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ORIGINAL ARTICLE

Causative organisms and antimicrobial susceptibility in jaundiced infants with significant bacteriuria

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Abstract

Background: Jaundice may be one of the first signs of urinary tract infection (UTI) in infants. The most common pathogen is Escherichia coli. Currently recommended antibiotic treatment for neonatal UTI is ampicillin and an aminoglycoside. Recently, increasing ampicillin and gentamicin resistance in strains of *E. coli* has been isolated. The aim of this study was to determine causative organisms and antimicrobial susceptibility in jaundiced infants with significant bacteriuria (SB).

Methods: We evaluated admitted afebrile, asymptomatic infants younger than 1-month old with hyperbilirubinemia (total bilirubin >15 mg/dl) requiring phototherapy between January 2011 and December 2015. A total of 615 asymptomatic jaundiced infants were enrolled. Urinalysis and urine cultures were performed on all jaundiced infants. A urine culture was defined as SB if a single pathogen with more than 10^5-colony forming units per milliliter (CFU/ml) by sterile urinary collection bag or 10^4 CFU/ml by catheterization was isolated.

Results: A total of 88 (14.3%) of 615 asymptomatic jaundiced infants had positive urinary culture. *E coli* was the most common cultured bacteria (40 cases, [45.5%]). *Enterococcus faecalis* was the second most common bacteria (17 cases, [19.3%]). Seven cases (8.0%) of *Streptococcus agalactiae* and six cases (6.8%) of *Klebsiella pneumoniae* were also identified. Ampicillin sensitivity was found in 22.5% of *E. coli* infections, gentamicin sensitivity was found in 84.2%, and extended-spectrum β-lactamases were found in 7.5%.

Conclusion: *E. coli* was the most common causative organism for infants with SB. We suggest modifying current empiric antibiotics by changing gentamicin to amikacin for neonatal Gram-negative bacterial infections.

Keywords: *Escherichia coli*; Extended-spectrum β-lactamases; Hyperbilirubinemia; Significant bacteriuria

1. INTRODUCTION

Jaundice is common during the neonatal period, and about 60% of newborn infants become clinically jaundiced. The causes of neonatal hyperbilirubinemia include ABO incompatibility, G-6-PD deficiency, breast milk feeding, polycythemia, and cephalohematoma.[1,2] Many previous studies have shown that urinary tract infection (UTI) is an important cause of neonatal hyperbilirubinemia.[3–14] The incidence of bacteriuria in infants with hyperbilirubinemia ranges from 5.5 to 21.1%.[3–9]

Escherichia coli is the most common causative organism for infants with significant bacteriuria (SB),[3,5,15] and currently recommended antibiotic treatment for neonatal UTI is ampicillin and aminoglycoside. Recently, increasing ampicillin and gentamicin resistance in strains of *E. coli* has been isolated.[15,16] The aims of this study were to determine the causative organisms and antimicrobial susceptibility for jaundiced infants with SB.

2. METHODS

We evaluated admitted afebrile, asymptomatic jaundiced infants <30 days requiring phototherapy in the intermediate care nursery between January 2011 and December 2015. All jaundiced infants had total bilirubin levels >15 mg/dl. A total of 615 infants were enrolled in this study. Between January 2011 and December 2014 (period 1), all jaundiced infants with SB received antibiotic therapy for 7 days. There were 495 jaundiced infants in period 1. Because the jaundiced infants with SB were afebrile, asymptomatic, and had normal laboratory findings, including normal complete blood count (CBC), differential count, and C-reactive protein (CRP) values, they did not have evidence of systemic infection. Neonatologists at our hospital decided to observe and follow-up for 1 year, without giving them routine antibiotics.

Between January 2015 and December 2015 (period 2), none of the jaundiced infants with SB in period 2 received antibiotic therapy, but were observed closely. There were 120 jaundiced infants in period 2. The infants with SB in period 2 were followed up for bacteriuria for 1 year, and age, gender, birth bodyweight, admission body weight, admission duration, maternal blood type, infant's blood type, and type of feeding were recorded. Blood samples were taken from all infants, and their CBC, reticulocyte count, CRP, blood type, direct and total bilirubin, and

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glucose-6-phosphate dehydrogenase (G-6-PD) levels were evaluated. Urinalysis and urinary culture obtained by sterile urinary plastic bag collection or bladder catheterization were performed for all 615 asymptomatic, jaundiced infants. Urine was collected in a sterile way using a urinary collection bag in men and bladder catheterization in women.

A urine culture was defined as SB if a single pathogen with more than 100 000 colony-forming units per milliliter (CFU/ml) by urinary collection bag or 10 000 CFU/ml by catheterization was detected. Pyuria was defined as the presence of ≥10 white blood cells (WBC) per high-powered field (HPF) of microscopy. Causative organisms and antimicrobial susceptibility to positive urinary cultures were also analyzed. The enrolled patients were divided into SB or no SB groups according to the results of the urinary culture. All SB patients underwent renal ultrasound examination. Patients with abnormal ultrasound (hydronephrosis or renal pelvis dilatation) results underwent a voiding cystourethrogram (VCUG) examination. All infants with congenital malformation, who were more than 1-month old, or who had multiple organisms isolated from urinary cultures were excluded from this study. This study was approved by the Ethical Committee at Chung Shan Medical University Hospital. The institutional review board (IRB) number was CSMUH No: CS 14150.

The data were analyzed using IBM SPSS version 22 for Windows (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed by Student's t-tests. Categorical data of the groups were analyzed by a Chi-square test. A p value <0.05 was considered statistically significant.

3. RESULTS

A total of 615 afebrile, asymptomatic jaundiced infants requiring phototherapy were enrolled in this study. All infants received urinalysis and urinary culture examination. Of these 615 jaundiced infants, 88 (14.3%) had positive urinary culture results, and 527 (85.7%) had negative urinary culture results. The basic characteristics of the studied infants are listed in Table 1. There was no significant difference ($p > 0.05$) with regard to birth weight, admission age, gender, or feeding practice between the SB group and the no SB group in period 1. There was a significantly longer ($p < 0.01$) duration of admission in the SB group than in the no SB group in period 1 and period 2. The mean peak bilirubin levels in the SB and no SB groups in period 1 were 17.6 ± 2.5 mg/dl and 17.6 ± 2.7 mg/dl, respectively, and the mean peak bilirubin level was 17.0 ± 2.8 mg/dl in the SB group in period 2. All jaundiced infants were treated with phototherapy, and none required an exchange transfusion.

The laboratory data of the 88 infants with SB are summarized in Table 2. Most infants (74 cases) in the SB group had direct bilirubin levels less than 1 mg/dl, 12 infants had direct bilirubin levels between 1.0 and 1.5 mg/dl, and only two infants had direct bilirubin levels between 1.51 and 2.0 mg/dl. All direct bilirubin levels were less than 10% (ranging from 4.3% to 9.8%) of the total bilirubin in the SB group. Only one infant in the SB group had a CRP value of 1.05 mg/dl, the other 87 infants in the SB group had CRP values less than 1 mg/dl. Most infants (79 cases) in the SB group had blood WBC values between 5000 and 15 000 cells/mm^3 and only nine infants in the SB group had blood WBC values between 15 001 and 20 000 cells/mm^3; however, all of them had an immature to total neutrophils (I/T) ratio of less than 0.2. None of the infants had blood WBC values less than 5000 cells/mm^3.

A total of 18 infants in the SB group had pyuria, 15 had positive urinary leukocyte esterase, and three had negative urinary leukocyte esterase. All infants with pyuria had negative urine nitrite results. Four infants in the SB group had abnormal renal ultrasound examinations (hydronephrosis or renal pelvis dilatation), and all received radiographic VCUG examinations. Vesicoureteral reflux (VUR) was graded as previous report.[17] Only one patient had unilateral grade II VUR.

Table 1

Basic characteristics of jaundiced infants with or without significant bacteriuria

	Period 1		Period 2
Characteristics	**SB (n = 72)**	**No SB (n = 423)**	**SB (n = 16)**
Birth weight (g)	3184.7 ± 527.0	3078.8 ± 1280.4	3028.2 ± 406.5
Admission age (d)	6.1 ± 2.9	6.4 ± 4.3	5.0 ± 2.0
Gender			
Male	36	219	12
Female	36	204	4
Mothers' blood type	20	136	5
A	14	97	4
B	34	175	6
O	4	15	1
AB	21	126	5
Infants' blood type	21	103	5
A	25	169	5
B	5	25	1
O			
AB			
Feeding practice			
Breast feeding	37 (53.4%)	226 (51.4%)	8 (50%)
Mixed feeding	32 (44.4%)	177 (41.8%)	7 (43.8%)
Formula feeding	3 (4.2%)	20 (4.7%)	1 (6.2%)
Duration of admission (d)	9.1 ± 3.4	5.4 ± 3.5*	5.9 ± 0.5*
Peak total bilirubin level (mg/dl)	17.6 ± 2.5	17.6 ± 2.7	17.0 ± 2.8

Data are mean ± SD, or number (n); SB = significant bacteriuria.

*$p < 0.01$, compared with SB group in period 1.

Table 2

Laboratory data of jaundiced infants with significant bacteriuria

	Period 1 (n = 72)	Period 2 (n = 16)
Peak total bilirubin level (mg/dl)	17.6 ± 2.5	17.0 ± 2.8
Range		
15.0–20.0	67	14
>20	5	2
Direct bilirubin level (mg/dl)	0.77 ± 0.3	0.39 ± 0.1
Range		
1.51–2.0	2	0
1.0–1.5	12	0
<1.0	58	16
CRP (mg/dl)	0.31 ± 0.17	0.09 ± 0.10
Range		
1–1.5	1	0
<1	71	16
WBC (cells/mm^3)	11 005 ± 3013.2	10 698 ± 2606.3
Range		
15 001–20 000	7	2
5000–15 000	65	14
<5000	0	0
Pyuria	18	0
With positive leukocyte esterase	15	0
With negative leukocyte esterase	3	0

Data are mean ± SD, or number (n).
CRP = C-reactive protein; WBC = white blood cells.

Organisms cultured from the urine in the SB group are listed in Table 3. *E. coli* was the most common cultured bacteria (40 cases, [45.5%]). *Enterococcus faecalis* was the second most common bacteria (17 cases, [19.3%]). The other main causative organisms were *Streptococcus agalactiae* (7 cases [8.0%]) and *Klebsiella pneumoniae* (6 cases [6.8%]). All 72 infants with SB in period 1 received 7 days of antibiotic therapy according to their urinary bacterial antimicrobial sensitivities. None of the 16 asymptomatic jaundiced infants with SB in period 2 received antibiotic therapy, but were observed closely, and all returned for post-discharge follow-up in the newborn follow-up clinic of our hospital for 1 year. SB resolved spontaneously in all 16 infants with SB in period 2. All 88 jaundiced infants received hearing screening tests, and none had abnormal hearing test results. The patient with VUR resolved spontaneously later. Table 4 shows the antimicrobial susceptibility to the main causative organisms for study infants with SB. *E. coli* was the most common cultured bacteria (45.5%). Ampicillin sensitive in 22.5%, gentamicin sensitive in 84.2%, ceftazidime sensitive in 89.5%, trimethoprim–sulfamethoxazole sensitive in 54.6%, and amikacin, piperacillin–tazobactam, ertapenem, meropenem, imipenem sensitive in 100% of *E. coli* infections. Extended-spectrum β-lactamases (ESBL) were found in 7.5% of *E. coli* infections. *E. faecalis* was the second most common bacteria (19.3%) in this study. Vancomycin, penicillin, teicoplamin, linezolid, and daptomycin sensitivity was found in 100% of *E. faecalis* infections, ampicillin sensitivity was found in 94.1%, and ciprofloxacin sensitivity was found in 83.3%.

S. agalactiae was isolated in 8% of patients, and 100% were sensitive to penicillin, vancomycin, teicoplamin, linezolid, ceftriaxone, and cefepime. *K. pneumoniae* was isolated from 6.8% of patients in this study, and ampicillin resistance was found in 100%, gentamicin sensitivity in 83.3%, and amikacin, piperacillin–tazobactam, ampicillin–sulbactam, ertapenem, meropenem, and imipenem sensitivity in 100% of *K. pneumoniae* infections. ESBL-positive was found in 16.7% of the *K. pneumoniae* infections in this study.

Table 3

Organisms cultured from urine with significant bacteriuria

	Period 1 (n = 72)	Period 2 (n = 16)	Total (n = 88)
Bacteria	**n (%)**	**n (%)**	**n (%)**
Escherichia coli	31 (43.1)	9 (56.3)	40 (45.5)
Enterococcus faecalis	14 (19.4)	3 (18.8)	17 (19.3)
Streptococcus agalactiae	7 (9.7)	0 (0)	7 (8.0)
Klebsiella pneumonia	4 (5.6)	2 (12.5)	6 (6.8)
Enterococcus species	4 (5.6)	1 (6.2)	5 (5.7)
Staphylococcus aureus	4 (5.6)	0 (0)	4 (4.5)
Enterobacter aerogenes	3 (4.2)	0 (0)	3 (3.4)
Serratia marcescens	2 (2.8)	1 (6.2)	3 (3.4)
Enterobacter cloacae	2 (2.8)	0 (0)	2 (2.3)
Citrobacter koseri	1 (1.4)	0 (0)	1 (1.1)

4. DISCUSSION

Common causes of neonatal hyperbilirubinemia include isoimmune-mediated hemolysis (e.g., ABO or RH(D) incompatibility), erythrocyte enzymatic defects (e.g., G-6-PD deficiency), inherited red blood cell membrane defects (e.g., hereditary spherocytosis or elliptocytosis), breast milk jaundice, and intestinal obstruction.[18] Many previous studies have shown that bacteriuria is an important cause of neonatal hyperbilirubinemia.[3–14] The incidence of bacteriuria in jaundiced infants has been reported in different studies as being between 5.5% and 21.1%.[3–9] Our study showed that 14.3% of admitted asymptomatic jaundiced infants requiring phototherapy had SB.

Two patients in our study had direct bilirubin levels between 1.51 and 2.0 mg/dl and 12 patients had direct bilirubin levels between 1.0 and 1.5 mg/dl; however, all direct bilirubin levels were less than 10% of the total bilirubin in the SB group, and all were considered indirect hyperbilirubinemia.[19] The same finding has been reported in previous research.[6–8,14] The American Academy of Pediatrics published guidelines outlining the management of healthy newborns with hyperbilirubinemia,[20] which recommended urinalysis and urine cultures to evaluate sepsis or UTI in cases with elevated direct bilirubin levels. Our study showed that most asymptomatic-jaundiced infants with SB had indirect hyperbilirubinemia and did not have elevated direct bilirubin levels.

In this study, the most commonly isolated organism from the urine culture was *E. coli* (45.5%). *E. faecalis* was the second most common bacteria (19.3%). Similar findings have been reported by previous studies.[3,4,15] Our study found that only 20.5% of cases in the SB group had pyuria (≥10 WBC/HPF). Of the 18 patients with pyuria, 15 (83.3%) had positive leukocyte esterase results, and none had positive nitrite results. The same finding has been reported by previous studies.[4–7]

Only one infant in the SB group had a CRP value of 1.05 mg/dl, and the other 87 infants in the SB group had CRP values of less than 1 mg/dl. Nine infants in the SB group had blood WBC values between 15 001 and 20 000 cells/mm^3; however, all nine infants had an immature/total neutrophils (I/T) ratio of less than 0.2. None of the infants in our study had leukopenia (WBC < 5000 cells/mm^3). Most jaundiced infants with SB in this study had indirect hyperbilirubinemia, normal CRP values, and normal CBC and WBC values. All jaundiced infants were asymptomatic, and none had evidence of systemic infection. None of the 16 asymptomatic jaundiced infants with SB in period 2 received antibiotic therapy; however, SB resolved spontaneously within 1 year. We believe that the SB of most asymptomatic jaundiced infants was transient. If their hematological laboratory findings are normal, their SB may resolve spontaneously later. It has been

Table 4

Antimicrobial susceptibility to main causative organisms for study infants with significant bacteriuria

	Causative organisms: percent (%) sensitive to antibiotics			
Antibiotics	***Escherichia coli* (n = 40)**	***Enterococcus faecalis* (n = 17)**	***Streptococcus agalactiae* (n = 7)**	***Klebsiella pneumoniae* (n = 6)**
Amikacin	100%			100%
Gentamicin	84.2%			83.3%
Ampicillin	22.5%	94.1%		0%
Piperacillin/tazobactam	100%			100%
Ampicillin/sulbactam	60.6%			100%
Ertapenem	100%			100%
Meropenem	100%			100%
Imipenem	100%			100%
Cefazolin	79.0%			83.3%
Ceftazidime	89.5%			83.3%
Ceftriaxone	86.8%		100%	83.3%
Cefepime	90.9%		100%	83.3%
Ciprofloxacin	90.9%	83.3%		100%
Levofloxacin	91.9%		100%	100%
Trimethoprim–sulfamethoxazole	54.6%			83.3%
ESBL-positive	7.5%			16.7%
Vancomycin		100%	100%	
Penicillin		100%	100%	
Teicoplamin		100%	100%	
Moxifloxacin			100%	
Linezolid		100%	100%	
Daptomycin		100%		

ESBL = extended-spectrum β-lactamases.

reported that some infants with asymptomatic bacteriuria might recover without the use of antimicrobial agents.[21–23]

Of the isolated *E. coli* infections, 22.5% were ampicillin sensitive, 84.2% were gentamicin sensitive, 60.6% were ampicillin–sulbactam sensitive, 54.6% were trimethoprim–sulfamethoxazole sensitive, and 100% of *E. coli* infections were amikacin and piperacillin–tazobactam sensitive. ESBL-producing phenotype was isolated in 7.5% infants with *E. coli* infections in this study.

Taheri et al. reported that *E. coli* was the dominant organism in 76.3% of neonates with UTIs and 95.9% of them were ampicillin resistant.[15] Friedman et al. also reported that ampicillin-resistant *E. coli* were isolated in 75% and 53% of early and late-onset neonatal *E. coli* infections, respectively.[16] They also reported that gentamicin-resistant *E. coli* was found in 50% of early-onset and 16% of late-onset neonatal *E. coli* infections.[16] ESBL-producing *E. coli* infections have been described in recent studies.[24–26] Resistance to cephalosporins inducing third-generation cephalosporins are commonly found in ESBL-producing *E. coli* infections.[27] In this study, cefazolin sensitivity was found in 79.0% of *E. coli* infections, ceftazidime sensitivity in 89.5%, ceftriaxone sensitivity in 86.8%, and cefepime sensitivity in 90.9%. Quinolones resistant ESBL-producing *E. coli* had also been reported.[27] Ciprofloxacin sensitivity was found in 90.9% of *E. coli* infections in this study and levofloxacin sensitivity in 91.9%. Although carbapenem-resistant *E. coli* has been reported,[28,29] all *E. coli* infections were sensitive to ertapenem, meropenem, and imipenem in this study.

E. faecalis was the second most common organism isolated in this study. Ampicillin sensitivity was found in 94.1% of patients with *E. faecalis* infections, ciprofloxacin sensitivity in 83.3%, and penicillin, vancomycin, teicoplanin, linezolid, and daptomycin sensitivity in 100%. *S. agalactiae* was the third most common organism isolated in this study. All patients were sensitive to penicillin, vancomycin, teicoplanin, linezolid, ceftriaxone, cefepime, and levofloxacin.

K. pneumoniae was the fourth most common organism isolated in this study. Ampicillin resistance was found in 100% of *K. pneumoniae* infections, and gentamicin sensitivity in 83.3%. ESBL-producing *K. pneumoniae* was found in 16.7% of patients. All patients with *K. pneumoniae* infections were sensitive to amikacin, piperacillin–tazobactam, and ampicillin–sulbactam. Although carbapenem-resistant *K. pneumoniae* infections have been reported previously,[30–33] all our patients with *K. pneumoniae* infections were sensitive to ertapenem, meropenem, and imipenem.

Traditionally, ampicillin plus gentamicin or ampicillin plus cefotaxime has been used as empiric therapy for neonatal UTI or neonatal sepsis.[34–36] Glikman et al. reported that gentamicin resistance was evident in 16% of Gram-negative pathogens, while only 3% were amikacin-resistant. ESBL-positive was noted in 14% of Gram-negative isolates.[36] It was reported by Li et al. that 69.7% of *E. coli* infections were sensitive to gentamicin and 100% were sensitive to amikacin.[37] They also reported that 80.65% of *Klebsilla* species infections were sensitive to gentamicin and 100% were sensitive to amikacin.[37] In this study, gentamicin resistance was found in 15.8% of *E. coli* infections, and ESBL-positive was noted in 7.5%. Gentamicin resistance was found in 16.7% of *K. pneumoniae* infections, and ESBL-positive was noted in 16.7%. All patients with *E. coli* or *K. pneumoniae* infections were sensitive to amikacin. Many previous reports have shown that potential adverse effects, including nephrotoxicity in amikacin, were no more than gentamicin in neonates.[38–40] We suggest that modification of current empiric antibiotics for amikacin-based regimens should be considered, mainly in newborn infants with Gram-negative bacterial infections.

Our study has some limitations. First, it was a single-center study. Second, not all of the 615 asymptomatic jaundiced infants received bladder catheterization or suprapubic puncture to obtain samples for urinalysis or urinary culture. Usually, urine was collected in a sterile way using a urinary collection bag for men and bladder catheterization for women.

In conclusion, 14.3% of asymptomatic jaundiced newborn infants requiring phototherapy had SB. *E. coli* was the most

common (45.5%) causative organism. Of the patients with *E. coli* infections, 22.5% were sensitive to ampicillin, 84.2% were sensitive to gentamicin, and all were sensitive to amikacin, piperacillin–tazobactam, and carbapenem. ESBL-producing *E. coli* was found in 7.5% of these patients. We suggest modifying current empiric antibiotics by changing gentamicin to amikacin for neonatal Gram-negative bacterial infections.

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