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Effect of N-Acetylcysteine on Inflammation Biomarkers in Pediatric Acute Pyelonephritis

A Randomized Controlled Trial

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Introduction. This study was designed to investigate the effect of N-acetylcysteine (NAC), as a potent and safe antioxidant, on inflammatory biomarkers of acute pyelonephritis in pediatric patients.

Materials and Methods. Children (< 15 years old) admitted with a diagnosis of pyelonephritis were recruited in a randomized placebo-controlled trial. They were randomly allocated to 2 groups and recieved placebo or NAC effervescent tablets with daily dose based on their weight, for 5 days. The children were evaluated for serum procalcitonin level, leukocyte count, C-reactive protein (CRP), serum creatinine, and clinical symptoms on the 1st and the 5th days.

Results. Seventy patients, 35 in each group, with a mean age of 5.54 ± 3.10 years completed the study. There was no significant difference between the two groups in the amount of changes in procalcitonin levels after 5 days (P = .90). Within-group analysis confirmed CRP reduction in both groups (P < .001); however, between-group analysis did not show significant difference in CRP reductions, either (P = .65). No significant differences were found between the two groups in the day of resolving pyuria (P = .46), day of resolving bacteriuria (P = .81), or reductions in leukocyte count (P = .64) and neutrophil count (P = .49).

Conclusions. A short period of NAC administration with the recommended doses could not lead to a significant decrease in inflammation biomarkers. Studies on higher doses and longer duration of NAC administration along with evaluation of the long-term effects of the intervention by tools such as renal scntigraphy are suggested.

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INTRODUCTION

Many studies have confirmed the existence of inflammatory responses leading to kidney diseases (including renal scaring) following acute pyelonephritis in children with febrile urinary tract infections.[1-6] Bacteria can cause renal inflammation through mechanisms such as stimulating epithelial cells that release inflammatory mediators, inducing epitelial cell apoptosis, damaging the integrity of the connective tissue, and invasive effects on renal tissue. The severity of the inflammation determines the severity of urinary tract infection.[2] Pyelonephritis triggers inflammatory process in renal parenshyma. This is intermediated by production of reactive nitrogen and oxygen species and suboptimal performance

of the antioxidant systems.[7] Loss of the balance between antioxidant defense system and oxidants production in cells, which is called *oxidative stress*, usually happens in many inflammatory diseases including pyelonephritis.[8,9]

There are various markers in blood, urine, and kidney tissue that can be used as indicators of oxidative stress status.[10] In addition, there are several biomarkers that have been studied as predictors of scar or high-grade vesicoureteral reflux in pediatric acute pyelonephritis such as procalcitonin and urine β2-microglobulin.[11-14] Couples of oxidation and reduction, including glutathione and glutathione disulfide, nicotinamide adenine dinucleotide phosphate and its reduced form, nicotinamide adenine dinucleotide and its reduced form, and reduced and oxidized thioredoxin, are active within cells. However, reduction in the capacity of antioxidants in a cell mainly results from a decrease in reduced glutathione and increase in its oxidized form. Since glutathione is the most abundant intracellular free thiol, oxidative stress mainly means the deficiency of glutathione and its precursor, cysteine.[8]

Antioxidant supplements have been intensively studied to reverse oxidative stress process in various diseases. In acute and chronic pyelonephritis, administration of antioxidants has been associated with favorable outcomes through inhibiting the inflammatory process and eventually controling the symptoms as well as delaying accompanying complications.[15-20] Although common antioxidants, eg, vitamin C, vitamin K, and lipoic acid, can directly neutralize free radicals, they are not capable of replacing cysteine required for the synthesis of glutathione.[21] Consequently, it is not surprising that the cysteine precursor, N-acetylcysteine (NAC), is more powerful than other antioxidants in the treatment of diseases associated with oxidative stress.[8] In addition, NAC acts through other mechanisms such as restoration of disulfide bonds in proteins, accumulation of free radicals, and binding to metals.[22-24] Compared with cysteine , NAC is less toxic, less prone to oxidation, and more soluble in water. Also, its use is superior to the use of cysteine by injection.[25]

N-acetylcysteine is a potent antioxidant and has beneficial effects on the prevention and treatment of inflammatory or infectious conditions,[26-37] and it is a safe drug confirmed by its profile of adverse reactions which is similar to those of or less than placebo.[8,38,39] Accordingly, it is hypothesized that NAC may have desired therapeutic effects in children with acute pyelonephritis. Therefore, given the lack of similar studies on patients with acute pyelonephritis in children or adults, and the importance of acute pyelonephritis in pediatric patients, the present study was designed to investigate the effects of NAC on inflammatory biomarkers of acute pyelonephritis in pediatric patients.

MATERIALS AND METHODS

Study Design

This study was a double-blind randomized placebo-controlled trial. The particiapnts and the researchers and clinicans involved in the study were blinded to the allocations. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT2013112015465N1) and the clinicaltrials.gov (NCT02080182).

Participants and Setting

The study population consisted of children admitted to a university-affiliated children hospital (infectious and nephrology units) with a definite or probable diagnosis of acute pyelonephritis confirmed by clinical symptoms, blood and urine laboratory findings, and results of the dimercaptosuccinic acid (DMSA) scan. The inclusion criteria were an age between 1 and 14 years and a definite or probable diagnosis of acute pyelonephritis. The exclusion criteria were concurrent acute or chronic inflammatory and infectious diseases.

Intervention

After randomization using a balanced (permuted) block randomization method, the patients in the treatment group received NAC effervescent tablets (600 mg; Hexal, Germany) and the placebo group received placebo effervescent tablets, each for 5 days. The dosage was as follows: children with a body weight of 30 kg and greater, 900 mg/d; children with a weight between 30 kg and 8.5 kg, 600 mg/d; and those with a weight less than 8.5 kg, 70 mg/kg/d. The patients also received their routine antimicrobial drug regimen. The patients and their parents, prescriber, and the examiner who measured and recorded outcomes were blinded to the allocations.

Outcome Measures

Demographic and clinical data were collected by asking directly from the parents or from the patient records. The children were evaluated based on the results of the serum levels of procalcitonin, C-reactive protein (CRP), and creatinine; leukocyte count; and clinical symptoms (fever, urinary frequency and urgency, dysuria, and suprapubic or flank pain) on the 1st day (baseline) and the 5th day. Serum samples were stored in -70°C and procalcitonin was measured using an enzyme-linked immunosurbent assay. The incidence of possible adverse effects also recorded in both study groups.

Sample Size Calculation

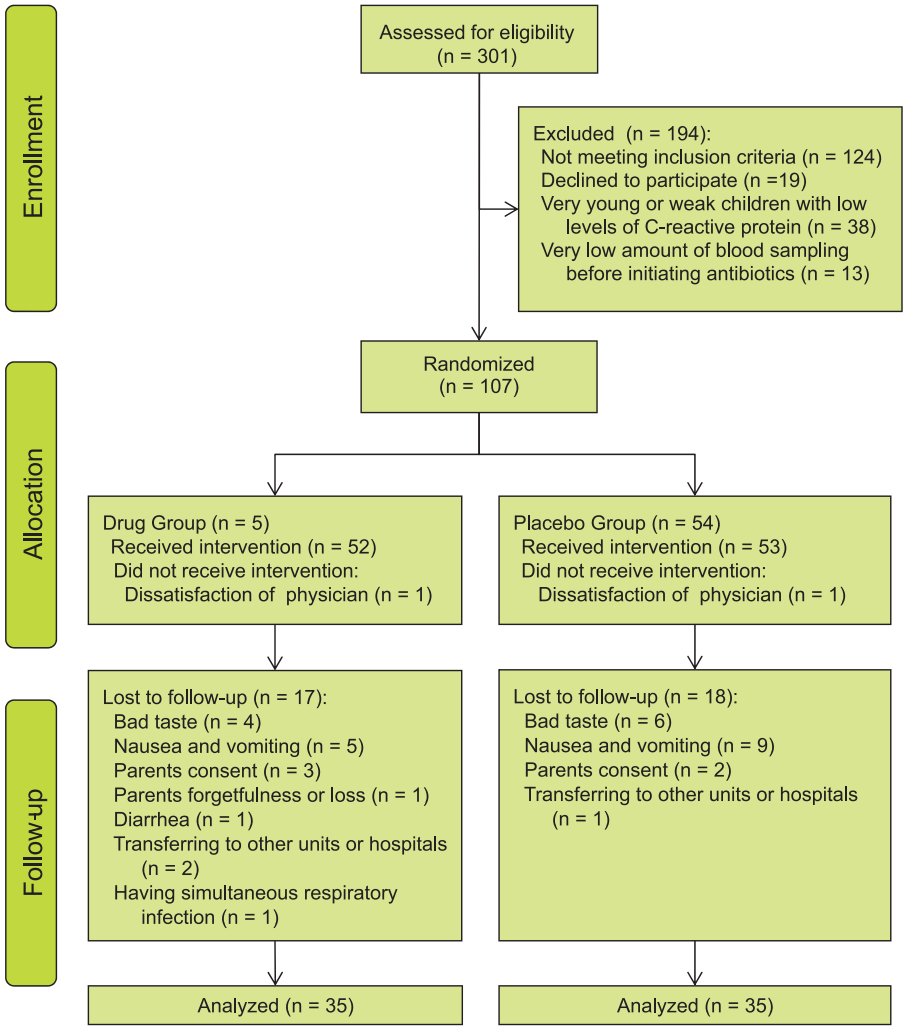
A sample size of 26 patients in each group was calculated based on the expected changes to the procalcitonin (as primary variable) assuming a power equal to 80%. Considering 20% dropout, 32 patients were entred into each study group.

Statistical Analysis

Based on the qualitative and quantitative nature of the study variables and their distribution, the Student *t* test, Mann-Whitney U test, and chi-square test were applied using the SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, Ill, USA). A *P* value less than .05 was considered significance.

RESULTS

Overall, 70 patients completed the study (35 in each group). The participation flow diagram of the study is presented in the Figure. Patients in the treatment group received 42.51 ± 13.44 mg/kg/d of NAC, and overall, 2588.57 ± 855.00 mg



The CONSORT flow diagram.

of NAC during the study period. Demographic and clinical characteristics of the study groups are shown in Table 1. *Escherichia coli* was the most common cause of infection (Table 2). Urine culture of some patients showed no colonies of bacteria; however, these patients were also included in our study because of other confirmig criteria suggesting "probable UTI."

Antibiotic regimens of patients were prescribed based on the Pediatric Infectious Research Center guidelines. Antibiotic regimens used for the study groups are shown in Table 3. No difference was observed between the two groups based on their antibiotic regimens (P = .56). Only in 6 patients in the drug group and 3 patients in the placebo group, the initial antibiotic regimen was changed, which was not significant (P = .29).

On average, procalcitonin levels decreased in both groups after the interventions; however, the mean changes were not significantly different between the two groups (P = .74; Table 4). The CRP levels were significantly changed in both groups after the intervention, but the mean changes were comparable between the two groups (P = .65; Table 4).

DISCUSSION

The results of this study showed that in children with acute pyelonephritis, doses of NAC applied for a period of 5 days did not make significant changes in inflammatory markers, including procalcitonin, CRP, and leukocyte count compared to placebo. Also, NAC had no significant reduction in the secondary outcomes such as day of resolving pyuria or bacteriuria. To interpret our results, we divided similar studies into 2 groups. One group are studies in which antioxidants other than acetylcysteine are used for the control of infection and inflammation in acute pyelonephritis and the

Table 1. Demographic and Clinical Characteristics of the Study Groups*

Group	Study Groups		*P*	All
	Treatment (n = 35)	Placebo (n = 35)		
Sex				
Female	29 (82.8)	33 (94.3)		62 (88.6)
Male	6 (17.1)	2 (5.7)	.26	8 (11.4)
Age				
Range	1 to 13	1 to 11		1 to 13
Mean ± standard deviation	5.56 ± 3.21	5.52 ± 3.03		5.54 ± 3.10
Median (25th - 75th quartiles)	4.5 (4.00 to 7.00)	6 (3.00 to 8.00)	.79	5.00 (3.75 - 8.00)
Weight				
Range	9.5 to 44.0	7.0 to 50.0		7.0 to 50.0
Mean ± standard deviation	19.39 ± 9.03	19.95 ± 10.80		19.67 ± 9.89
Median (25th - 75th quartiles)	16 (13.00 - 24.25)	18 (11.40 - 24.50)	.98	17.50 (12.15 - 25.12)
Admitting unit				
Nephrology	31 (88.6)	28 (80.0)		59 (84.3)
Infectious diseases	4 (11.4)	7 (20.0)	.51	11 (15.7)
Medical history				
Neurogenic bladder	12 (34.3)	12 (34.3)		24 (34.3)
Inpatient urinary tract infection	10 (28.6)	12 (34.3)		22 (31.4)
Outpatient urinary tract infection	9 (25.7)	9 (25.7)		18 (25.7)
Reflux nephropathy	5 (14.3)	5 (14.3)		10 (14.3)
Kidney calculi	6 (17.1)	3 (8.6)		9 (12.9)
Myelomeningocele	4 (11.4)	3 (8.6)		7 (10.0)
Catheterization	3 (8.6)	2 (5.7)		5 (7.1)
Paralysis	2 (5.7)	0		2 (2.9)
Polycystic kidney	1 (2.9)	0		1 (1.4)
Single kidney	1 (2.9)	0		1 (1.4)
Cancer	1 (2.9)	0		1 (1.4)
None	11 (31.4)	9 (25.7)	.97	20 (28.6)
Being on antibiotic prophylaxis	12 (34.3)	9 (25.7)	.43	21 (30.0)

*Values in parentheses are percentages unless otherwise specified.

Table 2. Pretreatment Laboratory Results*

Group	Study Groups			All
	Treatment (n = 35)	Placebo (n = 35)	*P*	
Pyuria				
2 to 5	5 (14.3)	2 (5.7)		7 (10.0)
6 to 10	2 (5.7)	1 (2.9)		3 (4.3)
11 to 20	5 (14.3)	5 (14.3)		10 (14.3)
21 to 30	5 (14.3)	5 (14.3)		10 (14.3)
31 to 40	3 (8.57)	2 (5.7)		5 (7.1)
41 to 50	1 (2.9)	0 (0.00)		1 (1.4)
51 to 60	1 (2.9)	0 (0.00)		1 (1.4)
71 to 80	1 (2.9)	0 (0.00)		1 (1.4)
Many	12 (34.3)	20 (57.1)	.59	32 (45.7)
Bacteriuria				
None	8 (22.9)	6 (17.1)		14 (20.0)
Rare	2 (5.7)	1 (2.9)		3 (4.3)
Few	8 (22.9)	9 (25.7)		17 (24.3)
Moderate	3 (8.6)	5 (14.3)		8 (11.4)
Many	14 (40.0)	14 (40.0)	.88	28 (40.0)
Leukocyte count, × 10^9/L				
Mean ± standard deviation	10.51 ± 4.46	13.44 ± 6.03	.10	12.15 ± 5.30
Median (25th - 75th quartiles)	9.90 (7.70 - 12.30)	12.10 (8.10 - 18.00)		11.20 (7.80 - 16.30)
Neutrophils, %				
Mean ± standard deviation	61.69 ± 20.06	63.36 ± 16.22		63.43 ± 16.59
Median (25th - 75th quartiles)	64.00 (52.00 - 76.50)	66.0 (50.00 - 76.00)	> .99	64.00 (51.50 - 77.00)
Erythrocyte sedimentation rate, mm/h				
Mean ± standard deviation	40.52 ± 25.53	50.12 ± 31.01		45.46 ± 28.68
Median (25th - 75th quartiles)	37.00 (20.00 - 59.00)	50.00 (20.00 - 80.00)	.21	40.50 (20.00 - 72.75)
Blood urea nitrogen, mg/dL				
Mean ± standard deviation	10.63 ± 3.82	11.06 ± 5.31		10.84 ± 4.49
Median (25th - 75th quartiles)	10.00 (8.00 - 13.00)	10.00 (9.00 - 12.00)	.75	10.00 (8.00 - 12.25)
Serum creatinine, mg/dL				
Mean ± standard deviation	0.69 ± 0.16	0.71 ± 0.21		0.70 ± 0.18
Median (25th - 75th quartiles)	0.70 (0.60 - 0.70)	0.70 (0.60 - 0.80)	.70	0.70 (0.60 - 0.72)
Urine culture				
Escherichia coli	19	20		39
Contamination	3	6		9
Klebsiella pneumoniae	2	0		2
Pseudomonas aeruginosa	0	1		1
Enterococcus species	1	2		3
Enterobacter species	1	0		1
ESBL Escherichia coli	1	1		2
None	7	5	.56	12

*Values in parentheses are percentages unless otherwise specified.

other one includes studies in which acetylcysteine is used as an antioxidant and anti-inflammatory medication for conditions other than pyelonephritis. The only available study on the antioxidant effects of acetylcysteine on acute pyelonephritis was an animal (mice) study. In this study, pyelonephritis was induced by *Pseudomonas aeruginosa*, confirmed by the presence of free radicals of oxygen and nitrogen species, and intraperitoneal acetylcysteine with a dose of 10 mg/kg could significantly reduce oxidative stress and neutrophil counts as well as bactericidal titers.[7]

Several studies on the effects of antioxidants other than acetylcysteine have been done in acute pyelonephritis. In most of these studies, antioxidants were prescribed for short periods of a few days and during the process of inflammation and infection of the tissue, subsequently long-

Table 3. Antibiotic Regimens of the Study Groups*

Antibiotic	Study Groups		All
	Treatment (n = 35)	Placebo (n = 35)	
Ceftriaxone + amikacin	19 (54.3)	14 (40.0)	33 (47.1)
Ceftriaxone	8 (22.9)	6 (17.1)	14 (20.0)
Meropenem	1 (2.9)	5 (14.3)	6 (8.6)
Ceftazidime + amikacin	2 (5.7)	3 (8.57)	5 (7.1)
Imipenem	2 (5.7)	2 (5.7)	4 (5.7)
Ceftizoxime + amikacin	1 (2.9)	1 (2.9)	2 (2.9)
Ceftizoxime	0	1 (2.9)	1 (1.4)
Cefotaxim e + amikacin	1 (2.9)	0	1 (1.4)
Amikacin	0	1 (2.9)	1 (1.4)
Meropenem + amikacin	0	1 (2.9)	1 (1.4)
Cefotaxime	0	1 (2.9)	1 (1.4)
Ceftazidime	1 (2.9)	0	1 (1.4)
Total	35 (100)	35 (100)	70 (100)

*Values are frequency (percentage).

Table 4. Changes in Inflammatory Markers and Adverse Effects*

Group	Study Groups		*P*
	Treatment (n = 35)	Placebo (n = 35)	
Changes in procalcitonin, ng/mL			
Mean ± standard deviation	-26.20 ± 243.78	-8.92 ± 176.64	
Median (25th - 75th quartiles)	0 (-148.75 - 53.56)	4.71 (-85.32 - 94.8)	.74
Reduction in C-reactive protein, mg/L			
Mean ± standard deviation	65.84 ± 35.51	65.45 ± 29.29	
Median (25th - 75th quartiles)	63.00 (46.65 - 79.50)	68 (51.70 - 85.00)	.65
Day of resolving pyuria			
Mean ± standard deviation	3.51 ± 1.98	4.23 ± 2.31	.46
Day of resolving bacteriuria			
Mean ± standard deviation	2.03 ± 1.46	2.71 ± 1.92	.81
Amount of leukocyte reduction, × 10^9/L			
Mean ± standard deviation	5.29 ± 5.94	6.62 ± 5.72	
Median (25th - 75th quartiles)	7.9 (1.00 - 9.50)	5.6 (2.95 - 10.25)	.64
Amount of neutrophil reduction, %			
Mean ± standard deviation	28.49 ± 18.19	19.65 ± 25.93	
Median (25th - 75th quartiles)	27.20 (25.00 - 38.20)	16.50 (2.00 - 45.50)	.49
Adverse effects			
Nausea and vomiting	5 (14.3)	3 (8.6)	
Bad taste	4 (11.4)	3 (8.6)	
Coughing	1 (2.9)	1 (2.9)	
Sneezing	1 (2.9)	0	
Bad smell	0	1 (2.9)	
Diarrhea	0	1 (2.9)	> .99

*Values in parentheses are percentages unless otherwise specified.

term results were analysed using DMSA scan to check for renal parenchyma scars. Dalirani and colleagues conducted an investigation on 76 children with acute pyelonephritis, in which the role of vitamin A in slowing the progression of renal scars or prevention of acute pyelonephritis was studied. Children were divided in 2 groups of ceftriaxone therapy alone or ceftriaxone in combination with vitamin A. Findings of DMSA were compared before treatment and 6 months later. It represented significant changes in the progression of renal damage in the two groups. The group that received vitamin A had significantly fewer scars after 6 months.[19] Although, the effect

of vitamin A in reducing scar development in the long-term can be due to its anti-inflammatory and antioxidant effects, other mechanisms such as re-epithelialization of damaged cells seems to be more important than its antioxidant activity.[40] In addition, several animal studies have shown that the severity of renal scars in rats with vitamin A deficiency is higher than those with normal vitamin A levels.[41]

In another animal study, the effects of vitamins C and E in reducing the risk of renal scars was shown.[18] In patients with chronic pyelonephritis, cytoflavin as add-on therapy of pyelonephritis, could reduce the intensity of lipid peroxidation process whilst maintaining antioxidant status.[16] Caffeic acid phenethyl ester, the active compound of propolis from the beehive with antioxidant, anti-inflammatory, and anti-bacterial effects, was investigated to prevent oxidative damage in pyelonephritis caused by *Escherichia coli* in rats. It was able to increase antioxidant enzyme activity and the histopathologic examination showed that the drug could reduce the inflammation caused by bacterial activity.[17] In two other studies, corticosteroids, administered in the acute phase of pyelonephritis, reduced levels of interleukins and the appearance of scars.[42,43] In the current study, although we did not examine the renal scars 3 or 6 months after intervention, we determined variations in the serum procalcitonin and CRP which are confirmed as biomarkers for the progression of renal scars over a few months after the infection.[12,13]

The second set of studies includes those in which the anti-inflammatory and antioxidant effects of acetylcysteine on diseases and conditions other than acute pyelonephritis have been evaluated. These studies are also divided into two groups. One group of studies are those in which acetylcysteine is used for a limited period of few days, that from this point of view are similar to our study. The second group are studies in which acetylcysteine is administered for several weeks to several months. Molnar and coworkers[44] studied the prophylactic effect of NAC, as a short-term infusion before and during abdominal surgery, on the reduction of CRP and procalcitonin in patients undergoing surgery. Procalcitonin, CRP, and microalbuminuria levels were determined before surgery and after surgery on a daily basis for 3 days. No significant differences were observed in the levels of microalbuminuria and procalcitonin; however, the 1st- and 2nd-day CRP levels were significantly less in the NAC group compared to placebo group.[44]

In another study,[45] the effect of add-on therapy with NAC was evaluated in the treatment of inflammation and oxidative stress in severe burns. N-acetylcysteine was used as a bolus dose of 150 mg/kg, followed by 12 mg/kg/h for 5 days. Blood samples were taken before treatment and up to 5 days after treatment, and the amount of oxidants and antioxidants (malondialdehyde, protein sulfhydril groups, reduced glutathione, myeloperoxidase, catalase, and superoxide dismutase, tumor necrosis factor-α, interleukin-6, interleukin-8, and interleukin-10), as well as multiple organ dysfunction score were measured. The result showed that NAC was able to significantly reduce oxidative stress through decreasing oxidants and increasing antioxidants over days 2 to 6.[45] Acetylcysteine doses used in this study were much higher than those used in similar studies including our study. The observed effects of NAC may owe mainly to the high doses used in this study.

To date, many studies have used NAC to prevent kidney damage caused by contrast media. In a placebo-controlled study, patients who received prophylactic doses of NAC, 600 mg, orally, twice a day, before and after administration of contrast media, had a smaller decline in kidney function in comparison to the placebo group.[46] In other studies on various diseases, acetylcysteine has been prescribed in low doses for more than 4 weeks to control inflammation and chronic infections. In all of them, acetylcysteine was able to reduce inflammatory markers and its antioxidant effects was confirmed.[47-51]

CONCLUSIONS

Evidence showing usefulness of antioxidants to control inflammatory processes, share one of these circumstances: administration of a high dose of the antioxidant for a short time; administration of lower recommended doses of the antioxidant for several weeks to several months; or measurement of surrogate outcomes such as the rate of decline in kidney function or concentration of interleukins and not based on the biomarkers of damage and inflammation. In addition, in some studies, the long-term monitoring, eg, renal scintigraphy

were used several months after acute infection. Therefore, our findings is in favor of the fact that taking antioxidants with usual doses for short periods of few days cannot lead to a significant decrease in inflammatory biomarkers such as procalcitonin, CRP, and leukocyte count. It is suggested that in future studies higher doses and longer duration of acethylcysteine administration be studied along with evaluation of the long-term effects of the intervention by tools such as DMSA renal scintigraphy.

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CONFLICT OF INTEREST

None declared.

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