



Frequency and Susceptibility of Bacteria Caused Urinary Tract Infection in Neonates: Eight-Year Study at Neonatal Division of Bahrami Children's Hospital, Tehran Iran

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Abstract

Background: Susceptibility pattern of organisms causing urinary tract infection (UTI) in neonate would potentially improve the clinical management by enabling clinicians to choose most reasonable first line empirical antibiotics. This study aimed to this end by studying isolated organisms from neonates with UTI in an inpatient setting.

Methods: Current retrospective study has recruited all cases of neonatal UTI diagnosed through a suprapubic/ catheterized sample, admitted to Neonatal Division of Bahrami Children's Hospital, Tehran, Iran, from June 2004 to June 2012.

Results: *Escherichia coli* was the dominant (64.4%) bacteria among a total of 73 cases (69.9% boys and 30.1% girls; aged 14.14 ± 7.68 days; birth weight of 3055.85 ± 623.00 g) and *Enterobacter* (19.2%), *Klebsiella* (12.3%), and *Staphylococcus epidermidis* (4.1%) were less frequent isolated bacteria. *E. coli* was mostly resistant to ampicillin (93.6%), cefixime (85.7%) and cephalexin (77.3%), and sensitive to cefotaxime (63.6%). *Enterobacter* found to be most resistant to amikacin (100%), ampicillin (92.85%), and most sensitive to ceftizoxime (71.4%).

Conclusion: A high ratio (> 92.85%) of resistance toward ampicillin was observed among common neonatal UTI bacterial agents. Having this finding along with previous reports of emerging resistance of neonatal uropathogens to ampicillin could be a notion that a combination of a third generation cephalosporin and an aminoglycoside would be a more reasonable first choice than ampicillin plus an aminoglycoside.

Keywords: Urinary tract infection, Neonates, Antimicrobial susceptibility, Hospital, Iran

Introduction

UTI is a common problem in infants and young children (1, 2); however, its frequency, symptoms and causative organisms varies in accordance with sex, age, and gender (3). Unlike other age groups neonates present with non-specific signs and symptoms (4) warranting a complete sepsis workup followed by a 7 to 14 day-course of antibiotic therapy (2), typically parenteral ampicillin plus an aminoglycoside (5) or a third-generation cephalosporin (6, 7). Recent reports on emerging patterns of resistance toward empirical antibiotics (8-12), especially ampicillin (13-17), have made the

early choice of antibiotics a more challenging decision (8). The criticalness of issue lies in the fact that those diagnosed earlier and treated accordingly, are less likely to bear long-term consequences imposing an increased burden on health care systems (18).

Clinical manifestations of UTI in neonates are mostly non-specific and of a systemic nature (15) like fever, irritability, lethargy, vomiting, growth failure, abnormal urination- namely oliguria, polyuria or malodorous urine, and jaundice (14, 19-21). the non-specific presentations often make UTI

hard to diagnosis; however, its reported prevalence ranges from 4- 25% (22) in in very low weight infants (birth weight \leq 1000 g) to 0.1-1% in term infants (23). Additionally, UTI in newborns could lead to urosepsis or neonatal sepsis that is why it is often managed as a case of sepsis (24).

Most UTIs in infants are caused by gram-negative bacilli (23, 25-27). *E. coli* has been the most prevalent organism causing UTI in all ages including neonatal period (1, 21, 28-30) accounting for as many as 80% of isolates in many studies (25). Other Enterobacteriaceae causing UTI in neonates include *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Providencia*, *Morganella*, *Serratia*, and *Salmonella* (6, 26, 27). Gram-positive bacteria like *Staphylococcus* and *Enterococcus* have less been retrieved from neonates with UTI (2, 26).

Appropriate management essentially mandates knowledge of most prevalent pathogens along with their susceptibility pattern. This is not possible unless a continuous surveillance is done and let therapeutic choices to be updated accordantly. Having said that, it is an accepted practice that neonatal units" take into account their prevailing antibiotic sensitivities of local bacterial isolates" (31, 32). These motivated researchers to retrospectively review all UTI cases managed in an inpatient setting of neonatal division and aim to this end. The primary intention of this study was to see the frequency of UTI causative organisms in neonates admitted to Neonatal division of Bahrami Children's Hospital over an eight-year period. Secondly it meant to elucidate antibiotic susceptibility pattern of isolated uropathogens.

Materials and Methods

Study design and setting

The study accomplished at the Neonatal Division of Bahrami Children's Hospital-Tehran, Iran, the largest tertiary pediatric center in the eastern end of Tehran. All cases over an eight-year period (June 2004 to June 2012) constituted the population of current study

The source of extracted data were the hospital records of the patients regarding age (day), sex,

date and method of urine sample collection, urine culture results, and antibiogram reports. The latter routinely was based on the report of Laboratory Unit of Bahrami Children's Hospital which reports antibiogram by semi-quantitative approach based on diffusion technique, and the available laboratory standards.

Inclusion criteria and definitions

Current study designed as a case series using simple non-random sampling to recruit all cases with diagnosis of UTI admitted to Neonatal division of Bahrami Children Hospital –Tehran, Iran in 2004-to-2012 period. In this study, UTI was defined (6) as: i) a pure growth of single bacteria from a urine sample obtained by suprapubic aspirate, ii) $\geq 10^3$ CFU/ml from a urine sample obtained by catheterization.

Cases with more than one episode of UTI were separately analyzed if they occurred more than 14 days apart. Only the result of the first positive urine culture was extracted. In the event of two separate initial positive cultures, result of suprapubic aspirate was taken into account.

Exclusion criteria

Cases diagnosed on the basis of a urine bag sample were not included in the study. Those with incomplete records, including absence of two confirmatory progress notes regarding urine sample collection method were excluded from the study. To increase accountability of results, only those cases included which had a physician progress note and nursing staff note on the way urine is collected.

Mixed growth urine cultures denoting growth of two or more organisms in one sample were excluded, as they are likely to represent contaminated samples. Episodes with urine samples growing fungal organisms were also excluded.

Data analysis

All extracted data entered in SPSS (Ver. 17) software spreadsheets. Ultimately, quantitative data displayed as minimum, maximum, means, standard deviation, and qualitative data as the relative frequency.

Ethical approval

All research ethics and regulations adopted by the Iranian Medical Commission of Scientific Research Council were considered in every steps of this study and researchers will adhere to it. Academic honesty and trustworthiness, impartiality and avoiding certain trends have been respected; however, the study was not posed with any other ethical prohibition and was approved by the Research Ethics Committee of the Tehran University of Medical Sciences.

Results

A total of 73 cases (mean age, 14.14 ± 7.68 days; mean birth weight of 3055.85 ± 623.00 grams; and mean admission weight of 3180.55 ± 610.25 grams) fulfilled the inclusion criteria and recruited in the study. Besides, 14 cases were excluded from the study population. Boys constituted 69.9% (51 neonates) of the study population, bringing a boys-to-girls ratio of 2.32.

Four different bacteria were isolated from retrospectively assessed cases, namely *E. coli*, *Enterobacter*, *Klebsiella*, and *S. epidermidis*. No cases of *Proteus*, *Pseudomonas*, *Serratia*, *S. aureus*, *Enterococcus* were found over the study period.

E. coli was the most prevalent organism of the study with a relative frequency of 64.4% (47 cases) followed by *Enterobacter* with a relative frequency of 19.2% (14 case). However, frequency of isolated organisms as well as their relative frequency in study population is represented in Table 1

Table 1: Distribution of organisms isolated from the urine in the study

	Freq.	Relative Freq.
<i>E. coli</i>	47	64.4
<i>Enterobacter</i>	14	19.2
<i>Klebsiella</i>	9	12.3
<i>S. epidermidis</i>	3	4.1
Total	73	100.0

In this study, *E. coli* found to be mostly resistant toward ampicillin (93.6% (44 cases)), cefixime 85.7% and cephalexin 77.3% respectively. The most sensitivity of *E. coli* toward the antibiotics commonly used as first line neonatal empirical therapy were toward cefotaxime (63.6%); however, its most susceptibility was to norfloxacin (100%) and ciprofloxacin (100%) respectively in 14 and 12 patients. The general overview of *E. coli* susceptibility pattern toward all applied discs is summarized in Table 2.

Table 2: Distribution of study *Escherichia coli* antibiotic susceptibility pattern

Antibiotic	Resistance		Sensitivity		Total used discs
	Freq	Relative Freq.	Freq.	Relative freq.	
Ampicillin	44	93.6	3	6.4	47
Tmp-smx	22	48.9	23	51.1	45
Nalidixic acid	11	23.4	36	76.6	47
Nitrofurantoin	8	17	39	83	47
Gentamicin	22	59.5	15	40.5	37
Amikacin	17	56.7	13	43.3	30
Ceftriaxone	9	50	9	50	18
Ceftazidime	7	53.8	6	46.2	13
Cefotaxime	4	36.4	7	63.6	11
Cephalexin	17	77.3	5	22.7	22
Ceftizoxime	15	78.9	4	21.1	19
Cefixime	12	85.7	2	14.3	14
Ciprofloxacin	0	0	12	100	12
Norfloxacin	0	0	14	100	14

Enterobacter susceptibility pattern was representative of a high resistance to amikacin (100%) and ampicillin (92.8) respectively in 4 and 13 cases, and high sensitivity to ceftazidime (100%) and norfloxacin (100%) respectively in 5 and 6 cases; nonetheless, its most susceptibility toward commonly used neonatal empirical therapy antibiotics was in face of ceftizoxime (71.4%). The detailed overview of *Enterobacter* antibiogram is depicted in Table 3. Notably less fre-

quent isolated uropathogens of this study, *Klebsiella* and *S. epidermidis*, were found to be completely (100%) resistant to ampicillin. Moreover *Klebsiella* showed no sensitivity to cefixime and ceftizoxime. Contrarily *Klebsiella* was most sensitivity to TMP-SMX and nitrofurantoin. *S. epidermidis* was found to be highly sensitive to Gentamicin (100%). Table 4 and 5 have summarized cumulative susceptibility pattern of *S. epidermidis* and *Klebsiella*.

Table 3: Distribution of study *Enterobacter* antibiotic susceptibility pattern

Antibiotic	Resistance		Sensitivity		Total used discs
	Freq.	Relative freq.	Freq.	Relative freq.	
Ampicillin	13	92.9	1	7.1	14
Tmp-smx	6	42.9	8	57.1	14
Nalidixic Acid	1	7.1	13	92.9	14
Nitrofurantoin	5	35.7	9	64.3	14
Gentamicin	9	69.2	4	30.8	13
Amikacin	4	100	0	0	4
Ceftriaxone	2	28.6	5	71.4	7
Ceftazidime	0	0	5	100	5
Cephalexin	3	75	1	25	4
Ceftizoxime	2	28.6	5	71.4	7
Norfloxacin	0	0	6	100	6

Table 4: Distribution of study *S. epidermidis* antibiotic susceptibility pattern

Antibiotic	Resistance		Sensitivity		Total used discs
	Freq.	Relative Freq.	Freq.	Relative Freq.	
Ampicillin	3	100	0	0	3
Tmp-smx	2	66.7	1	33.3	3
Nalidixic Acid	1	33.3	2	66.7	3
Nitrofurantoin	1	33.3	2	66.7	3
Gentamicin	0	0	3	100	3
Ciprofloxacin	1	33.3	2	66.7	3

Table 5: Distribution of study *Klebsiella* antibiotic susceptibility pattern

Antibiotic	Resistance		Sensitivity		Total used discs
	Freq.	Relative Freq.	Freq.	Relative Freq.	
Ampicillin	9	100	0	0	9
Tmp-smx	2	22.2	7	77.8	9
Nalidixic Acid	2	22.2	7	77.8	9
Nitrofurantoin	4	44.4	5	55.6	9
Gentamicin	3	50	3	50	6
Amikacin	4	50	4	50	8
Ceftriaxone	2	66.7	1	33.3	3
Ceftazidime	3	75	1	25	4
Cefotaxime	2	66.7	1	33.3	3
Cephalexin	4	80	1	20	5
Ceftizoxime	3	100	0	0	3
Cefixime	3	100	0	0	3

Discussion

Current study showed *E. coli* to be the most prevalent (64.4%) organism causing UTI in neonates admitted to Neonatal Division of Bahrami Children's Hospital over an eight-year. Besides gram negative bacteria comprised the leading cause (95.8%) of UTI in the study population. This finding is in agreement with most of past studies (e.g., 1, 21, 28-30) over the subject.

It is already known that UTI incidence in boys exceeds that of girls in first few months of life; however, this sex-related dominancy would change toward girls by end of first year and thereafter (2, 6). Based on epidemiological data on neonatal UTI, this boys-to-girls incidence ratio estimated as 2 to 1 (6). Current study 69.9% frequency of UTI among boys comes to a boys-to-girls ratio of 2.32, which is compatible with foreseeable higher incidence of in boys.

On an overview of previous national studies, *E. coli* has been reported as the leading uropathogen in neonates with UTI with various relative frequencies: 80.5% in Qazvin (14), 76.5% in Tehran (20), 76.3% in Tehran (33), 50% in Kashan (34), and 50% in Uromia (35). Unlike previous national based studies, *Proteus* (14), *Pseudomonas* (14, 35), *Serratia* (36), *S. aureus* (20) were not retrieved in this study.

In compare to other age groups, continuous assessment of uropathogen epidemiology in neonatal period is of profound significance, as UTI is hard to diagnose at this age group and could potentially lead to systemic infection leaving potential life threatening and long term sequel. Moreover this would enable clinicians to choose an empirical therapy regimen that is most clinically and epidemiologically ideal till further microbiologic results are available. Furthermore it is an accepted practice that neonatal divisions take into account the prevailing antibiotic sensitivities of local bacterial isolates before opting an empirical regimen (32). Having said all these, to our knowledge, this is an area which has least been under attention of neonatal divisions across the country. Most of previous studies on neonatal UTI were focused on

the relationship of neonatal UTI and some non-specific signs and symptoms such as neonatal jaundice.

Recent observed resistance patterns towards antibiotics commonly being used in empirical therapy of neonates with UTI and or sepsis, namely ampicillin along with aminoglycoside or a third-generation cephalosporin (13-17), have raised concern over the efficacy of current treatment protocols and even the need for changes in present regimens (9-12). Resistant toward ampicillin has been reported by many studies (13-17). However, there are few studies assessing susceptibility pattern of neonatal UTI organisms toward a wide spectrum of antibiotics (8, 31, 32).

On the view point of susceptibility to neonatal empirical therapy antibiotics at this study, *E. coli* was resistant to ampicillin in 93.6%, ceftizoxime in 78.9% gentamycin in 59.5% and amikacin in 56.7% cases. Less frequently isolated organisms also showed different but consistent susceptibility patterns: *Enterobacter* resistance was: 92.9% to ampicillin, 69.2- 100% to aminoglycosides (Gentamycin and Amikacin), and 0-28.6% to third-generation cephalosporins; *Klebsiella* and *S. epidermidis* were found to be sensitive to Gentamycin 50% and 100% respectively.

Comparing our results with few past national-based studies is representative of some shift in sensitivity patterns of uropathogens isolated from neonates with UTI. Movahedian et al. (34) reported *E. coli* resistant ratio to be 78.9%, 64.7%, 5.25%, and 5.25% toward cephalixin, ampicillin, amikacin, and gentamycin respectively in 2007. Our study found a dramatic almost ten-fold resistance to amikacin and gentamycin and 144% increase -in resistance rate to ampicillin; however, the resistance to cephalixin has a little decreased. It is not clear whether this change in susceptibility pattern of *E. coli* toward ampicillin, amikacin, and gentamycin is secondary to overusage of these antibiotics, as one of accepted empirical regimen, or it is due to an original different in susceptibility patterns in Kashan and Tehran cities, where the studies accomplished. On the same comparative view to Movahedian et al study, *Klebsiella* susceptibility toward ampicillin, cephalixin, and gentami-

cin has not changed but *Klebsiella* exhibits an almost ten-fold resistance rate to amikacin.

Strengths and limitations

The strengths of our study include: i) the large sample size relative to low prevalence of urinary tract infection in term neonates, 0.1% to 1% (23). It needs to be mentioned that in Bahrami Children Hospital, pre-term neonates with diagnosis of sepsis most often would be admitted to NICU than Neonatal Division where our study accomplished. ii) the long period of the study which enabled researcher to recruit larger number of cases. iii) the accountability of the urine samples included in the study (suprapubic aspirate or catheterization). All included cases were diagnosed upon a suprapubic aspirate or catheterizations which are the most accepted means (6, 37) of collecting urine sample in acute settings in need of instituting an empirical antibiotic. Besides, all cases with incomplete double-notes on the method of urine collection (physician note and nursing staff note) were excluded from the study population to: i) adhere to study inclusion criteria, ii) decreasing chance of the recruiting contaminated samples in the study.

Limitations of our study include its retrospective nature which made us to: i) inevitably miss some cases due to their incomplete records, ii) report the susceptibility results on the basis of number of individual antibiotic discs applied over total cases, iii) not having the chance of assessing isolated uropathogens toward a wide spectrum of antibiotics. Nonetheless, ampicillin was the sole antibiotic which had been applied to almost all studied cases.

Conclusion

According to previous studies (31, 32), the guiding key to choose the empirical antibiotic with the most efficacy, and the least side effect is understanding of causative organisms susceptibility pattern. Otherwise, it is less likely to manage as efficacious as possible. The susceptibility patterns not only are different over various centres but also vary over the time. The most prevalent organisms

implicated in this study were significantly resistant to ampicillin - a frequent combining to empirical antibiotic regimen. Having reviewed neonatal uropathogens over the past 8 years, authors believes a third generation cephalosporins plus an aminoglycoside would be a better choice to ampicillin plus an aminoglycoside as the first line of empiric therapy of neonatal UTI.

Lack of extensive and multi-central studies over neonatal UTI in Iran warrants prospective future studies on this subject, and authors believes the results of this study could stress the necessity to conduct such projects and motivate further researcher on assessing the subject.

Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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