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Diagnostic Accuracy of Interleukin-8 in Differentiation of Acute Pyelonephritis from Cystitis in Children

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ABSTRACT

Urinary Tract Infection (UTI) is a relatively common infection in children that can lead to serious complications such as renal scarring, hypertension and chronic renal failure. In this study we stressed the role of IL-8 in the diagnosis and differentiation between pyelonephritis and cystitis. This prospective descriptive study was conducted among 86 children one month to 14 years, who with clinical signs and symptoms of suspected urinary tract infections were referred to Ahvaz Aboozar hospital. Among 86 children studied 16 (18.6%) and 70 (81.4%) children were boy and girl, respectively. *E. coli* and *Klebsiella* were obtained from urine samples of 72 patients (83.7%) and seven patients (8.1%), respectively. The frequency of abdominal pain in pyelonephritis and cystitis groups was 10.4 and 18.4%, respectively. Vomiting in the pyelonephritis and cystitis groups was respectively 22.9 and 10.5%. The frequency of diarrhea in the pyelonephritis and cystitis groups was 4.2 and 2.6%, respectively. In general, dysuria was the most common symptom in the two groups (69.8%). Measurement of cytokines only takes a few hours and to do it is the easy and non-invasive. Based on the study system the mean IL-8/Cr for detecting pyelonephritis in level 7 has the sensitivity of 66% and the specificity of 72% and even the increased IL-8 after the initial experimental treatment can be a sign for the continued inflammation or antibiotic resistance. Obviously, in this recent case wider study must be carried out.

Key words: Urinary tract infection, pyelonephritis, cystitis, antibiotic resistance, inflammation

INTRODUCTION

Urinary Tract Infection (UTI) is a relatively common infection in children that can lead to serious complications such as renal scarring, hypertension and chronic renal failure (Bhat *et al.*, 2011; Hewitt and Montini, 2011). Approximately 8% of girls and 2% of boys in early childhood will have an episode of UTI (Koch and Zuccolotto, 2003). Symptoms of urinary tract infections in infancy are often nonspecific such as refusing of feeding, jaundice and failure of weight gain (Becknell *et al.*, 2015). As a result, often the diagnosis of urinary tract infection will be relied on urine culture results and the existence of leukocytes and bacteria in the urine and taking an uncontaminated urine sample without invasive procedures (such as a suprapubic aspiration or catheterization) is often difficult. Sometimes we cannot deny or prove UTI with a certainty and a significant number of children may have been receiving unnecessary treatment or diagnosis of the disease occurs with a delay. Differentiation between pyelonephritis and cystitis is also more

difficult. The incidence of renal scar after pyelonephritis varies from 5-57% (Lin *et al.*, 2003) and is associated with an increased risk of progressive renal damage. Laboratory findings such as Erythrocyte Sedimentation Rate (ESR), C-reactive Protein (CRP), leukocyte count and clinical findings such as fever or flank pain in differentiating pyelonephritis from cystitis flank pain are not accurate (Majd *et al.*, 1991; Nanda and Juthani-Mehta, 2009) and sensitivity of Dimercaptosuccinic acid (DMSA) renal scintigraphy in differentiation of pyelonephritis from cystitis is ranges from 86-91% (Majd *et al.*, 2001) and this is a good but invasive method. Hence, physicians prefer to use a non-invasive method for the diagnosis of pyelonephritis.

Bacteria causing UTI activates both systemic and local inflammatory responses in which the cytokines play a central role (Sheu *et al.*, 2006). Uropathogenic *Escherichia coli* that is the most common factor of UTI, stimulates the epithelial cells of the urinary tract and secretion of interleukin 8 (IL-8) (Funfstuck *et al.*, 2001). IL-8 has an important role in chemotaxis and the activation of leukocytes and causes an inflammation at the site of the infection (Agace *et al.*, 1993). IL-8 is very stable in the urine (against temperature and lapse time) and can be used for diagnosis of UTI without depending on the terms of sampling and transferring of samples (Friebe and Volk, 2008). IL-8 with a high concentration is seen in the urine of children with UTI (Jacobson *et al.*, 1994; Jantausch *et al.*, 2000). So, in this study we stressed the role of IL-8 in the diagnosis and differentiation between pyelonephritis and cystitis.

MATERIALS AND METHODS

Study design and population: This prospective descriptive study was conducted among 86 children one month to 14 years, who with clinical signs and symptoms of suspected urinary tract infections were referred to Ahvaz Aboozar hospital. The study was approved by the Ethical Committee of Ahvaz Jundishapur University of Medical sciences and all patients were signed the informed consent prior to enrollment.

Inclusion criteria: Patients with positive urine analyses (leukocytes in urine more or equal to 5 cells per high-powered field) and positive urine cultures (in the midstream urinary sample equal to or greater than 100,000 colonies of a single organism, in the sample urine with the catheter more than 10,000 colonies and in the suprapubic sample any number of gram negative bacteria or 1,000 colonies of gram-positive bacteria grow) (Majd *et al.*, 2001) were included.

Exclusion criteria: Patients with gross hematuria, surgery in a recent month, malignancy, renal failure (based on GFR less than 90 cc per 1.73 m^2 min^{-1} according to the formula KL/Pcr) (Bhat *et al.*, 2011), previously known immunodeficiency and recent use of antibiotics were excluded.

Methods: Based on the findings of DMSA scan all patients were divided into two groups of pyelonephritis and cystitis. Using a form to collect information from Project partner who was not aware of the details of each interleukin test, information about each patient was completed. Then, in the first 12 h of hospitalization before administering the first dose of antibiotics, 1 mL of their urine sample was collected and frozen at a -70°C. After reaching the number of samples at the designated value, the concentration of IL-8 of urine was measured by ELISA. Fourty eight hours after antibiotic treatment again, 1 mL of urine was collected and IL-8 was measured and to standardize samples, Cr level in urine was measured and the ratio of IL-8 to Cr was calculated. A Complete Blood Count (CBC), pyuria and acute phase reactants, including Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) were measured by standard methods in all patients.

Statistical analysis: At first, in order to analyze the data using descriptive statistics, including frequency distribution tables, graphs, central tendency parameters and dispersion parameters the variables were described then statistical tests such as T-test, Pearson correlation coefficient (or their non-parametric equivalents such as the Mann-Whitney and Spearman correlation coefficient) were used. Also, with the use of ROC curve the most suitable cutoff was calculated to determine sensitivity and specificity of IL-8. The significance level was considered as 0.05 and the relationship between IL-8 with other variables was investigated. The data were analyzed using SPSS 18.

RESULTS

Among 86 children studied 16 (18.6%) and 70 (81.4%) children were boys and girls, respectively. Patients' age range was 1.5-96 months with the average age of 24.5 (SD = 24.4) and median of 12.5 months and generally the ratio of boys to girls was 1 to 4.3 but at the age of 1-2 years, 100% of the cases were girls. The pyelonephritis and the cystitis groups were respectively 46 (53.5%) and 40 patients (46.5%). The pyelonephritis group nine boys (19.6%) and 37 girls (80.4%) were in the age range of 1.5 up to 84 months that 60, 17.4 and 15.2% of those were respectively in the age groups: under 1, 1-2 and 2-5 years. In cystitis group seven boys (17.5%) and 33 girls (82.5%) were in the age range of 1.5 up to 96 months that 35, 15 and 35% of them were respectively less than 1, 1-2 and 2-5 years old (Fig. 1).

E. coli and *Klebsiella* were obtained from urine samples of 72 patients (83.7%) and seven patients (8.1%), respectively. *E. coli* and *Klebsiella* in the pyelonephritis group in 85.4 and 8.3% of cases were isolated, respectively. In cystitis group also these organisms respectively in 81.3 and 7.9% of patients were causative of infection. In terms of clinical symptoms the fever higher than 38.5°C existed in 69 and 31.6% of cases, respectively in the pyelonephritis and cystitis groups. The frequency of abdominal pain in pyelonephritis and cystitis groups was 10.4 and 18.4%, respectively. Vomiting in the pyelonephritis and cystitis groups was respectively 22.9 and 10.5%. The frequency
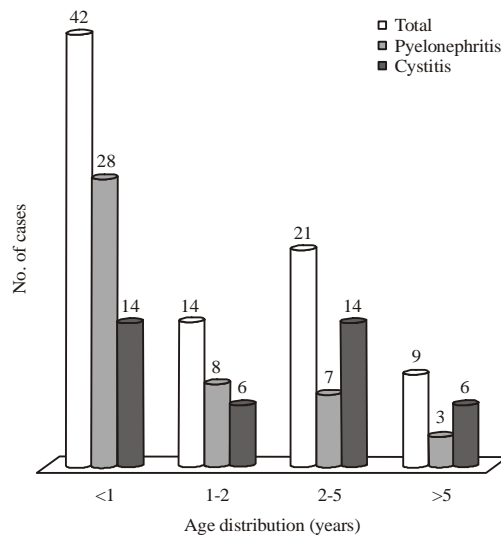

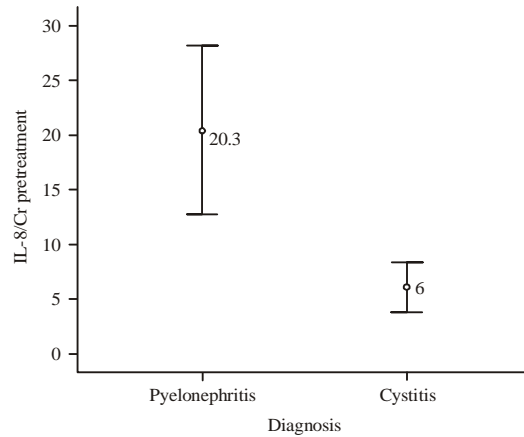Fig. 1: Age distribution of children studied based on the diagnosis

Fig. 2: Relationship between the level of IL-8/Cr urine before treatment with upper and lower urinary tract infection
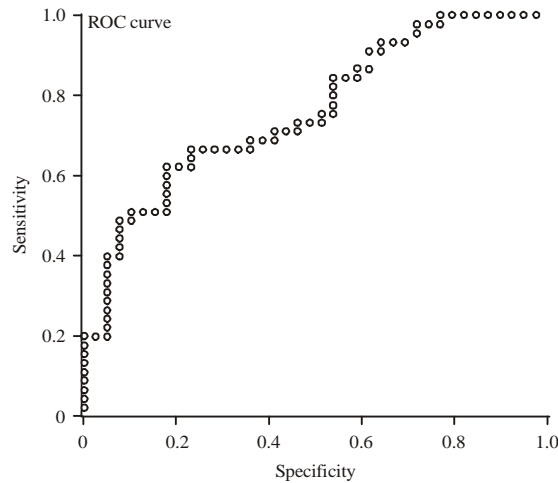

Fig. 3: Specificity and sensitivity level of IL-8/Cr before treatment for diagnosis of pyelonephritis

of diarrhea in the pyelonephritis and cystitis groups was 4.2 and 2.6%, respectively. In general, dysuria was the most common symptom in the two groups (69.8%) (Table 1).

In terms of inflammatory markers, average ESR was 75 and 27 in pyelonephritis and cystitis groups, respectively. ESR over 50 was reported in 80 and 10.5% of cases in the pyelonephritis and cystitis groups, respectively. The number of peripheral blood WBC was ranging from 6000 up to 33000 that an average of 16800 was obtained in pyelonephritis group and more than 15000 was reported in 62.5% of cases; the average number of WBC in peripheral blood in the cystitis group was 11800 and was more than 15000 in 10.4% of the cases. The median ratio of IL-8/Cr of urine in all patients before treatment was 6.66 and 48 h after treatment was 2.1.

In children with upper urinary tract infection the IL-8/Cr ratio was ranging from 1.48-126. 3 and its median before treatment was 13.1 3.1 and 48 h after treatment was 3.1. In children with lower urinary tract infections the IL-8/Cr ratio was ranging from 0.15 up to 30.8 and its median before treatment was 4.53 and 48 h after treatment was 1.1. A statistically significant correlation existed between the average IL-8/Cr before treatment and the upper urinary tract infection, i.e., the amount of interleukin in the upper infection was higher (p<0.0001) (Fig. 2 and 3). The mean

Table 1: Frequency percentage of symptoms in the studied patients with urinary tract infection by diagnosis

Variables	Fever (Body temperature>38.5°C) (%)	Fever (<3 days)	Abdominal pain (%)	Vomiting (%)	Diarrhea (%)	Urinary irritation (%)
Pyelonephritis	69.0	59.6	10.4	22.9	4.2	62.5
Cystitis	31.6	44.7	18.4	10.5	2.6	78.9

Table 2: A comparison between different inflammatory markers by sensitivity and specificity in the diagnosis of pyelonephritis

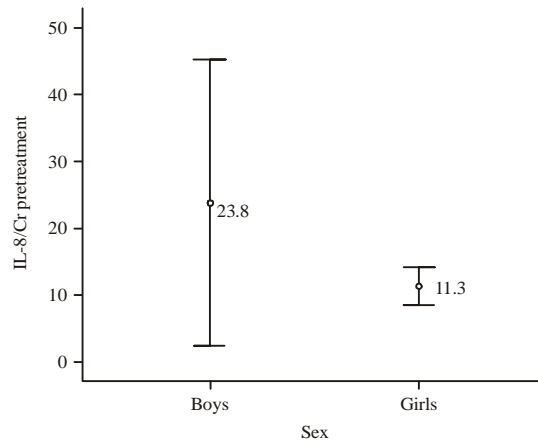| Intensity markers	IL-8	Leukocytosis (cell μL^{-1})	ESR (mm h^{-1})	Intensity of pyuria (cell hpf^{-1})
Cut-off point	7	15000	30	47
Specificity	72	78	65	55
Sensitivity	66	63	90	67

Fig. 4: Relationship between the levels of urinary IL-8/Cr before treatment by gender of the patients with urinary tract infection

IL-8/Cr in cut off 7 for differentiating pyelonephritis from cystitis had sensitivity 66% and specificity 72%. Sensitivity and specificity of other inflammatory markers have been calculated for comparing (Table 2). In both groups pyelonephritis and cystitis, 48 h after treatment the mean IL-8/Cr was reduced; however, its reduction in both groups was not statistically significant (p = 0.11). In this study 13 patients showed resistance to initial antibiotics and after treatment the level of IL-8 increased and when removing these urine cultures resistant to ceftriaxone in both groups from calculation, significant differences existed between IL-8/Cr before treatment and 48 h after treatment (p = 0.003).

The mean IL-8/ Cr in girls and boys group was respectively 11.3 (SD = 11.7) and 23.8 (SD = 40) that no significant relationship existed (p = 0.892) (Fig. 4). The mean IL-8/Cr at the age less than one year was 19.7 (SD = 26.4) and in the age more than one year was 7.7 (SD = 9.4), which a significant relationship was obtained using non-parametric Spearman correlation test (p = 0.008) (Fig. 5). A statistically significant relationship existed between the mean IL-8/Cr with ESR, CRP and the intensity of pyuria; in other words, the mean IL-8/Cr increases with the increase in ESR, CRP and urinary WBC (p = 0.001).

In terms of the relationship between the mean urinary IL-8/Cr with the peripheral blood White Blood Cell (WBC) count a significant correlation was obtained, i.e., by increasing the peripheral WBC, the mean IL-8 increases (p = 0.006) although it had no significant relationship with the
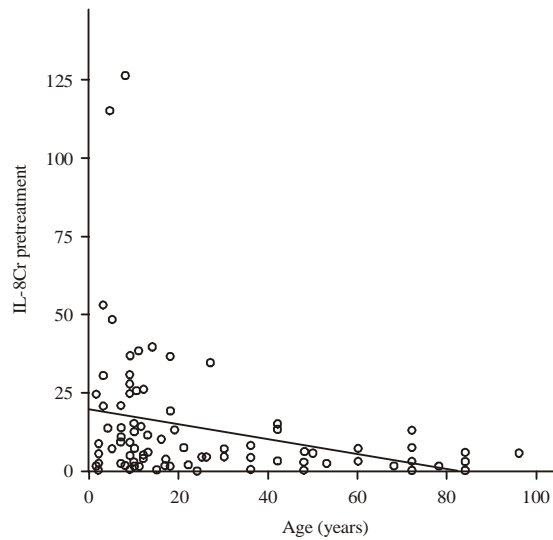
Fig. 5: Relationship between the levels of urinary IL8/Cr before treatment in the studied group with age

percentage of the peripheral blood neutrophil. In cases of urinary tract infection by *E. coli* the mean IL-8/Cr was 13.8 (SD = 21.7) and in other organisms, its mean was 13.1 (SD = 14.7) that no significant relationship existed (p = 0.6).

The prevalence of vesico uretral reflux in total patients studied was 19.8% that 72% of cases was in pyelonephritis and 28% in cystitis group; also, in cases of vesico uretral reflux the mean IL-8/Cr was 17.8 (SD = 29.5) and in cases without reflux its mean was 12.9 (SD = 18) that no significant relationship existed (p = 0.773).

In terms of the relationship between the duration of fever before the diagnosis of disease, a significant relationship existed between fever less than three days with the mean urinary IL-8/ Cr prior to treatment (p = 0.04); moreover, a significant relationship existed between severity of the fever greater than or equal with 38.5°C and with a mean of urinary IL-8/Cr before treatment (p = 0.02).

DISCUSSION

Urinary tract infection activates topical and systemic cytokine responses; also, release of cytokines from the site of infection triggers the fever, acute phase response and neutrophilic response (Sheu *et al.*, 2006). IL-8 is one of the important mediators of early inflammatory response and an agent for influx of neutrophils to the site of inflammation. Ko *et al.* (1993) showed a relationship between UTI and urinary tract cytokines and IL-8 induces the migration of the PMN cells into the urine. In some of the studies that examined the plasma concentrations of interleukins in patients with UTI, have considered fever and inflammatory markers as a criterion for the diagnosis of the pyelonephritis (Kassir *et al.*, 2001). It seems that it is not very reliable in children, but in the study the DMSA scans have been used to diagnose the pyelonephritis. Our current study has been conducted on children with UTI and showed a significant relationship exists between the mean IL-8/Cr before treatment and type of UTI (pyelonephritis or cystitis (p<0001). Moreover, the rate of infection in the upper IL is higher and can be used as an inflammatory marker in

differentiating the upper UTI from the lower one. The concentration of IL-8 was reduced in both groups but no significant correlation existed between the two groups. However, when the ceftriaxone-resistant cultures in the two groups were excluded from the computation a significant difference in reduction of IL-8 after treatment with IL-8 was observed. So, it seems the lack of reduction of IL-8 in 48 h after treatment has been due to the resistance of bacteria to ceftriaxone drug and because the inflammation continued, still IL-8 level remains high. The mean IL-8 in pyelonephritis group was 459 pg mL^{-1} that 90% of the patients in this group had a level higher than 23 pg mL^{-1}. Several studies have shown the increased IL-8 following UTI. Similarly (Oregioni *et al.*, 2005) reported that 92% of patients with UTI had IL-8 level higher than 25 pg mL^{-1} and the mean IL-8 was 627 pg mL^{-1} (Oregioni *et al.*, 2005). In addition, in (Taha *et al.*, 2003) study on 31 children, the highest level of IL-8 in urinary tract infection has been reported (548 pg mL^{-1}).

In the Cutoff of 200 pg mL^{-1} for IL-8, Rao *et al.* (2001) have mentioned 93 and 90%, respectively for the sensitivity and specificity in diagnosing UTI. Furthermore, in a study conducted by Jantausch *et al.* (2000). In the USA, when accepting 32 patients with UTI the amount IL-8 have been reported 5809 pg mL^{-1}, in 32 patients in the control group has been zero and in 48 h after treatment the IL-8 urinary levels has been reported lower (Jantausch *et al.*, 2000). Similar to our study, in a study in Taiwan that comparisons were performed between urinary IL-8 and 6 in patients with acute pyelonephritis, cystitis and healthy child (Sheu *et al.*, 2006) showed that the mean initial IL-8 and 6 in pyelonephritis is higher than the other groups (3165 pg mL^{-1}) and 48 h after treatment has been also reduced (8). In a study in California (Kassir *et al.*, 2001). Showed high concentration of cytokines (IL-8, 6 and 1) in the initial urine sample and reduction of the concentration in the samples after the first dose of antibiotics (12-24 h later) (Kassir *et al.*, 2001).

In our study, the mean IL-8/Cr in level of cut-off 7 has 66% sensitivity and 72% specificity for the diagnosis of pyelonephritis, due to the sensitivity and specificity of other inflammatory markers for the diagnosis pyelonephritis, it was found that the sensitivity and specificity of IL-8/Cr are approximately equal to other inflammatory markers. In two studies the sensitivity and specificity of IL-8 in the diagnosis of pyelonephritis were 86 and 83%, respectively (Sheu *et al.*, 2006; Taha *et al.*, 2003).

In our study, in terms of the age the most of pyelonephritis was in the age group of less than one year but in the cystitis group the most rates were in the age groups of less than one year old and two to five years old. All patients with urinary tract infection in the age group 2-5 years were female. The prevalence of urinary tract infection in the boys and girls was 18 and 81%, respectively. The ratio of boys to girls was 1 to 4.3 that was similar to the results of study conducted by Kari (Kassir *et al.*, 2001) in California (Sheu *et al.*, 2006).

In our study, the prevalence of urinary reflux was 19.8%, while the most common cause of urinary tract infections was *E. coli* (83.7%) and Klebsiella with 8.1% was in the second place the same as other studies. Similar to our study in Kassir *et al.* (2001) study 30% of patients with urinary tract infection had VUR and in 80% of cases the cause of UTI was *E. coli* (15); however, in Oregioni *et al.* (2005) study in France, prevalence of *E. coli*, *Klebsiella* and *Proteus* were 48, 11 and 9%.

In our study, no significant relationship existed between the mean IL-8/Cr with gender of patients (p = 0.892) but a significant relationship existed between the mean IL-8/Cr with age less than one year (p = 0.008). In Tullus *et al.* (1994a, b) study of IL6, 8 in the children's urine with pyelonephritis, no relationship existed between the IL6 and age but as our study the IL-8 quantities in less than one year old were significantly higher. However, in Taha *et al.* (2003) study

in the UK as well as in Benson's study in Sweden the IL-8 has been correlated with gender and age (Benson *et al*., 1996). In other studies also the highest level of IL-8 in urine of patients with UTI had no correlation with the gender and age of the patients (Benson *et al*., 1996; Ko *et al*., 1993). The different results of these studies indicate a need for a broader study in the field with a larger sample size.

In our study, statistically significant correlations existed between the mean IL-8/Cr with ESR, CRP, Leukocytosis, the severity of the fever, fever duration and the severity of Pyuria; however, no significant correlation existed between the mean IL-8/Cr and percentage of peripheral blood PMN and urinary reflux. Sensitivity and specificity of IL-8/Cr in diagnosing pyelonephritis is almost equivalent to the sensitivity and specificity of CRP, ESR and Leukocytosis in diagnosing pyelonephritis. Equally our study (Oregioni *et al*., 2005) in France, a direct relationship existed between PMN of urinary tract and the level Chemokine (Oregioni *et al*., 2005). In addition, in Taha *et al*. (2003) study in England as well as Benson in Swedish, Sheu *et al*. (2006) study, as our study, IL-8 had a relationship with Leukocytosis, ESR and CRP (Benson *et al*., 1996; Taha *et al*., 2003). Although in Jantausch *et al*. (2000) s study in George Washington, America, no relationship existed between the concentration of IL-8, 6 with duration of symptoms before the measurement, the amount and duration of fever, peripheral blood Leukocytosis, the percentage of PMN or band and the reflux as well as a poor relationship existed between the urine WBC count and IL6, 8 (Majd *et al*., 2001). Different results of these studies indicate that broader studies are necessary to be performed with a greater sample size.

In our study between no relationships existed between the mean IL-8/Cr with biological species inducing UTI. But in Jantausch *et al*. (2000) study in George Washington, America, the amount of urinary IL-8 in patients with UTI as a result of *E. coli* was higher (Majd *et al*., 2001).

CONCLUSION

Measurement of cytokines only takes a few hours and to do it is the easy and non-invasive. In cases very suspicious UTI that result of the cultivation still is not available the presence of IL-8 helps to decide about treatment of UTI, as other inflammatory markers are helpful, IL-8 can be a reliable marker to differentiate involvement of upper urinary tract and lower urinary tract. Based on the study system the mean IL-8/Cr for detecting pyelonephritis in level 7 has the sensitivity of 66% and the specificity of 72% and even the increased IL-8 after the initial experimental treatment can be a sign for the continued inflammation or antibiotic resistance. Obviously, in this recent case wider study must be carried out.

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