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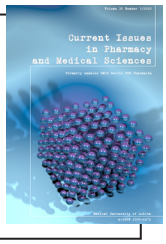

Risk factors in children with recurrent urinary tract infection among patients attending Al Zahra Teaching Hospital in Iraq

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ABSTRACT

Urinary tract infections (UTI) are considered one of the most common infections that occur in the pediatric age group, leading to very serious morbidity and mortality. The detection of risk factors for urinary tract infection helps in the management and prevention of the recurrence of the infection. This study attempts to review current information on UTIs and determine different risk factors in association. To study the risk factors that are associated with recurrent urinary tract infection in different age groups of childhood among children attending AL Zahra Teaching Hospital.

A case-control study was conducted in AL Zahra Teaching Hospital during the period from October 1st, 2021, to July 30th, 2022. It included 76 children with highly suggestive histories, their examination, and results of the investigations (e.g. urine cultures), as well as 150 healthy children who were taken as controls. The controls were without a history of recurrent UTI and were similar to patients in age, sex and other risk factors that were mentioned in the study. A completed questionnaire was given to each child's mother, and then the results were analyzed.

The study showed that non educated mothers OR (3.2), vesicouetrerall reflux OR (3), uncircumcised male OR (2.94), female gender OR (2.7), age groups below than 6 years OR (2.4), low social class OR (2.1) and residency in rural area (OR 2.5) contributed to UTI issues.

When compared to control groups, non educated mothers and vesicoureteral reflux were highly significant risk factors, and other risk factors such as female gender, uncircumcised male, age less than 6 years, low social class and rural area were significant for febrile recurrent urinary tract infection in children.

INTRODUCTION

Urinary tract infections (UTIs) are considered one of the most common infections that occur in children [1]. It may involve the upper part of the urinary tract and be called "pyelonephritis" or it may involve the lower part of the urinary tract and be called "cystitis". It may be difficult, if not impossible, to distinguish between pyelonephritis and cystitis based on clinical symptoms, especially in infants and young children [2].

Through the first year of life, the frequency of UTI is around 0.7% in females and 2.7% in uncircumcised males [3]. The incidence of UTI in febrile infants in the first two months of life is about 5% in girls and 20% in uncircumcised boys [3]. Through the first 6 months, uncircumcised boys have a 10- to 12-fold increased risk of having an UTI [3]. In the neonatal period, UTIs are more common in premature infants than in term infants. After one year of life, girls are more likely to have an UTI than boys [4]. It is estimated that 7.8% of all girls and 1.7% of all boys will have UTI by the age of 7. At the age of 16, 11.3% of all girls and 3.6% of all boys will have had a urinary tract infection [5,6].

Situations that interfere with the unidirectional flow of urine increase susceptibility to UTIs. This usually occurs with vesicoureteral reflux and obstruction [7]. Vesicoureteral

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reflux, which is one of the most common urological disorders in the pediatric age group, allows bacteria to ascend from the bladder toward the kidneys, resulting in the formation of residual urine after urination [8]. Vesicoureteric reflux can be due primarily or secondarily to the ectopic ureter, posterior urethral valve, or to prune belly syndrome [4]. Vesicourethral reflux is a serious factor in the recurrence of the UTI and the development of renal scarring [9]. Vesico-ureteral outflow happens in 25-30% of all children with UTIs [6].

The folly's catheter is considered a foreign body and serves as a breeding ground for bacteria, resulting in disorders such as ineffective urination, detrusor muscle instability, diabetes mellitus, constipation, obesity and vitamin D deficiency [10].

MATERIAL AND METHODS

Study design and setting: This was a case-control study conducted in AL Zahra Teaching Hospital in Najaf City during the period from October 1, 2021, to from October 1, 2021, to July 30, 2021, to July 30, 2022. It included 76 children with highly suggestive histories, as well as results of investigations (e.g. urine culture) who were taken as cases for recurrent UTI, and 150 healthy children who were taken as controls. Controls had no history of recurrent urinary tract infections and were similar to patients in age, sex and the other risk factors mentioned in the study.

After gaining permission from each child's mother, a questionnaire was given out to them. This included questions about the age of the child, sex, circumcision status (for males), presence or absence of vesicourethral reflux according to documented reports of a voidiongcystourethrogram, the education level of the mother, where they lived (rural or urban area), how many rooms in their home and how many members in family, if a toilet was present inside or outside their house and if the toilet was supplied by tap water or reservoir, their monthly income and if it covered their needs or not, family history of urinary tract infections, if the child was toilet trained or not, for an infant – if the child was term or pre-term and if he/she was breast or bottle fed, the frequency of diaper change and the child's diet (for children more than one year of age).

A full history was taken from the mother for each child about the symptoms of UTI, and the history of recurrent UTI (which means two or three episodes of UTI in 6 months or more than three episodes in one year). After a complete examination, the child was then sent for investigations, with the results analyzed. The age difference was one of the risk factors considered in the study, as well as gender, circumcision status for males, past history of Vesicourethral reflux (VUR), educational level of the mother, residency conditions and social class.

Inclusion criteria for cases: children from the age of 2 months to 12 years and presence of fever (a body temperature of 39°C or higher), signs and symptoms of UTI and a history of recurrent UTI, as well as positive result of a voiding cystourethrogram for VUR uncircumcised males. Exclusion criteria: children who have difficulty obtaining a medical history from their parents or who do not have a urine sample, children with other causes of high fever, such as respiratory viral infection or other causes of abdominal pain (like acute appendicitis or gastroenteritis), patients who received immunosuppressive drugs, pediatric patients who have received antibiotics in the last two weeks, children whose parents refuse to consent to participating in the study.

Sample collection

For all patients included in this research, according to the inclusion criteria, they were admitted to the hospital with specific and non-specific signs and symptoms. Sample collection was ordered using appropriate methods that prevented contamination of the sample. Urine collected varied according to toilet training or not. For non-toilet trained, samples were collected by a urine bag that sticks gently to the skin, and was done after cleaning the genital area and, after voiding. For toilet-trained children and circumcised males, samples were collected via mid-stream urine. The urine sample (in a sterile cup) was of 1-2 ml, and was collected after the patient drank a good amount of fluid (water) and after the cleaning of the genitalia with separation of the labia in females and retraction of the foreskin in uncircumcised males. These two methods are easily done and non-invasive, while other methods like catheterization and suprapubic aspiration are invasive and not always accepted by parents.

Sample procedure

Following proper sample collection, it was immediately sent to the lab for gross, microscopic and chemical examination. The macroscopic examination focused on variables that can be noticed by direct vision, including the volume of urine, its color, transparency, change in odor and specific gravity. The chemical properties were measured by urine test strips, and included urine PH and the amount of glucose and protein in the urine sample. The test strips contained pads soaked in chemicals that change color on contact with certain components in the urine sample, for example, the production of nitrite by certain types of bacteria that cause UTI, and presence of leukocyte esterase, which is an enzyme present in leukocytes and used as a marker for the detection of the number of white blood cells in the urine.

A light microscope was used in the initial investigation. First, the urine was centrifuged to better identify the solids. A drop of concentrated urine was then placed under a coverslip and examined at 10× and 40× magnification. The exact number of white blood cells (WBC) in the urine sample were detected by placing the sample in a counting chamber (a hemocytometer). Symptomatic patients were assessed as so if the number of WBC in the urine sample was greater than 3-6 cells. In asymptomatic patients, determination was at more than 10 cells.

According to current literature, the numbers and types of cells and/or materials, such as urinary casts, can yield great detail and may suggest a specific diagnosis. For example:

- Hematuria – associated with kidney stones, infections, and other conditions;
- Pyuria – associated with urinary infections;
- Eosinophiluria – associated with allergic interstitial nephritis and atheroembolic disease;

- Red blood cell casts – associated with glomerulonephritis and vasculitis;
- White blood cell casts – associated with acute interstitial nephritis, exudative glomerulonephritis, or severe pyelonephritis.

Another method that was used to confirm UTI is urine culture. This is a microbiological culture of a urine sample collected by the same maneuver. For pathogen isolation, urine samples are placed on a specific medium called cysteine-lactose electrolyte (CLED) medium and, afterwards, incubated at 37°C for at least 24 hours. In this part of the investigation, aout 0.01 ml of urine was inoculated using a sterile, calibrated wire loop. This separation was used for counting the colonies. Cass criteria were applied to determine the number of colonies. Numbers greater than 105 organisms per milliliter are considered significant. MacConkey Agar was used to to grow pure bacteria reservoirs from different isolates, which were then identified by using a specific standard identification system (the API 20 E system). When the lab investigations completed ,send the child were sent for abdominal ultrasound. The investigation utilized voidingcystourethrograms to detect any abnormality in the urinary tract such as VUR and others that are associated with the urinary infection and its recurrence.

RESULTS

The total number of patients enrolled as case study was 76 and number of enrolled as controls was 150. Of these, the number of individuals enrolled in the case study of the age group from 2 months to 6 years was 42, and that from 6 years to 12 years was 34. Of the controls, the breakdown is 55 and 95, respectively. The odds ratio was (2.1), CI (1.218_3.739) (Table 1).

Table 1. Age distribution in cases and control

Age Group * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
Age group/ Years	2 months – 6 years	42	55	97	2.1	1.218	3.739
	6 years – 12 years	34	95	129			
Total		76	150	226			

According to sex, the number of female patients in the case study was 52 and that of male patients was 24, while the number enrolled as control was 68 and 82, respectively. The odds ratio was (2.613), CI (1.462_4.670) (Table 2).

Table 2. Sex distributions in cases and controls

Sex * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
Sex	Female	52	68	120	2.613	1.462	4.670
	Male	24	82	106			
Total		76	150	226			

An additional and important risk factor for recurrent UTI was the presence of VUR, as indicated through voiding cystourethrogram (VCUG). The total number of case study patients with positive results for VUR was 24 (grading from III to V) and those with negative results for VUR was 52. Of the control group, the relevant figures are 20 and 130, respectively. The odds ratio was (3.000), CI (1.528_5.892) (Table 3).

Table 3. Frequency of VUR in cases and controls

VUR * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
VUR	Positive (grades III-V)	24	20	44	3.000	1.528	5.892
	Negative	52	130	182			
Total		76	150	226			

Circumcision was indicated as an important factor affected males with recurrent UTI. Herein, the number of patients who were uncircumcised was 15 and those who were circumcised was 9. The related figures for controls are 30 and 52, respectively. The odds ratio was (2.889), CI (1.128_7.400) (Table 4).

Table 4. Effects of circumcision in male in cases and controls

Circumcision * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
Circumcision	Uncircumcised males	15	30	45	2.889	1.128	7.400
	Circumcised males	9	52	61			
Total		24	82	106			

The level of education of the care giver (mother) was closely related to the recurrence of UTI. Accordingly, the number of the patients who had mothers with little or no education was 55, and those whose mothers had completed primary or secondary school was 21. The related fogues for the control was 68 and 82, respectively. The odds ratio was (3.158), CI (1.739_5.736) (Table 5).

Table 5. Effects of education in cases and control

Education * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
Education	Mothers with little or no education	55	68	123	3.158	1.739	5.736
	Mothers with some education completed primary or secondary school)	21	82	103			
Total		76	150	226			

The number of patients who were living in a rural area was 53, and those who were living in urban area was 23. The figures for the control group are 72 and 78, respectively. The odds ratio was (2.496),CI (1.391_4.481) (Table 6).

Table 6. Effects of residency in cases and controls

Residency * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
Residency	Rural	53	72	125	2.496	1.391	4.48
	Urban	23	78	101			
Total		76	150	226			

Based on the periodic family survey conducted by the Central Statistical Organization in Iraq during the past two decades, the definition of social class is based on daily income level. This is as follows:

- The poor or vulnerable class: 2-5 dollars (American) per day per person.
- Middle class: 6-10 dollars per day per person
- The rich class: more than $10 per day per person.

This division relies on international standards adopted by international organizations such as the World Bank, UNICEF and ESCWA. Taking into account the exchange rate of the Iraqi dinar against the American dollar, we found that those in the study group of low social class were 48, and those of middle social class were 28. The related figures in the control were 67 and 83, respectively. The odds ratio was 2.124, CI (1.205_3.742) (Table 7).

Table 7. Effects of social class in cases and controls

Social Class * GROUP		GROUP		Total	Odds ratio	95% CI	
		Patients	Controls			Lower	Upper
Social Class	Low	48	67	115	2.124	1.205	3.742
	Middle	28	83	111			
Total		76	150	226			

DISCUSSION

In children with febrile urinary tract infection UTI, wherein the usual presentation is nonspecific, part of the diagnosis should depend on the result of the urine culture. Urine microscopy significantly improves the reliability of microscopic urinalysis for the detection of UTIs. However, positive results neither detect all patients with UTIs nor do negative tests completely rule out infection. Hence, urine culture is the gold standard for the diagnosis of UTI in children [9], and diagnosis should depend on the result of the urine culture. Urine microscopy significantly improves the reliability of microscopic urinalysis for the detection of UTIs.

More than 30% of these children will have at least one recurrence through a period of 6-12 months [11,12], while 3-15% of all children with a first UTI will have scarring of kidney tissue through a period of one to two years after their first UTI [13,14]. In our study, we found that children aged 2 months to 6 years were at increased risk for recurrent UTI (odds ratio: 2.1). A study done by Panaretto K. *et al*. in 1999, by Dias C.S. *et al*. in 2010, and by Shim Y.H. *et al*. in 2009 [15,16], found that children younger than 6 months had a high risk for recurrent UTI. Moreover, another study undertaken by Mingin *et al*. [18] reported that of children with febrile UTI, 45% of the girls and 14% of the boys developed recurrent UTI. Pennesi *et al*. [19], in turn found that just 4.4% of children with UTI aged below 3 years had recurrent UTI after their first UTI, while another study done by Patrick H. *et al*. from 2001 to 2006 [20] found that children aged 2 years to 6 years, especially 3y-5y, were at high risk for recurrent UTI.

These differences in age groups may be related to parental habits such as drinking fluids in small amounts; milk feeding (not breast) only during this period; bad bathroom habits; infrequent diaper changes; improper wiping from posterior to anterior; not using cotton underwear; and so on. We discovered that the female gender is a risk factor for recurrent UTI, with a 52 (43.3%) incidence vs. male 24, odd ratio (2.6).This finding is aligned with a study done by Keren R. *et al*. in 2015 [9], which reported that risk factors for recurrent UTI are children with ages below 6 months, female sex, bladder and bowel dysfunction. VUR (severe grade) and renal damage. In a study undertaken by Svante Swerkersson [21], 47 episodes of recurrent febrile UTI were indicated in 36 (12%) children (15 (9%) boys, and 21 (15%) girls). This difference is attributed to differences in the study sample and the number of female: male patients. Accordingly, VUR was considered an important factor for recurrent UTI. This study found that children with VUR had an increased risk for recurrent UTI, with an odds ratio of 3.000, which was highly significant.

In a study done by Patrick H. *et al*. [20], it was also found that children with VUR were at high risk for recurrent UTI. Moreover, Hidas G. *et al*. and Jodal U. *et al*. reported that recurrent febrile UTI was related to the presence and severity of VUR, occurring in 22% of children with VUR grades III-V [22, 23]. In accordance with the present study results, Panaretto *et al*. [15] reported that abnormal urinary tract situation such as VUR occurred more often in children with recurrent UTI.

In our study, we found that uncircumcised males had a higher risk for recurrent UTI than did circumcised males; this result is similar to several previous studies undertaken by Patrick H. *et al*. from 2001 to 2006 and another study done by Ron Keren *et al*. from 2007 to 2011 in Philadelphia USA [9,20]. This outcome may be attributed to the habit of delaying circumcision. for males according to religion and beliefs. In contrast, in Iraq, the family may not know the importance of circumcision.

The level of education of the mother was another important factor that was associated with recurrent UTI, where the child of a non-educated mother was at increased risk for recurrent UTI. The odds ratio (3.158) was significant in another study undertaken by Ron Keren *et al*. from 2007 to 2011 [9], which found that the child of a mother who or poor or little education was at increased risk for recurrent UTI. This indicates that increased maternal awareness of the risk of UTI, its causes, complications, and prevention may decrease the risk of recurrent UTI in their kids.

What is more, in our study, we found that children who live with their families in rural areas and children from families of low social class are at increased risk for recurrent UTI. In a study completed by Kavitha J. *et al*. In 2018 [24], it was reported that most children with low socio-economic status were from rural areas,. The study therefore targeted this group of the community. Herein the risk of UTI was attributable to poor hygiene, the source of water supply, a lack of a healthy diet, a delay in seeking medical advice, and improper use of antibiotics.

CONCLUSION

The study recognized different risk factors for recurrent UTI. Pediatricians should be made aware of these risk

factors. The results of this study contribute to the development of clinical prediction rules that can complement existing clinical practice guidelines. When compared to control groups , non educated mothers and vesicoureteral reflux were highly significant risk factors. Other risk factors, such as female gender, uncircumcised male, age less than 6 years, low social class, and rural area were significant for febrile recurrent urinary tract infection in children.

RECOMMENDATIONS

More research is needed to detect age-specific risk factors for UTIs, as the majority of physicians depend on clinical features to diagnose a UTI. The study also needs further extensive research to detect and evaluate other risk factors for recurrence of UTI (such as constipation, anatomical obstruction, pinworm infestation, tight clothes, wiping from back to front, and toilet training). Additional research is needed for the detection of risk factors associated with improper use of antibiotics for UTI and the use of antibiotic prophylaxis to prevent recurrence of UTI and renal scars.

LIMITATIONS

Because of the lack of adequate information from the mother about the use of antibiotics as treatment and prophylactic, we cannot include antibiotic susceptibility in this study.

Due to financial and laboratory limitations , we did not study viral, parasitic and fungal infections at the same time.

As the course of the study was short, we did not perform a microscopic examination of the stool that would help identify many parasitic infections.

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