Neonatal Urinary Tract Infection: Clinical Response to Empirical Therapy versus *In vitro* Susceptibility at Bahrami Children's Hospital- Neonatal Ward: 2001-2010

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Abstract- Urinary tract infection (UTI) is a neonatal life threatening infection which is usually treated with ampicillin plus an aminoglycoside or a third-generation cephalosporin. Recently, growing number of *Escherchia coli* species resistant to ampicillin and aminoglycosides have raised concerns regarding the necessity to change the empirical therapy. This motivates us to determine neonatal UTI clinical response to the used empirical antibiotics. This study was designed as a Case Series. All neonates admitted to Bahrami Children Hospital, Tehran, Iran, during 2001- 2010 with a diagnosis of UTI surveyed by simple non-random sampling. Totally, 97 cases (including 83 (85.6%) term, 8 (8.2%) post-term and 6 (6.2%) preterm neonates) with a mean age of 15.85 ± 7.05 days at admission ,average weight of 3195.57 ± 553g at birth and 3276.29 ± 599.182 g at admission were studied. Ampicillin resistance in 93 cases (95.9%), gentamicin resistance in 51 cases (52.6%) and trimethoprim- sulfamethoxazole resistance in 44 cases (45.4%) were the leading resistances in this study. *Escherichia coli* was the dominant organism in 76.3% (74 patients) of study population which was resistant to ampicillin in 95.9% (71 cases). Despite the observed resistant to initial empirical regimen antibiotics (especially ampicillin), 81.4% of patients responded to empirical therapy. However, we believe till conductance of more detailed studies regarding the relationship between empirical therapy and antibiogram concordance, physicians take ampicillin-resistant E coli infection issue into accounts from the first steps of management of critically ill neonates.

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Keywords: Neonate; Urinary tract infections; Ampicillin resistance; Echerichia coli; Sepsis

Introduction

Urinary tract infection (UTI) is a common pediatric infection including neonates with a prevalence of 0.1% to 1% in term infants (1), and predominance of male sex (2 to 1 ratio) (2); however, it is considerably more common in very low weight infants (birth weight ≤ 1000 g) with a prevalence between 4% and 25% (3). The clinical manifestations of UTIs in newborn infants are extremely variable, ranging from severe illness to nonspecific signs and symptoms, such as growth failure, vomiting, diarrhea, fever, irritability, lethargy, abnormal urination- namely oliguria, polyuria or malodorous urine, and jaundice (4,5).

It is not clear whether neonatal UTI occurs secondary to bacteremia, an important issue that is associated with high morbidity and mortality rates in newborns infants, or causes it (2). However, neonatal UTI generally consider as a serious bacterial illness requiring the complete sepsis workup for sepsis, followed by 7 to 14 days of parenteral antibiotics (6). In the published American Academy of Pediatrics recommendations for diagnosis, treatment, and evaluation of initial UTI in febrile infants and young children, there is no suggested recommendations for infants of 2 month old or less (7); nevertheless, usual treatment for febrile neonates consists of ampicillin plus an aminoglycoside or a third-generation cephalosporin (2,8).

This regime was first suggested when group B streptococcus infection was dominant and antibiotic resistances were rare (9).

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Escherichia coli has been the most prevalent cultured organism of neonatal urinary tract infections in many studies (10-12); however, other Gram-negative bacilli such as *Klebsiella spp*, *Enterobacter*, and *Seratia spp* are also involved (1,2,13-14). Recently, growing number of *Escherichia coli* species resistant to ampicillin and aminoglycosides isolated from neonates with UTI (15) have raised concerns regarding the necessity to amend the common empirical therapy (15-17). Respectively, the present study aimed to determine neonatal urinary tract infection clinical response to the common empirical antibiotic regimen and then compared the clinical results with antibiogram pattern, as to portray a schematic efficacy of current empirical therapy efficacy.

Materials and Methods

This study was designed as a case series to analyze all neonates with UTI admitted to Bahrami Children Hospital-Neonatal Ward, Tehran, Iran, during 2001-2010. Simple non-random sampling method was implemented. UTI was defined as isolation of any bacteria from a bladder aspirate or counts of 10^3 or higher colony-forming units per milliliter of catheterized urine (2). Inclusion criteria were those cases diagnosed on the basis of supra pubic aspiration or catheterization; furthermore, cases with incomplete records were later excluded from the study.

The population study records surveyed retrospectively to acquire data regarding sex, birth weight, admission weight, gestational age, age on admission, cultured organism, the necessity to change antibiotic regimen during admission interval due to clinical unresponsiveness, and concordance of prescribed empirical therapy with urine susceptibility. A questionnaire was filled for every neonate and finally 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.

In this study, *empirical therapy* refers to "the antibiotic regimen used first in the treatment of admitted neonates with diagnosis of UTI", *antibiogram* refers to "antibiotic susceptibility of cultured organism isolated from urine of neonates with UTI", and *concordance of empirical therapy and antibiogram* refers to "the degree of similarity between empiric antibiotics adminstered in the treatment and sensitive antibiotics based on urine culture antibiogram".

Also, in this study *clinical responsiveness* is considered as a subjective criterion which retrospectively extracted from the patient records by reviewing progress notes denoting reduced fever, improved neonatal reflexes, restfulness and improved feeding, control of vomiting and other symptoms of neonatal septicemia. Furthermore, *clinical unresponsiveness* refers to the necessity to alter patient's antibiotic regimen in the first 48 hours of admission (before the availability of urine culture antibiogram) due to lack of response based on clinical criterion as explained for *clinical responsiveness*, deterioration of patient status, or positive urine culture after 48 hours of antibiotic therapy

All research ethics and regulations adopted by the Iranian Council of Scientific Research- Medical Commission in 1991 were considered in every steps of this study and researcher 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.

Results

In this study, 97 neonates including 83 (85.6%) term, 8 (8.2%) post term and 6 (6.2%) preterm neonates) were analyzed. Boys constituted 66% (64 neonates) of the study population. On hospitalization neonates had got a mean age of 15.85±7.05 days, and 3276.29±599.182 g (mean birth weight of 3195.57±553.009 g).

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

	Frequency	**relative frequency**
Escherichia coli	74	76.3
Proteus	10	10.3
Enterococcus	7	7.2
Staph Epidermis	3	3.1
Enterobacter	3	3.1
Total	97	100.0

Table 2. Distribution of study *In Vitro* antibiotic resistance pattern (observed in the study population and % relative to each column).

	Escherichia coli	Proteus	Enterococcus	Total
Ampicillin	71(95.9%)	10 (100%)	6 (85.7%)	93 (95.9%)
Amikacin	22 (29.7%)	4 (40%)	3 (42.9%)	31 (32%)
Ceftriaxone	14 (18.9%)	2 (20%)	2 (28.6%)	20 (25.8%)
Ceftizoxime	20 (20.6%)	3 (30%)	2 (28.6%)	20 (25.8%)
Ceftazidime	12 (12.4)	3 (30%)	0	15 (15.5%)
TMP-SMX	34 (45.9%)	3 (30%)	3 (42.9%)	44 (45.4%)
Gentamycin	39 (52.7%)	3 (30%)	4 (57.1%)	51 (52.6%)

Escherichia coli was the dominant isolated organism in the study with a relative frequency of 76.3% (74 cases); however, the other isolated organisms are also depicted in table 1.

Ampicillin was the antibiotic to which the most resistance observed (95.9% (93 cases)), followed by gentamycin resistance in 51 cases (52.6%) and Trimethoprim- sulfamethoxazole (TMP-SMX) in 44 cases (45.4%). On the other hand, no resistance to vancomycin, and imipenem was reported. Also, total number of organisms resistant to empirical antibiotics along with relative resistance percentage of each organism to these is outlined in table 2.

In this study, 81.4% study population (79 cases) responded to the prescribed empirical therapy as evidenced by clinical responsiveness, and only 18.5% (18 cases) faced clinical unresponsiveness. On the other hand, *concordance of empirical therapy and antibiogram* in the study was as follows: full (in both antibiotics) in 14 cases (14.4%), moderate (only one antibiotic) in 62 cases (63.9%), and none in 21 case (21.6%). We then analyzed *clinical responsiveness* in comparison with *concordance of empirical therapy and antibiogram*, as is depicted in table 3. Interestingly, both antibiotic administered in the empirical regimen of 20.3% neonates with clinical response (16 cases) were non-concordant with susceptible antibiotics based on antibiogram. On the other hand, 22.2% neonates faced lack of clinical response to empirical therapy (4 cases) despite full concordance of antibiotics used in the empirical therapy with antibiogram susceptibility results. However, the most prevalent *empirical therapy and antibiogram* concordance pattern is moderate one.

Discussion

Urinary tract infection (UTI) in neonates is more common in very low birth weight (birth weight ≤1000 g) and preterm infants (2,3,18); however mean population weight in this study was 3276.29±599.182 and term infants constituted majority (85.6%) of cases, both of which can be due to the fact that our study population included only those admitted to neonatal ward of Bahrami Children Hospital, Tehran, Iran where as a general policy very low birth weight and pre term newborns preferably are admitted to Neonatal Intensive Care Unit and mostly discharge from there straight away.

Escherichia coli was the leading organism (76.3%) of neonatal urinary tract infection in this study-consistent with many previous studies, including Safar et al (19) and Zorc *et al.* (10) with a relative frequency of 80% and Shaw et al. (11) with a relative frequency of 89%. Furthermore, boys were the predominant sex in this study, which is almost in agreement with what is acclaimed in the literature (2,20-22).

Table 3. Clinical responsiveness among different patterns of empirical therapy and antibiogram concordance.

		Empirical therapy and antibiogram concordance			Total
		Full	Moderate	None	
Clinical response	Frequency (Percentage)	10 (12.7%)	53 (67.1%)	16 (20.3%)	79 (100.0%)
	Relative frequency in total	10.3%	54.6%	16.5%	81.4%
No Clinical Response	Frequency (Percentage)	4 (22.2%)	9 (50.0%)	5 (27.8%)	18 (100.0%)
	Relative frequency in total	4.1%	9.3%	5.2%	18.6%
Total	Frequency (Percentage)	14 (14.4%)	62 (63.9%)	21 (21.6%)	97 (100.0%)
	Relative frequency in total	14.4%	63.9%	21.6%	100.0%

In recent years, an increased ampicillin resistance rate among *Escherichia coli* isolated from newborn infants has been observed (2); Friedman *et al*., (15) reported *Escherichia coli* ampicillin resistance as high as 75% of in early onset sepsis cases and 53% in late onset; Joseph *et al* also showed a shift of early-onset *Escherichia coli* infection from a less fulminant disease caused by ampicillin-sensitive organisms to a more fulminant disease caused by ampicillin-resistant organisms; an issue that they postulated to be due to maternal intra partum ampicillin therapy (16,17); Safar *et al* study on uropathogens in 3 hospitals in Sari also revealed ampicillin (82%-100%) and trimethoprim-sulfamethoxazole (50%-90%) resistance as the most frequent antibiotic resistance patterns among different uropathogens (19).

Antibiotic susceptibility pattern explicitly differ among various countries and also different medical centers within every country, this motivated us to conduct the current study, as there have been few studies in this respect in our country. However, as expressed in the results resistance to Ampicillin (95.9%), Gentamycin (52.6%), TMP-SMX (45.4%) were the most observed resistance pattern of five uropathogens isolated from urine culture of neonates admitted to Neonatal Ward of Bahrami Children Hospital with the diagnosis of UTI in a ten year interval. The first two leading mentioned antibiotics are usually used in the empirical treatment of neonatal sepsis and UTI.

Nevertheless, despite the observed resistant of five urinary isolated organisms of this study- including *Escherichia coli* as the leading one- to initial empirical regimen antibiotics (especially ampicillin) , 81.4% (79 cases) responded to empirical therapy. However, considering the importance of the issue, authors propose the necessity to conduct further anterograde case-control or cohort studies on this issue to offer more reliable basis to assess empirical therapy and antibiogram concordance relationship in the newborn infant with urinary tract infection. However, meanwhile physicians should be aware of the possibility of ampicillin-resistant *Escherchia coli* infection in critically ill neonates and take this issue into accounts from the first steps of management.

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