number (percentage), mean \pm standard deviation. *T-test was used to compare the difference in means between the two groups. ^fChi-square analysis was used to compare the difference in proportions. [†]Monte Carlo exact test was applied. The significance level was considered at $P < 0.05$.

respectively). The mean age at presentation was 2.63 ± 2.0 days in the UTI subjects in comparison to 3.51 ± 1.5 in the non-UTI subjects, $p = 0.022$. The hospitalization period was significantly longer in UTI-positive cases compared to negative cases (6.21 ± 1.2 vs. 4.6 ± 1.5 days, $p = 0.042$).

A statistical association was observed between the mean duration of phototherapy and positive urine culture ($p = 0.033$), UTI-positive neonates received phototherapy for 75.91 ± 19.8 h, while UTI-negative neonates were received 63.33 ± 21.0 h of phototherapy.

As demonstrated in Table 2, premature rupture of membranes was the most common obstetrical complication, occurring in 22.2% of mothers of UTI-positive neonates. The frequency of clinical manifestations among UTI and non-UTI subjects is also demonstrated in Table 2. None of the studied neonates had a fever. Poor suckling was the frequent clinical finding displayed among two study groups but without significant association with UTI.

On review of the laboratory results of the participated cases (Table 3), the mean total serum bilirubin level was significantly different between UTI and non-UTI subjects (18.68 ± 0.9 mg/dl vs. 14.01 ± 1.4 mg/dl, respectively, $p = 0.044$). The number of white blood cells (WBCs) increased more in UTI positive neonates than in UTI negative neonates ($13.65 \pm 0.7 \times 10^3$ vs. $7.56 \pm 0.3 \times 10^3$, $p < 0.001$). In both groups

investigated, the other CBC measures were within normal limits. The levels of ALT and AST were within the acceptable limits. Table 3 also showed the results of urine analysis. Positive pyuria results were indicated in all UTI neonates, while sterile pyuria results were found in 7% of non-UTI neonates.

Renal ultrasounds were performed for all neonates with positive culture results during the NICU stay. Ultrasonography revealed a posterior urethral valve with mild hydronephrosis in one male with *E. coli* infection (2.7 %), whereas the rest were normal. In this case, follow-up by ultrasound and voiding cystourethrogram (VCUG) for evaluation was recommended.

Table 3: Laboratory investigations (blood and urine analysis) of the studied cases

	Neonates with UTI (No = 36)	Neonates without UTI (No = 104)	p-value
Total serum bilirubin (mg/dL)	18.68 ± 0.9	14.01 ± 1.4	0.044*
Direct serum bilirubin (mg/dL)	0.49 ± 0.03	0.52 ± 0.02	0.510
White blood cells WBCs (×1000/mL)	13.65 ± 0.7	7.56 ± 0.3	< 0.001*
HB g/dl	16.31 ± 1.8	15.21 ± 2.1	0.110
Platelets (×1000/mL)	261.54 ± 64.7	266.50 ± 54.0	0.150
Creatinine, mg/dL	0.7 ± 0.22	0.5 ± 0.16	0.991
ALT level (U/L)	36.61 ± 8.8	36.11 ± 9.1	0.940
AST level (U/L)	27.51 ± 7.3	28.21 ± 7.1	0.850
CRP mg/dL			
Negative	32 (88.9%)	90 (86.5%)	0.580 [†]
Positive	4 (11.1%)	14 (13.5%)	
RBCS > 5/HPF			
Yes	1 (2.7%)	4 (3.8%)	0.061 [†]
No	35 (97.3%)	100 (96.2%)	
Pyuria > 5 WBC/HPF			
Yes	36 (100%)	7 (6.9%)	< 0.001 [†]
No	0 (0.0%)	97 (93.1%)	

*T-test was used to compare the difference in means between the two groups. †Fisher's exact test was used to compare the difference in proportions. CRP C-reactive protein, WBC white blood cell count. The significance level was considered at P < 0.05.

In multivariable logistic regression analysis (Table 4), jaundiced neonates with an increase in WBCs in their blood had 6.9 times higher odds of developing UTI compared to those with low values [AOR = 6.90; 95% CI (2.79–17.28), p = 0.001]. Pyuria was significantly related to positive urine culture and its presence in urine analysis increases the risk of UTI by 5.55 times. The odd of developing neonatal UTI is significantly higher also with small for gestational age neonates [AOR = 4.07; 95% CI (1.06–11.05), p = 0.021], neonates who received prolonged duration of phototherapy [AOR = 3.50; 95% CI (1.99–8.62), p = 0.034], and neonates born from mothers who had a history of obstetric complications [AOR = 2.92; 95% CI (1.02–5.99), p = 0.001].

Table 4: Multivariable logistic regression analysis for prediction of UTI in studied cases

Variables	95% CI	AOR	p-value
Gestational age in weeks	1.06–11.05	4.07	0.021
Gender (male)	0.43–3.29	1.10	0.070
Onset of jaundice (day)	0.11–2.78	0.53	0.951
Age at presentation (day)	0.60–1.41	1.10	0.066
Hospitalization period (day)	0.20–2.56	0.80	0.091
Duration of phototherapy (hour)	1.99–8.62	3.50	0.034
Maternal obstetric complications (yes)	1.02–5.99	2.92	0.001
Total serum bilirubin (mg/dL)	0.20–4.33	1.90	0.081
WBCs ×10 ³	2.79–17.28	6.90	0.001
Pyuria constant	1.09–4.62	5.55	< 0.001
constant			< 0.001

CI: Confidence interval, AOR; Adjusted odds ratio; Adjusted R² = 0.54; Model sensitivity = 66.1%. Variables with a P value of < 0.05 in bivariate analysis were entered in the multivariate model.

Discussion

Urinary tract infection (UTI) is a microbial invasion of the urinary tract tissues expanding from the renal cortex to the urethral meatus [20]. Hyperbilirubinemia may be the earliest symptom of UTI in young neonates [5], [21], [22]. Hyperbilirubinemia in UTI is related to hemolysis induced by strains of *E. coli* and other Gram-negative organisms. Because infants' conjugation mechanisms are still immature, even minor hemolysis can cause an increase in serum bilirubin levels [2]. On the other hand, indirect hyperbilirubinemia may predispose to UTI in jaundiced neonates through changing bactericidal activity in the blood serum of jaundiced neonates, rendering them more susceptible to infections. Moreover, high bilirubin levels relax the ureter and bladder muscles, resulting in difficulty in passing urine, and urine stasis [23].

This study intended to detect if the urinary tract infection is a significant cause of unexplained indirect hyperbilirubinemia in jaundiced neonates who need treatment and should it be involved in routine workup of those neonates.

In this study, the proportion of UTI among the jaundiced subjects after exclusion of all other etiologies of hyperbilirubinemia was 25%, which agrees with the studies done in Lebanon and Egypt by Omar *et al.* [24] and Rashed *et al.* [9]. They reported UTI prevalence rates of 21% and 25%, respectively. Mutlu *et al.* [5] and Ozcan *et al.* [20] reported rates of 18% and 16.7% in the studies conducted in Turkey. Low rates of 5.5% and 3.8%, respectively, were detected by Chen *et al.* in Taiwan [25] and Zarkesh *et al.* in Iran [26].

Among jaundiced neonates with positive UTIs, the most common organism cultured in NICU was *Escherichia coli*. Similar results were also obtained by a couple of studies conducted in Turkey [4], [27]. In other studies, *Klebsiella pneumoniae* was found to be the utmost isolated agent among positive UTI jaundiced neonates [11], [21], [24]. However, in Ozcan *et al.* [28] study, *Enterobacter* spp. was the commonly isolated microorganism. The methods for obtaining urine specimens and the threshold values to accept the results compatible with UTIs differ among the studies. Inconsistencies in the diagnostic procedures utilized in these studies could explain the variety of the outcomes. However, it is not confirmed whether the geographical or environmental factors in Aswan may contribute to the bacteriologic and epidemiologic characteristics of UTIs.

In accord with Hoseiny *et al.* [29], the highest susceptibility rates were shown for amikacin. In contrast, meropenem was the most sensitive antibiotic in the study done by Trihono *et al.* [3].

A high proportion of the positive UTI cases admitted to NICU (72.2%) were males and this comes in agreement with several studies in Egypt [9] and outside

Egypt [3], [4], [12], [21], [26]. Our explanation may be that uncircumcised males during the early neonatal period have the highest risk of urinary tract infection.

In agreement with Mutlu *et al.* [5], neonates with UTI had a smaller gestational age in contrast to those without UTI. On the contrary, some studies have found that neonates with UTIs had a higher gestational age [12], [30]. Smaller for gestational age has an immature hepatic system that limits bilirubin excretion and RBCs lifecycle, as well as the related delay in feeding entry, which accelerates the rise in serum bilirubin level in this newborn [31].

Similar to earlier studies [12], [21], [24], [26], [32], the current study demonstrated no significant difference between the weight of UTI and non-UTI subjects. Furthermore, no significant difference was found between the two studied groups of jaundiced infants concerning the mode of delivery and this is similarly agreed by Omar *et al.* [24].

The timing of jaundice presentation in neonates with a positive UTI was significantly earlier than in neonates with a negative UTI. Our findings are consistent with those of previous studies [25], [28] but differ from those of others [12], [33], which claimed that positive UTI newborns presented late.

The study realized that jaundiced newborns with a mother's history of obstetric complications had greater positive UTI results. Several investigators agreed that the existence of maternal complications was a major predictor of the development of UTIs [3], [9], [22].

Similar to the previous studies [24], [28], our findings showed that neonates with UTI had considerably elevated measurements in serum bilirubin levels than those without UTI. However, according to several studies [4], [21], [25], [32], there are no significant differences between UTI and non-UTI subjects regarding serum bilirubin levels. Hyperbilirubinemia can be produced by direct bacterial and endotoxin-mediated products, which can enter the biliary system in several ways [2].

As a result of the inflammatory processes, the white blood cell count in the UTI group was significantly higher than in the non-UTI group. This result is consistent with the earlier studies [22], [32]. They recommended that CBC testing be utilized as a routine screening approach even in asymptomatic hyperbilirubinemia.

In terms of CRP values, there was no significant difference between the two studied groups. CRP findings in jaundiced neonates with UTI were reported positive by Rashed *et al.* [9], and negative by Mutlu *et al.* [5]. Prolonged jaundice had significantly high CRP [32]. CRP has low sensitivity when used as a screening sign for inflammatory diseases, which could explain the disparities in these results [34].

Pyuria was reported to be present in 58.3%, 52%, and 33% of neonates with UTI in three distinct

studies [9], [21], [25]. Pyuria was found in 100.0% of UTI subjects and 19.2% of non-UTI subjects in this study. The presence of inflammatory cells in a negative urine culture is known as sterile pyuria [35]. According to Shahian *et al.* [21], even moderate dehydration in jaundiced infants can result in the presence of WBC in their urine. Pyuria is not a sensitive marker for detecting UTIs in jaundiced infants, and it may result in an overestimation of UTI cases [36].

In our study, the mean duration of phototherapy in neonates with UTIs was much longer than those of non-UTI neonates. Early diagnosis of UTIs in these infants could reduce the amount of time they need to be treated with phototherapy. In cases of poor phototherapy response, the presence of UTI should be considered [12].

In contrast to prior studies, which recommended that neonates with prolonged jaundice should only be screened for UTIs [3], [4], [21], [25]. Our study is consistent with Omar *et al.* study [24], which recommended early screening for all infants with unexplained indirect hyperbilirubinemia, especially when all other causes of hyperbilirubinemia have been ruled out. According to our findings, testing for UTIs should be included in the workup of neonates who develop jaundice in the early neonatal period.

Among UTI-positive cases, there were no significant ultrasonographic abnormalities. One case was only identified to have a posterior urethral valve with mild hydronephrosis by ultrasonography. In this case, all inflammatory indicators were negative, suggesting that the hydronephrosis was produced by a mechanical obstruction caused by the posterior urethral valve rather than a UTI. However, in a study by Ozdogan *et al.*, they found that roughly 30% of jaundiced infants with UTI had abnormal findings in renal ultrasonography [27].

Limitation of the study

The sampling type is convenient, but we tried to collect all the jaundiced neonates with UTIs who met the inclusion criteria during the period of study. The lack of ability to assess the role of some risk factors as role of circumcision in decreasing the prevalence of UTI as all participated males were not circumcised, also lack of follow-up of subjects.

Conclusions

UTI is substantially prevalent among neonates admitted to the NICU with unexplained indirect hyperbilirubinemia. The most commonly isolated microorganism was *E. coli*. Amikacin showed the highest susceptibility rates. The importance of routine

UTI screening (urine culture) as part of the clinical assessment of unexplained hyperbilirubinemia was highlighted in this study, particularly in neonates with leukocytosis with a high number of WBCs in their blood, pyuria, small for gestational age, prolonged phototherapy, and those born from mothers with a history of obstetric complications.

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