

# Role of Zinc Supplementation in the Treatment of Children with Culture-Proven Febrile Urinary Tract Infection

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## ABSTRACT

**Objectives:** To compare the efficacy of zinc plus antibiotics versus antibiotics alone in the treatment of culture-proven febrile urinary tract infection in children

**Methodology:** This randomized control trial was conducted at FFH, Rawalpindi. Children with culture-proven UTI requiring IV antibiotics were enrolled in the study (n=70) divided into two groups. Group A was given zinc in addition to the antibiotic while group B received antibiotic only. The results of the two groups were then compared and the difference in the clinical response.

**Results:** In our study total of 70 patients were enrolled, 35 patients in each group. The mean age was  $7.69 \pm 2.5$  years in group A and  $8.3 \pm 2.2$  years in group B. There were 62.9% males in group A and 60% in group B, females were 37.1% in group A and 40% in group B. The mean duration of illness was  $6.9 \pm 2.4$  days in group A and  $8 \pm 4.1$  days in group B. Efficacy was 82.9% in group A and 57.1% in group B, p-value 0.019.

**Conclusion:** There was early clinical recovery and significant reduction in the time of hospital stay in patients given zinc along with the antibiotic treatment.

**Keywords:** Zinc, urinary tract infection, febrile UTI

### Authors' Contribution:

<sup>1,2</sup>Conception; Literature research; manuscript design and drafting; <sup>3,4</sup>Critical analysis and manuscript review; <sup>5</sup>Data analysis; Manuscript Editing.

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## Introduction

Urinary Tract Infection (UTI) is considered one of the most common causes of hospital admission with an estimated incidence of 1.28 per 1000 in girls and 0.18 per 1000 in boys younger than 14 years and a prevalence of 5.3% in febrile infants.<sup>1</sup> Symptoms of UTI include fever, anorexia, and dysuria, frequency and flank pain. These patients are more susceptible to renal scars and other possible complications (growth retardation, hypertension, proteinuria, and chronic renal failure).<sup>1</sup> Any pathogenic microorganism can cause UTI, yet bacteria are responsible for more than 90% of the cases.<sup>2</sup> Escherichia coli (E. coli) is the most common

organism causing UTI in children.<sup>3</sup> Apart from that the Infectious Diseases Society of America has highlighted a section highlighted tic-resistant bacteria (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) under the acronym "the ESKAPE pathogens", capable of "escaping" the bactericidal action of antibiotics.<sup>4</sup> This group of bacteria represents a challenge for empirical antibiotic treatment of complicated UTIs. The bacteria also produce other substances such as toxins, hemolysin, and colony-necrotizing factors. These agents disrupt epithelial integrity, permit bacterial invasion, and, therefore,

enhance the risk of infection.<sup>5</sup> Local bladder-wall defense mechanisms, such as the production of mucous and secretion of antimicrobial peptides, the uroepithelium expresses toll-like receptors, they can lead to uroepithelial cell activation and production of inflammatory mediators such as cytokines which generate a local inflammatory response to facilitate eradication of the invading bacteria.<sup>6</sup> Zinc element is crucial for free radical detoxification, antioxidant defense, and immune system function in humans. It plays a critical role in many cell functions in the body. Among the physiological functions of zinc are growth, cell division, and reproduction of immune system activity.<sup>7,8</sup> In studies, zinc consumption has been effective in reducing the fever period and accelerating recovery from infection in children.<sup>9</sup> Studies have reported that this trace element also has antibacterial properties, and investigated its role in different infectious disorders, especially in reducing the incidence and severity of diarrhea, pneumonia, and possibly malaria. In previous study done in children with culture-proven UTI it was found that children treated with zinc along with antibiotics had less febrile illness on the fourth day of illness as compared to patients treated without zinc i.e. 33.3% versus 66.7%.<sup>10</sup> The rationale of this study is to determine the role of zinc in decreasing febrile illness in children having culture proven febrile UTI. Now in the current era of antibiotic resistance sole treatment with antibiotics is not effective and there is a dire need to find supportive therapies for the treatment of UTI and prevention of renal scarring and antibiotic resistance.

## Methodology

The study was conducted at Department of Pediatrics, Fauji foundation hospital Rawalpindi, from February 25, 2022 till August 24, 2022. Sampling Technique was Non probability consecutive sampling. Sample size was calculated using WHO calculator. Expected sample size is 35 children in each group. Inclusion criteria was

Patients aged 3 to 12 years, patients of both gender and children with proven febrile UTI admitted in hospital for intravenous antibiotic therapy. Patients of both genders. Children with culture proven febrile UTI admitted in hospital for intravenous antibiotic therapy. The Children with vesicoureteral reflux, renal abscess, urinary tract obstruction, renal hypoplasia, ectopic kidney and any unilateral or bilateral renal anomaly detected on ultrasonography were excluded from the study. After approval from hospital ethical board, patients fulfilling the inclusion criteria were enrolled from children ward of Fauji Foundation Hospital. A written informed consent was taken from parents after explaining the purpose of study. Demographic data including age, gender and duration of disease was noted. A complete history was taken, and the physical examination was performed. Patients were randomly divided in two groups using block randomization generated by computer software. Children in group A were given antibiotics according to sensitivity pattern along with zinc 1mg/kg/day in oral form once a day. Children in group B were given only antibiotics according to sensitivity pattern. Adequate hydration was given in both groups along with antipyretics for fever control. Temperature charting was done in all the children. Effectiveness was noted as no fever after 4 days of treatment. Data was recorded in specially designed proforma. Data was entered and analyzed using SPSS version 22.0. Mean and standard deviation was calculated for quantitative variables like age duration of disease. Frequency and percentage were calculated for categorical variables like gender and efficacy (improvement in fever after 4 days). Effectiveness in both groups was compared using chi square test, p-value  $\leq 0.05$  was taken as statistically significant. Effect modifiers like age, gender and duration of diseases was addressed through stratification of data. Post stratification chi square was applied. P value  $\leq 0.05$  was taken as statistically significant.

## Results

In our study total 70 patients were enrolled, 35 patients in each group. Mean age was  $7.69 \pm 2.5$  years in group A and  $8.3 \pm 2.2$  years in group B. Table I.

Table I: Age of sampled population						
Age	Group	N	Mean	Standard Deviation	SD Error Mean	P value
	Group A (Zinc and antibiotic)	35	7.69	2.598	.439	0.262
	Group B (Antibiotic)	35	8.34	2.248	.380	

Table II: Gender of Sampled Population					
Group	Group	Count	Gender		Total
			Male	Female	
	Group A (Zinc and antibiotic)	Count	22	13	35
		%age	62.9%	37.1%	100.0%
	Group B (Antibiotic)	Count	21	14	35
		% age	60.0%	40.0%	100.0%

p-value 0.806

Table III: Mean duration of illness						
Duration (days)	Group	N	Mean	Standard Deviation (SD)	SD Error Mean	p-value
	Group A (Zinc and antibiotic)	35	6.94	2.496	.422	0.156
	Group B (Antibiotic)	35	8.09	4.133	.699	

Table IV: comparison of efficacy in both groups					
Group	Group	Count	Efficacy		Total
			Yes	No	
	Group A (Zinc and antibiotic)	Count	29	6	35
		% within Group	82.9%	17.1%	100.0%
	Group B (Antibiotic)	Count	20	15	35
		% within Group	57.1%	42.9%	100.0%

p-value 0.019

There were 62.9% males and 37.1% females in group A and 60% males and 40% females in group B Table II.

Table V: Data stratification for efficacy in both groups and age groups							
Age groups				Efficacy		Total	P vale
				Yes	No		
3-7 years	Group	Group A (Zinc and antibiotic)	Count	14	3	17	0.589
			%	82.4%	17.6%	100.0%	
		Group B (Antibiotic)	Count	9	1	10	
			%	90.0%	10.0%	100.0%	
	Total		Count	23	4	27	
			%	85.2%	14.8%	100.0%	
8-12 years	Group	Group A (Zinc and antibiotic)	Count	15	3	18	0.009
			%	83.3%	16.7%	100.0%	
		Group B (Antibiotic)	Count	11	14	25	
			%	44.0%	56.0%	100.0%	
	Total		Count	26	17	43	
			%	60.5%	39.5%	100.0%	

Mean duration of illness was  $6.9 \pm 2.4$  days in group A and  $8 \pm 4.1$  days in group B. as shown in Table III. Efficacy was 82.9% in group A and 57.1% in group B, p-value 0.019 given in Table IV Data stratification was done for age group, and duration of illness is given in Table V and VI.

## Discussion

Urinary tract infection (UTI) is the most common disease of the urinary tract system and the second prevalent infection in children after viral flu.<sup>11</sup> Unlike adults, UTI in children does not have characteristic symptoms and sometimes occurs with atypical presentations such as weight loss, growth failure, anorexia, jaundice, and fever of unknown origin.<sup>12</sup> Early diagnosis and appropriate treatment are important because of the associated disease

complications such as sepsis and bacteremia, and late complications such as hypertension, chronic kidney failure, and reflux nephropathy.<sup>13</sup> Zinc is the 2nd most abundant mineral in the body and its existence is important for synthesis and metabolism of proteins and nucleic acids, as well as for the stability of cell membranes.<sup>14</sup> Zinc acts as a cofactor for over 200 enzymes, and it is essential for many metabolic functions of a cell. In general, physiological functions are dynamically linked to zinc, including growth, cell division, puberty, reproduction, and regulation of host's immune system. The immune system function is impaired even in cases of moderate zinc deficiency.<sup>15,16</sup> Severe zinc deficiency reduces immune system function. Zinc is also one of the body's protective mechanisms against rare diseases.

Table IV: Data stratification for efficacy in both groups and duration of illness							
Duration of illness				Efficacy		Total	P value
				Yes	No		
Equal to <7 days	Group	Group A (Zinc and antibiotic)	Count	12	4	16	>0.99
			%	75.0%	25.0%	100.0%	
	Group B (Antibiotic)	Count	12	4	16		
		%	75.0%	25.0%	100.0%		
	Total	Count	24	8	32		
		%	75.0%	25.0%	100.0%		
>7 days	Group	Group A (Zinc and antibiotic)	Count	17	2	19	0.002
			%	89.5%	10.5%	100.0%	
	Group B (Antibiotic)	Count	8	11	19		
		%	42.1%	57.9%	100.0%		
	Total	Count	25	13	38		
		%	65.8%	34.2%	100.0%		

This mineral is necessary for the development and activity of T lymphocytes. Zinc deficiency causes a reduction in cellular immunity and duration of some diseases such as diarrhea. Zinc plays a role in the production of interferon- $\gamma$ , interleukin2, and tumor necrosis factor- $\alpha$ .<sup>17,18</sup> This study was done to determine effectiveness of zinc in treating urinary tract infection in children. In our study total 70 patients were enrolled, 35 patients in each group. Mean age was  $7.69 \pm 2.5$  years in group A and  $8.3 \pm 2.2$  years in group B. There were 62.9% males group A and 60% in group B, females were 37.1% in group A and 40% in group B. Mean duration of illness was  $6.9 \pm 2.4$  days in group A and  $8 \pm 4.1$  days in group B.

Efficacy was 82.9% in group A and 57.1% in group B, p-value 0.019. In studies, zinc consumption has been effective to reduce the fever period, accelerate recovery in during infection in children.<sup>9</sup> Studies have reported that this trace element also has antibacterial properties, and investigated its role in different infectious disorders and reduce the incidence and severity of diarrhea, pneumonia, and possibly malaria. In previous study done in children with culture proven febrile UTI it was found that children treated with zinc along with antibiotics had less febrile illness at fourth day of illness as compared to patients treated without zinc i.e. 33.3% versus 66.7%. There was no significant difference

between the study (zinc) and control groups in terms of the time of fever stop or the frequency of negative urine culture (none of the measurements), urinary incontinence, and dribbling. In the zinc group, the number of days with dysuria, urinary frequency, and urgency was significantly less, and the recovery time was reported faster. Abdominal pain and dysuria, however, were longer in the zinc group, which was likely due to the abdominal pain after taking zinc.<sup>10</sup> A study was done in Iran to determine zinc deficiency as risk factor for UTI. In this case-control study, which was conducted on children with UTI who were referred to 17th Shahrivar and 22nd Bahman hospitals, Mashhad- Iran, during 2016-2017, patients suspicious of UTI were assessed by urine culture. The urine sample of the patients who were not toilet trained was collected using urinary bags, and those who were toilet trained were asked to collect the clean catch midstream urine. Demographic data, urinary symptoms, type of cultured microorganism, and colony count were recorded. Overall, 104 children (52 cases and 52 controls) were included. The groups had significant differences regarding sex, age, and weight ( $P < 0.05$ ). Serum zinc level was  $60.0 \pm 17.1$   $\mu\text{g/dl}$  in the case group and  $83.0 \pm 15.7$   $\mu\text{g/dl}$  in the control group ( $P = 0.001$ ). After being adjusted for demographic factors, the zinc deficiency proved to be a significant predictor of UTI (OR= 8.633, 95% confidence interval=3.084-24.171,  $P < 0.001$ ).<sup>19</sup> Noorbakhsh et al. reported that serum zinc level was significantly lower in UTI cases.<sup>20</sup> Mahyar et al. reported the reduction of serum zinc levels to be significantly associated with the risk of developing pyelonephritis. Inflammatory cytokines are reported by some studies to be linked with zinc deficiency in infections.<sup>21</sup> Zinc is an important micronutrient, which plays a crucial role in cellular growth and differentiation through the synthesis of proteins and nucleic acids. It is a key cofactor for around 200 enzymes. Zinc deficiency can bring impaired immunity, as it is important for the development and function of T-lymphocytes.<sup>22,23</sup> Furthermore,

this micronutrient has a role in the production of cytokines, including interleukin-2, interferon- $\gamma$ , and tumor necrosis factor- $\alpha$ .<sup>24</sup> The dearth of this nutritional element increases the chance of infectious diarrhea, tuberculosis, and lower respiratory infection. It is believed that zinc supplementation can lower the risk of different infections in children through improving the immune system.<sup>25</sup>

## Conclusion

According to the obtained results, zinc can be used for clinical improvement in cases of severe dysuria and frequent urination among children with UTI.

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