

**Original Article**

# Urinary tract infection and indirect hyperbilirubinemia in newborns

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**Citation:** Omar C, Hamza S, Bassem AM, Mariam R. Urinary tract infection and indirect hyperbilirubinemia in newborns.

**North Am J Med Sci** 2011; 3: 544-547.

**doi:** 10.4297/najms.2011.3544

## Abstract

**Background:** Jaundice is a common problem during the neonatal period. About 60% of the full term and 80% of premature infants develop jaundice. It can be associated with serious illnesses such as Urinary tract infections. **Aims:** The aim of this study is to evaluate the incidence and prevalence of urinary tract infection in newborns with indirect hyperbilirubinemia and to find a relationship with prolonged jaundice. **Patients and Methods:** We retrospectively evaluated asymptomatic, jaundiced neonates for evidence of a urinary tract infection. Data reviewed including demographic and historical data were included with data of blood studies, radiological evaluation and treatment. **Results:** 32 neonates of 152 cases had urinary tract infection. Most commonly isolated organisms were Klebsiella and Escherichia coli. Maximum duration of phototherapy was 4 days in the urinary tract infection group versus 7 in the non-urinary tract infection group. Intensive phototherapy was used in 18.7% in the urinary tract infection group versus 29.16% in the non-urinary tract infection group. None of the newborns in the urinary tract infection group underwent exchange transfusion therapy. **Conclusion:** Urinary tract infection can occur in asymptomatic, jaundiced newborns. Thus, it may be the first in these babies before other signs become evident.

**Keywords:** Jaundice, phototherapy, neonatal period.

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## Introduction

Jaundice is one of the most common problems during the neonatal period. About 60% of the full term and 80% of premature infants develop jaundice [1]. Unconjugated hyperbilirubinemia (UHB) is common and is associated with a variety of physiologic and pathologic conditions [2]. This occurs as a result of excessive bilirubin formation and because the neonatal liver cannot clear bilirubin rapidly enough from the blood. [3] Greater awareness is needed among all health workers about the description, causes, risk factors, effective treatment, and sequelae of neonatal jaundice [4]. The American Academy of Pediatrics (AAP) has published guidelines outlining the management of healthy newborns with hyperbilirubinemia, which includes maternal ABO and Rh typing, direct Coombs' test, blood and Rh (D) typing of infants' cord blood, and a total serum bilirubin level [5]. Laboratory tests recommended in case of readmission of the newborn for phototherapy or exchange transfusion in addition to the above mentioned

are complete blood count with differential and smear, reticulocyte count, ETCO (if available), G6PD if suggested by ethnic group or geographic origin or if poor response to phototherapy, urine for reducing substances, sepsis workup if suggested by clinical picture [6].

Indirect hyperbilirubinemia can be associated with severe illnesses such as hemolytic disease, metabolic and endocrine disorders, enzymatic deficiencies of the liver, and infections [7]. Sepsis is responsible for less than 2% of such cases [1]. Urinary tract infections (UTI) are attributed as the main reason for prolonged jaundice, and it is well known that UTI can occur without apparent signs, and jaundice is an important and sometimes the presenting feature of UTI [7].

The first objective of this study is to determine the incidence of urinary tract infections in asymptomatic, jaundiced newborns admitted to Makassed General

Hospital (MGH) under 4 weeks of age, and the second objective is to find a relationship between prolonged neonatal jaundice and UTI.

## Patients and Methods

Charts of jaundiced newborns below 4 weeks of age who were admitted to ICN or nursery at MGH from January 1<sup>st</sup>, 2004 till April 1<sup>st</sup> 2009 were reviewed. The demographic features including name, sex, date of admission, age at presentation, mode of delivery, mode of anesthesia, use of oxytocin or cytotec, type of assistance used, presence of cephalohematoma, bruising or caput succedaneum, weight at birth and at admission, age at onset of jaundice, baby's and mother's blood group, direct and indirect coomb's test, TSH and G6PD levels, mode of collection of the urine culture, type of organism revealed, result of urine analysis, bilirubin level at presentation and maximum level reached during hospitalization, CRP, WBC, blood culture, type of feeding, use and duration of antibiotics, duration of phototherapy, intensive phototherapy and exchange transfusion, final diagnosis, duration of hospital stay, discharge status, VUCG and ultrasound of the kidneys and urinary tract.

Urine was collected in a sterile way using a urine bag in males and catheterization in females. All samples were sent to the laboratory for microscopical analysis and culturing. Culture was considered positive when a single pathogen with more than 10,000 colony forming units/ml were discovered by catheterization or more than 10,000 colony forming units/ml if urine collected by bag. Urine culture was repeated if more than one pathogen was discovered or if the number of colonies did not match the above criteria.

Excluded charts were those of newborns more than four weeks of age, cases with direct hyperbilirubinemia, those having UTI not coinciding with the time of onset of jaundice, cases with co-morbidities causing indirect hyperbilirubinemia and septic condition or any sign of infection in the newborns during jaundice.

### Statistical analysis

Data were analyzed using Statistical Package of Social Sciences (SPSS) version 16.0 program using whole numbers, frequencies, means ( $\pm$ SD), median (minimum-maximum). Chi-squared tests were used to test differences between participants. *P* values < 0.05 were considered significant.

## Results

### Study population and demographics

All charts of newborns admitted to Makassed General Hospital intensive care unit from January 2004 till April 2009 was reviewed. Charts of 375 asymptomatic, jaundiced newborns were collected. Of these jaundiced newborns a urine culture was done in 179 (47.7%). 27 charts were excluded because of co-morbidities. The resulting 152 charts became the target of our study. All of

the newborns with positive urine culture result were full term whereas 114 (95%) newborns of the negative urine culture group were full term and only 6 (5%) were preterms. 19 (59.4%) of the positive urine culture group and 57 (47.5%) of the negative urine culture group were males, while 13 (40.6%) of the first group and 63 (52.5%) of the second group were females, male to female ratio was 1:1.46. 6 (19.4%) of the first group and 27 (23.1%) of the second group started to get jaundiced before 24 hours of life, the majority of newborns in both groups (24 and 83 in the first and second groups respectively) started to become jaundiced in the interval between 24 and 168 hours (8 days). Only 1 (3.2%) newborn from the first group and 7 (6%) of the second group started to become jaundiced after the 8<sup>th</sup> day of life. Concerning the mode of delivery 24 (75%) newborns of the first group and 86 (53.44%) of the second group were delivered vaginally and 8 (25%) from the first group and 33 (27.7%) of the second group were delivered by cesarean section. Exclusive breast milk was given to 15 (48.4%) and 55 (46.6%) of newborns from the first and second group respectively, nearly the same number of the newborns received mixed formula and breast milk feeding in both groups (48.4% and 51.7% respectively). Only a very small number received formula feeding (3.2% and 1.7% respectively). The demographic characteristics of patients with positive and negative urine culture are presented in Table 1. No statistically significant differences were found between the two groups with regard to gestational age, gender, age at onset of jaundice, mode of delivery and type of feeding.

**Table 1** Demographic characteristics of infants with positive and negative urine cultures

Characteristics	Urine Culture		P-Value
	Positive Urine Culture (n=32)	Negative Urine Culture (n=120)	
Gestational Age			0.197
Full term	32 (100%)	114 (95%)	
Preterm	0 (0%)	6 (5%)	
Gender			0.233
Male	19 (59.4%)	57 (47.5%)	
Female	13 (40.6%)	63 (52.5%)	
Age at Onset (hrs)			0.726
≤ 24	6 (19.4%)	27 (23.1%)	
24-168	24 (77.4%)	83 (70.9%)	
> 168	1 (3.2%)	7 (6%)	
Mode of Delivery			0.758
NVD	24 (75%)	86 (72.3%)	
C-Section	8 (25%)	33 (27.7%)	
Feeding			0.837
BM	15 (48.4%)	55 (46.6%)	
Formula	1 (3.2%)	2 (1.7%)	
Mixed	15 (48.4%)	61 (51.7%)	

Data are represented as Mean (SD) and Number (%).

### Incidence of UTI

Of 152 cases enrolled, positive urine cultures were found in 32 neonates (21.1%). Bacterial pathogens isolated from urine culture were: Klebsiella 15 cases (46.87%), E. coli 12 cases (37.5%), Pseudomonas 2 cases (6.25%),

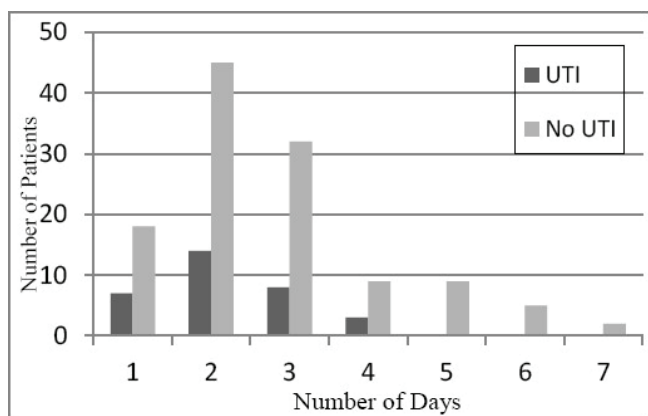
Enterobacter 1 case (3.12%), GBS 1 case (3.12%), and Staph aureus 1 case (3.12%) (Table 2).

**Table 2** Pathogens isolated from urine culture in hyperbilirubinemic neonates

Organism	Number (%)
<i>Klebsiella</i>	15 (46.87%)
<i>E coli.</i>	12 (37.5%)
<i>Pseudomonas</i>	2 (6.25%)
<i>Enterobacter</i>	1 (3.12%)
<i>GBS</i>	1 (3.12%)
<i>Staph aureus</i>	1 (3.12%)
Total	32 (100%)

**Table 3** Intensive Phototherapy

	Intensive Phototherapy		Exchange
	Yes	No	
Urine culture			
Positive	6 (18.75%)	26 (81.25%)	0 (0%)
Negative	35 (29.16%)	85 (70.84%)	4 (3.3%)
P-Value	0.274		



**Fig. 1** Duration of phototherapy in UTI and non-UTI groups

*Age at presentation*

Before the age of 8 days, jaundice was seen in 27 (84.3%) newborns of the UTI group and 100 (83.4%) of the non-UTI group. While after the age of 8 days jaundice was seen in 5 (15.6%) of the newborns with UTI and 20 (16.6%) of newborns without UTI.

*Age at onset of jaundice*

31 (96.7%) of newborns in the UTI group, and 110 (91.7%) of newborns in the non-UTI group started to have yellowish discoloration of skin before the age of 8 days while only one (3.3%) newborn with UTI and 10 (8.3%) of newborns without UTI started to have jaundice after the age of eight days.

*Outcomes*

All newborns in both groups were treated with phototherapy. The maximum duration of treatment in the UTI group was 4 days with the majority of newborns (14 cases) receiving 2 days of phototherapy. In the non-UTI group the maximum duration of phototherapy was 7 days

with the majority of newborns (45) receiving 2 days of phototherapy. Intensive phototherapy was used in 6 (18.7%) in the UTI group and 35 (29.16%) of the non-UTI group (Table 3). None of the newborns in the UTI group underwent exchange transfusion therapy versus the non-UTI group where 4 (3.3%) of the newborns underwent exchange (Figure 1).

Although not part of the study design, 32 of 32 newborns diagnosed with UTI had renal ultrasounds performed. Urinary tract abnormalities were found in 7 (21.87%) patients, which included pelvi-calyceal system dilatation. No abnormalities were found in voiding cystourethrogram obtained in 12 out of the 32 newborns in the UTI group.

**Discussion**

*Bilirubin Metabolism*

Bilirubin is produced by the catabolism of hemoglobin. Compared with older children and adults, newborns have a high rate of hemoglobin catabolism and bilirubin production because of their elevated hematocrit and red blood cell volume per body weight, and their shorter life span of red blood cells (70 to 90 days). Although bilirubin production is elevated in newborns, conjugation and clearance of bilirubin intake can cause delayed clearance of bilirubin [8].

In most jaundiced neonates, only unconjugated bilirubin is found in the blood, and the accumulated bilirubin is distributed by the circulation throughout the body and produces clinical jaundice. It generally is assumed that to cross intact cell membrane barriers the bilirubin must be free, or dissociated, from its albumin binding [9].

UTI in newborn infants affects 1 in 3 babies with proven bacterial infection [10], and the incidence is higher in low birth weight and preterm infants as well as febrile or hyperbilirubinemic patients [7, 11].

Some studies have indicated that jaundice maybe the first sign of a UTI. Bilgen in a series of 102 patients with asymptomatic unexplained indirect hyperbilirubinemia, UTI was diagnosed in (8%) of cases [1]. Garcia and Nager in a series of 160 asymptomatic jaundiced infants found positive urine culture in 7.5% of the infants younger than 8 weeks [5].

Our study showed similar results but with greater prevalence of UTI where in a series of 152 asymptomatic jaundiced newborns 32 (21%) had urinary tract infection all documented by urine cultures (Table 2).

*E. coli* is the most common etiologic agent of urinary tract infection, as found in older patients. *Klebsiella* and *Pseudomonas* species are encountered less frequently. Gram-positive bacteria, with the exception of *Enterococci*, are rare causes of urinary tract infections [9, 12].

The most common organism discovered in our study was *Klebsiella* with 15 (46.87%) cases, the second most

common was the *E. coli* with 12 (37.5%) cases. Other organisms with almost the same percentage were *Pseudomonas*, *Staph. Aureus*, *GBS*, and *Enterobacter*. A study conducted by Jafarzadeh and Mohammadzadeh in Neonatal Research Center in Iran had similar results of our study with *Klebsiella* the most common organism encountered [1].

Garcia et al. reported that infants with the onset of jaundice after eight days were more likely to have UTI [13], our study showed that almost all of the newborns with asymptomatic jaundice who were diagnosed to have UTI presented before the age of 8 days. This data was supported by a study done by Hülya Bilgen et al. in 2003 where they found that the onset of jaundice was <7 days in most of their cases [7].

Although Garcia et al [1] reported that patients with an elevated conjugated bilirubin fraction were more likely to have UTI, none of our patients had a high direct bilirubin level [7].

Concerning the duration of phototherapy our data showed that patients from the UTI group received phototherapy for a maximum of 4 days with the majority of patients receiving only 4 days, while patients in the non-UTI group received a maximum of 7 days of phototherapy with a similar majority receiving 2 days of phototherapy. Exchange transfusion was needed only in the non-UTI group. The fact that our patients needed phototherapy for only a short period of time and that intensive phototherapy was used in only 18% of the cases compared to 81% in the second group may be indicative of the fact that our practice of early detection of the UTI in these newborns may lead to a lesser need of phototherapy intensity and duration as well.

## Conclusion

UTI can occur in asymptomatic, jaundiced newborns. Thus, jaundice may be the first sign of UTI in these babies before other signs become evident. We recommend that testing for a UTI be part of the diagnostic evaluation of asymptomatic jaundiced newborns especially when no other obvious reason of jaundice is found. This may lead to early detection and treatment of these newborns leading to lesser long term complications of the urogenital tract especially the kidneys. We could also achieve shorter

duration of phototherapy and consequently hospital stay which decreases the risk of nosocomial infection and the cost of hospital stay.

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