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Infectious inflammation in children with acute pyelonephritis

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Dear Editor,

Urinary tract infection is one of the most common bacterial infections among infants and young children [1,2]. Nearly two-thirds of children with febrile urinary tract infection have acute pyelonephritis (APN) [3]. The incidence of renal scarring after APN ranges from 26.5% to 57.0% [2]. Therefore, in the management of pediatric APN, prompt and effective antibiotic treatment is very important to prevent long-term complications such as renal scar, hypertension, and renal failure [4]. Some children with APN need adjuvant steroids along with appropriate antibiotics (Table 1) [1-4]. This is because renal scarring is thought to be caused by an excessive immune response to the uropathogen (i.e., infectious inflammation) rather than the direct invasion of the uropathogen into the renal parenchyma [1,5]. In other words, immune defense during APN can be a double-edged sword [6]. The same immune cells and molecules involved in this protective process may also be involved in deleterious inflammation, including kidney damage [5,6]. Here, we wish to make some comments on infectious inflammation in children with APN by presenting our own experience.

A 5-year-old boy was hospitalized with fever and abdominal pain. He was previously healthy with no specific prenatal, past, and family history, including cardiac and renal problems. The patient showed periumbilical pain and nonprojectile vomiting, but did not complain of urinary symptoms such as dysuria, frequency, and hematuria. His height was 115 cm (50th percentile) and his weight was 23.9 kg (75th–90th percentile). Vital signs were as follows: blood pressure, 110/70 mmHg; heart rate, 134 beats/min; respiratory rate, 26 breaths/min; and body temperature, 39.7°C. On physical examination, there were no abnormalities except for tenderness in the lower abdomen. The blood test results on the day of admission were as follows: hemoglobin, 12.1 g/dL; hematocrit, 35.4%; white blood cell (WBC) count, 15,250/μL (neutrophil 87.5%); platelet count, 147,000/μL; erythrocyte sedimentation rate (ESR), 72 mm/hr; C-reactive protein (CRP), 10.2 mg/dL; blood urea nitrogen, 12.2 mg/dL; and creatinine, 0.42 mg/dL. Urinalysis results were as follows: pH, 5.5; WBC, 30–49/high-power field (HPF); red blood cell, 10–19/HPF; protein, +; nitrite, +; specific gravity, 1.022. Renal ultrasonography on hospital day 2 showed increased parenchymal echogenicity in both kidneys without hydronephrosis. Technetium-99m dimercaptosuccinic acid (DMSA) scan on hospital day 3 confirmed left APN with lower pole defect (differential renal function, 45.2%) (Fig. 1A). Empiric antibiotics (cefotaxime) were administered from the day of hospitalization, but his fever remained uncontrolled on the 3rd day of hospitalization. Amikacin was added to antibiotic treatment based on regional data that almost 20% of uropathogens are resistant to cefotaxime [7]. The next day, *Escherichia coli* >10^5 colony forming units per milliliter was isolated from the first and second urine cultures as the causative pathogen. Urine samples were collected via midstream clean-catch specimens. The pathogen was sensitive to both cefotaxime and amikacin, and the 3rd, 4th, and 5th cultures were sterilized with antibiotic treatment. Follow-up urine tests were also normalized. There were no other pathogens isolated from bacterial and viral studies, including blood cul-

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Table 1. Previous studies of adjuvant steroid therapy in children with acute pyelonephritis

Author	Country	No. of steroid group	Treatment regimen	Findings
Sharifian et al. [1]	Iran	34	DX, 0.6 mg/kg/day for 3 day	Significant decrease in urinary cytokines
Huang et al. [2]	Taiwan	19	MP, 1.6 mg/kg/day for 3 day	Relief of renal scars in high-risk groups[a]
Shaikh et al. [3]	USA	271	DX, 0.3 mg/kg/day for 3 day	Fewer renal scars in the DX group
Da Dalt et al. [4]	Italy	23	DX, 0.3 mg/kg/day for 4 day	>50% probability to reduce renal scars

DX, dexamethasone; MP, methylprednisolone.
[a]Patients who have a high risk of renal scar formation (increased inflammatory volume on DMSA [technetium 99m dimercaptosuccinic acid] scan or abnormal renal ultrasonography) [2].

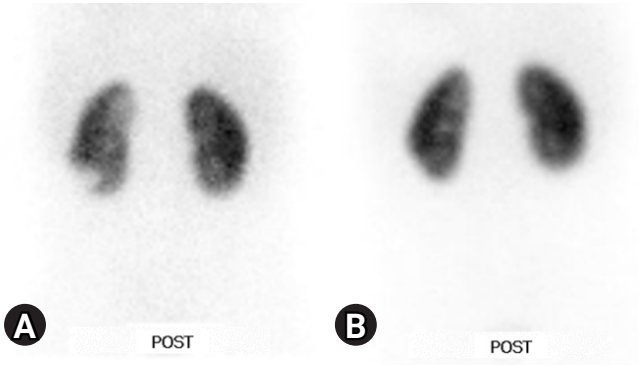

Fig. 1. Technetium-99m dimercaptosuccinic acid (DMSA) scan. (A) Early DMSA scan during hospitalization shows a focal photon defect in left lower renal cortex. (B) Late DMSA scan 3 months after discharge shows no cortical abnormalities in either kidney.

ture and respiratory virus polymerase chain reaction. However, despite appropriate antibiotics and microbiological improvement, the patient showed persistent fever through the 7th day of hospitalization. No organ dysfunction such as shock, oliguria, or seizure was observed, but he appeared lethargic and refused food. The body temperature was 36.5°C to 39.5°C, and antipyretics were needed more than twice a day. Abdominal computed tomography was performed on hospital day 7 to rule out renal abscess formation, and there were no specific findings other than left APN. In the follow-up blood test, WBC count (7,380/μL) was normal, but ESR (56 mm/hr) and CRP (6.4 mg/dL) were still elevated. Considering the possibility of an excessive immune response to uropathogens, short courses of oral steroids (prednisolone 1 mg/kg/day for 5 days) were added as adjuvant therapy. His fever resolved the next day after addition of steroid. No serious adverse events were observed during treatment with steroids. Three months after discharge, DMSA scan performed at the outpatient clinic showed no cortical abnormalities in either kidney (Fig. 1B).

For the management of allergic diseases, clinicians control the allergen and the exaggerated immune response to the allergen (allergic inflammation). Similarly, for the management of infectious diseases, clinicians may need to control both the pathogen and excessive immune response to the pathogen (infectious inflammation) [6,8]. We do not believe that adjuvant steroids are routinely recommended for the management of pediatric APN. However, some children with APN may require adjuvant steroids along with antibiotic treatment [1]. Huang et al. [2] reported that the most important risk factor for renal scar formation was the initial inflammatory volume on DMSA. Increased WBC count and CRP levels in blood tests and duration of fever after initiation of antibiotic treatment may be risk factors for renal complications [3,4]. In clinical and experimental studies, adjuvant steroids have been shown to reduce proinflammatory cytokine levels [1,2]. Because these cytokines have both systemic and renal effects, adjuvant steroids can control infectious inflammation and prevent kidney damage [5]. Fortunately, most infectious inflammation is self-limiting once the pathogen is eliminated with appropriate antibiotic treatment [1,6]. However, if the immune response becomes out of control, it can cause serious deterioration in the host [8,9]. For example, despite the elimination of the offending pathogen, a septic patient may develop shock and multi-organ dysfunction [10].

The application of adjuvant steroid therapy to control the untoward immune response during infectious episodes is not novel [5]. Adjuvant steroids have been reported to be effective and safe to treat a number of infectious diseases, such as bacterial meningitis, tuberculous pericarditis, infectious mononucleosis, and macrolide-refractory mycoplasma pneumonia [2,10]. However, many clinicians hesitate to prescribe steroids for active infection because of their immunosuppressive effects and potential long-term complications [10]. We were also concerned about the side effects of steroids. The safety of adjuvant steroids is supported by the safety of short courses of oral steroids (prednisolone 1–2 mg/kg for 3–5 days) in the treatment of infants and young children with bronchiolitis, croup, and asthma [2]. In actual practice, immunosuppressive effects and potential complications of steroids usually occur with high-dose and long-term use [8,9].

Based on the safety of short courses of oral steroids, adjuvant steroids were applied to our patient. We found that adjuvant steroids were safe and effective in controlling persistent fever and confirming infectious inflammation. According to the definition of postinfectious inflammatory reactions [8] and the guidelines for macrolide-refractory mycoplasma pneumonia [9], fever that persists for more than 72 hours after initiation of antibiotic treatment is considered inflammation requiring intervention. Indiscriminate use of steroids should be avoided, but prudent use of steroids can prevent deleterious inflammation and may reduce the prescription of multiple diagnostic tests and therapeutic agents. In conclusion, children with APN at a high risk of renal scarring may need adjuvant steroids to prevent renal inflammation. Similarly, children with APN whose fever persists despite appropriate antibiotics and microbiological improvement may require adjuvant steroids to control infectious inflammation. In this study, adjuvant steroids were applied based on clinical judgment without laboratory evidence such as cytokine evaluation. Subsequent studies are needed to supplement the limitations of this study.

Ethical statements

This study was approved by the Institutional Review Board of Bucheon St. Mary's Hospital, The Catholic University of Korea (IRB No. HC21ZASI0085), and the consent was waived due to the nature of the retrospective study.

Conflicts of interest

Jin Soon Suh is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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