CLINICAL ASPECTS AND EVOLUTION OF URINARY TRACT INFECTION IN PRETERM INFANTS

Magdalena I. Starcea[2,3], Mihaela Munteanu[3], Radu V. Russu[3], Ovidiu Brumariu[2], Delia Andreia Bizim[1], Ingrith C. Miron[2,3]

[1]Faculty of Medicine,"Gr. T. Popa" University of Medicine and Pharmacy, Iasi

[2]"Gr. T. Popa" University of Medicine and Pharmacy , Iasi

[3]Pediatric Nephrology Department, "Sf. Maria" Emergency Children's Hospital, Iasi

ABSTRACT

Objective. The aim of the study is a comparative analysis of cases of UTI in children 0-3 years (preterm and term infants) admitted to the IVth Pediatric Clinic , "Sf. Maria" Emergency Hospital for Children, Iasi, between January 2007 – December 2011.

Material and methods. We performed a retrospective study on a group of 298 children, age 0-3 years, hospitalized with urinary tract infection (UTI). We identified the features of preterm infants with UTI according to the degree of prematurity, UTI etiology, comorbidities, developmental issues, responsiveness to treatment, and impact of UTI on kidney.

Results. The study group was divided into term and preterm children (defined as gestational age less than 37 weeks, weighing less than 2500g). Preterm UTI risk was influenced by age, being 3 times higher compared with children aged 1-3 years. The average age of UTI was 8.8 months for preterms and 14.09 months for term babies. Most preterm children were classified in LBW category. The etiology of urinary infection was dominated in both subgroups by E. coli, Proteus mirabilis and Klebsiella pneumoniae. In preterm children, opportunistic bacteria (bacillus Pseudomonas, enterococci, Acinetobacter) determined 16% of UTIs, compared to only 2% in term children. Fever was the dominant clinical sign in all patients. Other signs on preterms were loss of appetite, prolonged jaundice, diarrhea, respiratory distress. The onset of acute renal failure occurred in 12.5% of preterm and only 1% of term children. First line antibiotherapy was effective in most cases. In microbial resistance, the most frequently involved were aminopenicillins, Sulfamethoxazole-Trimethoprim and cephalosporins.

Conclusions. The early diagnosis and treatment have an important role in reducing infectious morbidity, the risk of renal scarring and rapid nutritional rehabilitation in preterm infants.

Keywords: urinary tract infection, preterm infant, CAKUT, E.coli

Abbreviations

CAKUT = congenital anomalies of kidney and urinary tract
CBC = cell blood count
CFU = colony forming unit
ELBW = extreme low birth weight
LBW = low birth weight
NPV = negative predictive value
PPV = positive predictive value
UTI = urinary tract infection
VLBW = very low birth weight

INTRODUCTION

Urinary tract infection is an important cause of morbidity and mortality in small children. It lies at the basis of about a quarter of reasons for addressing a pediatric practitioner. It is often the clinical expression of obstructive uropathy. UTI (urinary tract infection) is also one of the major causes of hypertension and chronic renal failure in adolescents and young adults.

A preterm newborn is a child with a gestational age less than 37 weeks and weighing less than 2500 g at birth. Urinary tract infection in a preterm differs from that in a term baby by prevalence, etiology, clinical presentation and subjacent malformations.

Coresponding author:
Magdalena I. Starcea, „Gr. T. Popa" University of Medicine and Pharmacy, 16 Universitatii street, Iasi

The nephrogenesis in this category of children is not complete, therefore any infectious, ischemic or toxic injury could cause kidney agenesis or abnormal development. In addition to this, in preterm babies, antimicrobial defense barriers are overcome, decreasing cell-mediated immunity, opsonines activity, phagocytosis and vitamin A level.

For all these reasons, the incidence of UTI is 4-25% in preterm children, compared with 5.3 - 7,5% for term newborns (1).

OBJECTIVES

The aim of this study is a comparative analysis of cases of UTI in children 0-3 years old (preterm and term infants) admitted to the IVth Pediatric Clinic – Pediatric Nephrology Department, "Sf. Maria" Hospital for Children Iasi, between January 2007 – December 2011.

MATERIAL AND METHODS

We performed a retrospective study on a sample of 298 children 0-3 years, hospitalized with urinary tract infection (UTI).

The study protocol included:

A. Demographic data : age, sex.

B. Diagnosis of UTI - supported by the presence of positive urine cultures (1-4) in terms of a clinical and biological suggestive aspect (fever, urinary and systemic signs, presence of inflammatory syndrome, pathological urinalysis, leucocyturia).

C. UTI specific features in preterm infants by: degree of prematurity (birth weight classification: LBW (low birth weight), VLBW (very low birth weight) and ELBW (extremely low birth weight), UTI etiology, comorbidities, evolutional features, responsiveness to treatment and impact of urinary infections on kidney.

Statistical analysis applied in this study was one-dimensional and multivariate model. We applied χ^2 test, sensitivity, specificity, predictive values (PPV and NPV) and efficiency test. Data were processed using statistical functions (SPSS 15).

We identified the clinical manifestations associated with UTI, the presence of urinary symptoms, morbidity states in preterm compared with term newborns. Biologically, we assessed the urinalysis urine cultures, leucocyturia, inflammatory syndrome and CBC (cell blood count).

The urine sampling was done by peripheral collection methods. We practiced direct microscopic examinations, leukocyte count, urine cultures and counting CFUs (colony forming units). We defined a positive urine culture the presence of more then 10^5 CFU/mm ^{3} correlated with more than 10 leucocytes /field. We evaluated the response and evolution under first-line antibiotherapy, and after correction, according to the antibiogram. We drew conclusions regarding the sensitivity of different etiologic agents to antibiotics. We analyzed the correlation between reno-urinary tract anomalies and the incidence of UTI in preterm infants by imagistic evaluation (kidney and bladder ultrasound, voiding cystourethrography, and static radionuclide studies with Tc99DMSA).

RESULTS

The study group consisted of 298 children aged 0 to 3 years, with ITU divided into 2 subgroups:

- subgroup 1 – children born at term and
- subgroup 2 – children with gestational age less than 37 weeks, weighing less than 2500 g.

Distribution of cases by gestational age (preterm or full term baby) weight, and sex are illustrated in Figures 1 and 2.

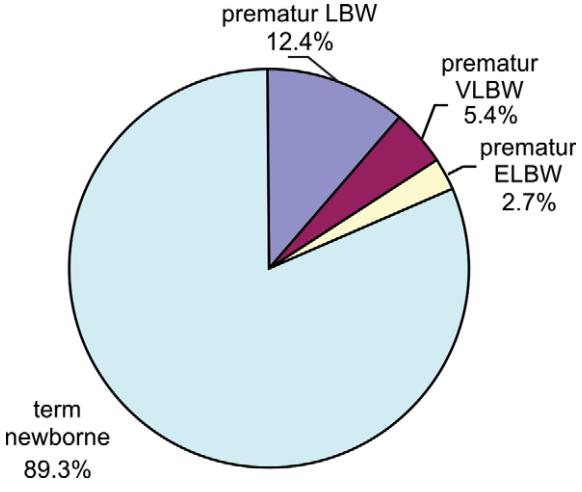

FIGURE 1. *Patients distribution according with gestational age and birth weigth*

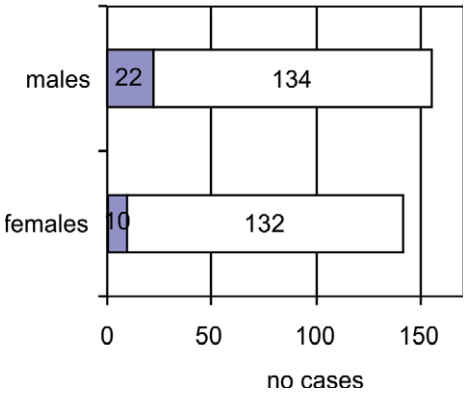

FIGURE 2. *Patients distribution according with gestational age and sex*

UTI risk in subgroup 2 is influenced by age, being 3 times higher in preterm newborn babies, compared with children aged 1-3 (p = 0.0004, HR = 3.23, CI 95%: 1.85 ÷ 5.64). PPV cases with UTI in children born prematurely was 72.5%.

The average age was 8,8 months on preterms, compared with 14.09 months of term babies Depending on the degree of prematurity, we observed that most children were classified in LBW rate (73.3%) and 20% of them in VLBW rate.

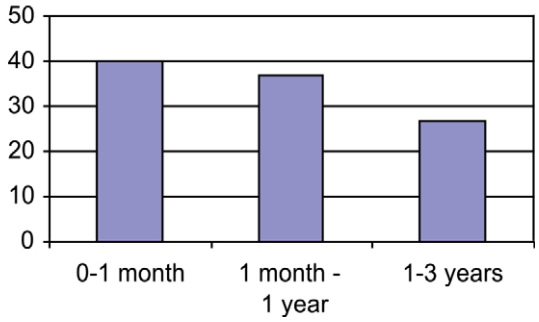

FIGURE 3. *Preterm patients distribution according with age group*

The etiology of urinary tract infection is dominated in both subgroups by E. coli (60% in term children, 50% in preterm infants), Proteus mirabilis (12.5% preterm children 13% term children) and Klebsiella pneumoniae (9.37 % in preterm infants, 7.37% in term children).

Opportunistic bacteria (Pseudomonas, Enterococcus, Acinetobacter) determines 16% of UTIs in preterms, compared to only 2% in term children.

Urine cultures were negative in 12% of preterms, although clinical symptoms were suggestive of UTI.

Clinical manifestations were different in the 2 subgroups, but fever was the clinical dominant sign in all patients (72% in subgroup 1 compare to 78% in subgroup 2). Loss of appetite was the first symptom in 55 % of preterms, compared to only 20% of those born at term. 25% of premature infants had prolonged jaundice (requiring phototherapy and induction). Also 25% of them were associated with diarrhea, 22% interstitial pneumonia, and 19% had respiratory distress.

In the subgroup of term infants, there was no case of respiratory distress or jaundice, and diarrhea and interstitial pneumonia were present in 10% of cases. In 22% of preterm babies, UTI started with febrile seizures (compared to 4% of term children). 15% of cases were associated dyspepsia (compared with 10% terms), and 6% had lethargy as a sign of UTI (compared to 2% on term infants).

The onset of UTI by acute renal failure/ injury occurred in 12.5% of preterms and only 1% of term children. Acute renal failure was secondary to sepsis in all cases. Urinary symptoms were similar in the two groups, summarized in Table 1.

Table 1. Urinary manifestations in the study group UTI relapses were present on 10% of preterms (50% with fever) and 15% on term infants (10% with fever). In the etiology of UTI, relapses prevailed with E. coli in term infants and bacterial associations (Candida sp + E.coli + Klebsiella pn) in preterms.

Relapse in most cases was due to noncompliance in prophylactic therapy. Kidney scars assessed by radionuclide studies with Tc99DMSA were present in 4% of children subgroup 1 and 5% of those of subgroup 2.

Radionuclide studies could not be carried out to all children with UTI relapse.

Renal and urinary malformations in each subset of the study are given in Table 2.

Tabel 2. CAKUT (congenital anomalies of kidney and urinary tract) in study group 68% of preterm and 56% of term infants developed anemia. In the first subgroup the The inflammation worsened the anemia. High neutrophilic count and leukocytosis was found in 75% and inflammatory syndrome in 68% of patients. 53% of preterms had different degrees of malnutrition (compared to 16% of term infants).

TABLE 1. *Urinary manifestations in study group*

	Modify urines	Disuria	Pollakiuria	Agitation on micturition	Hematuria	Modify urinary stream	No signs	AKI (acute kidney injury)
Sublot 1	55%	25%	20%	26%	6%	8%	19%	1%
Sublot 2	66%	6%	3%	32%	9%	6%	26%	12,5%

TABLE 2. *CAKUT in study group*

	Vesico-ureteral reflux	Hydro-nephrosis	Renal hypoplasia / Renal agenesis	Duplex kidney	Kidney stones
Sublot 1(19%)	32 patients (12%)	15 patients	1 patient	1 patient	2 patients
Sublot 2(37%)	7 patients (22%)	4 patients	4 patient	1 patient	

Approximately two thirds of all patients presented significant leucocyturia. The first line antibiotherapy was effective in most cases.

Escherichia coli has developed resistance in almost a quarter of patients. Antibiotics involved in microbial resistance were aminopenicillins (about 30% of cases), Sulfamethoxazole-trimethoprim (25% cases) and cephalosporins (25% cases), Nitrofurantoin and aminoglycosides (6% of cases).

Proteus mirabilis has developed resistance in 8% and 2% of preterm and term children, respectively.

Klebsiella pn. has developed resistance in nearly 5% of children both subgroups, especially to aminopenicillins.

Enterococcus has developed resistance to Sulfamethoxasole-trimethoprim and aminoglycosides, and Pseudomonas to cephalosporins and aminoglycosides.

40% of preterms had a positive history of multiple UTIs, 28% of whom did so as soon as birth.

In 6.5% of them, the UTI was detected during a sepsis.

In the neonatal period, the etiology was dominated by Enterococcus, Enterobacter, Klebsiella, and Acinetobacter, in 25% cases. In term children, relapse UTIs were found in 44% of patients, and only 9% of patients had recurrent UTI episodes after the newborn period.

DISCUSSIONS

Prematurity in infants and small children causes a greater susceptibility to infections (besides premature retinopathy, anemia and malnutrition), secondary to immunological deficits and organic immaturity that these children are born with. UTI falls among the most common infections in newborns and small children, with an incidence ranging from 4-25% in preterms (according to various studies), and 5.3-7,5% in term newborns (1,2,3).

Our study shows that UTI occurs three times more frequently in preterm than in term baby. The incidence of UTI in preterms was 10.75%, consistent with the literature (1,2). PPV of UTI cases in children born prematurely was 72.5%. In subgroup 2, gender distribution showed a predominance of UTI in boys (2,2:1) as in the study of Eliakim et al. (4). Other studies show a ratio of up to 6:1 in favor of little boys (3).

In term infants, the rate of UTI is higher for neonatal boys and in 1-3 years old girls.

The average age of children with UTI differs, being 8.8 months in former preterms, and 14 months in term children, data supported by field studies (3).

The clinical manifestations were different in the two groups. However, fever was a constant symptom present in both subgroups in 70% of the UTI episodes. This observation is similar to that of Khassawneh Mohammad et al (1). Loss of appetite, followed by failure to thrive was present in over half of preterm babies and the only symptom in 10% cases. A quarter of the preterm patients had prolonged jaundice and respiratory distress as signs of UTI onset (2). This signs were not found in term children, even though UTI occurred in the neonatal period. Francisco J. Garcia obtained similar data on jaundice as early sign in preterm newborns and infants with UTI (2,5).

Comorbidities were recorded in both study subgroups with a net predominance in preterms. Interstitial pneumonia was present in 22% of cases, diarrhea in 25% of cases. Gastroenteritis can increase the possibility of periurethral colonization, and the risk of UTI in malnourished and preterm infants. On these infants, the antimicrobial barriers are surpassed and cell-mediated immunity defense, opsonines activity, phagocytosis and the vitamin A levels are decreased (6).

The incidence of comorbidities increases with the severity of prematurity and prone to malnutrition which affects preterms' nutritional recovery and antimicrobial defense. UTI evolution is complicated by malnutrition in 53% of preterm infants, compared with 16% of term infants, observation consistent with the literature (1,5).

UTI onset by acute renal failure, secondary to a sepsis, occurred in both preterm and term infants, but the incidence was much higher in the first group (12.5% vs. 1%). Possible explanations for the high incidence of urosepsis in these children are the need of neonatal intensive care, subjected to invasive procedures, and prolonged parenteral nutrition. This clinical observation is supported by the study of M. Barton and colleagues (3).

In our study, the rate of neurological symptoms in preterm with UTI was 22% febrile convulsions and 6.25% lethargy, correlating with data from studies in the field (5, 6). Anemia was found in 50% of children of both subgroups, caused by nutritional deficiencies and infectious disease.

Significant white blood cell in urine improves diagnostic sensitivity and specificity of urine culture by increasing the sample predictive values. The presence of white blood cells in urine and a clinical and biological syndrome suggestive of UTI (fever, inflammatory syndrome) associated with

significant bacteriuria diagnoses a UTI in 91% of cases (with a variability of ± 0.04), decreasing the chance of a false positive diagnoses to 5 % (in terms of a NPV of 95%). A higher number of urine cultures (1-4, on average 2) on the same patient increases the sensitivity of the method at 97% (± 0,02). Urinary symptoms were similar in preterm and term infants, most often expressed by agitation on micturition and modify urines.

Preterms presented twice as many CAKUT, 22% being diagnosed with various degrees of vesicoureteral reflux (compared with 12% of term children). Bauer and al. and Goldman recommends routine retrograde voiding cystography and ultrasonography for CAKUT diagnosis in preterms with UTI (4,5).

The UTI etiology did not differ significantly in studied subgroups. The bacteria involved are Escherichia coli (60% in term infants and 50% in preterms), Proteus mirabilis (12.5% in preterms, 13% in term infants) and Klebsiella pneumoniae (9.37% in preterms, 7,37% in term newborn infants). The differences between the two subsets appear on the opportunistic bacteria (Pseudomonas, Enterococcus, Acinetobacter) that causes 16% of UTI in preterms, compared to only 2% in term infants.

Urine cultures were negative in 12% of preterms, although clinical symptoms were suggestive of UTI.

UTI relapses are found in equal numbers of children in both groups, but the etiology is dominated by E. coli in term newborn infants, as it is in the case of preterms by bacterial association. Clinical studies in the field indicates a different etiological predominance, with Klebsiella pn., Candida, Enterococcus and E. coli being the most involved preterms UTI (1, 5). Resistance to treatment of bacterial strains is a consequence of the excessive use of antibiotics in pediatrics. The antibiotic resistance to aminopenicillins ranked first then to Sulfamethoxazole-Trimethoprim and oral cephalosporins. The literature identified Trimethoprim resistance of Gram-negative bacilli in 9% of cases (4,6). This difference is explained by the predominant use of aminopenicillins in treatment and prophylaxis.

CONCLUSIONS

1. UTI is a common cause of morbidity in preterm infants, the risk of urinary tract infection increasing with a smaller gestational age .

2. Fever is a dominant sign of urinary infection in preterms (over 70% of cases), the rate declining along with the severity of prematurity.

3. UTI associated comorbidities are more frequent as the degree of prematurity increases and the age decreases, respiratory distress and prolonged jaundice being the most important.

4. Loss of appetite, followed by failure to thrive is present in more than half of preterm children with UTI.

5. The presence of white blood cells in urine, and a clinical and biological syndrome suggestive for UTI has the same diagnostic meaning regardless of birth weight.

6. CAKUT are found twice as often in preterm infants compared to term, imaging investigations becoming a necessity after the first episode of UTI.

7. The etiology of urinary tract infection in both subgroups is dominated by Escherichia coli, Proteus mirabilis and Klebsiella pneumoniae. The implication of opportunistic bacteria in the etiology of UTI is 8 times higher in preterm infants.

8. The etiology of UTI relapses in preterms is dominated by bacterial associations, while in the terms infants, by E. coli.

9. Aminopenicillins Sulfamethoxazole -Trimethoprim and first and second generation oral cephalosporins induce bacterial resistance most frequently.

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