

Corticosteroids for renal scar prevention in children with acute pyelonephritis

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Abstract

Question Acute pyelonephritis in children is of great concern and I usually refer these patients to a pediatrician or send them to the emergency department owing to the risk of renal scarring. Are steroids an acceptable treatment to reduce risk of scarring?

Answer Several agents have been studied in an effort to prevent renal scar formation following acute pyelonephritis in children. Use of corticosteroids, in conjunction with standard therapy for acute pyelonephritis, shows promising findings. However, evidence is very limited and steroids should not be offered on a regular basis as part of treatment.

Les corticostéroïdes pour la prévention des cicatrices rénales chez l'enfant atteint de pyélonéphrite aiguë

Résumé

Question La pyélonéphrite aiguë chez les enfants est très préoccupante et je demande habituellement une consultation en pédiatrie ou à l'urgence pour de tels patients en raison du risque de cicatrisation rénale. Les corticostéroïdes sont-ils un traitement acceptable pour réduire le risque de cicatrisation?

Réponse Divers agents ont fait l'objet d'études dans le but de prévenir la formation de cicatrices rénales à la suite d'une pyélonéphrite aiguë chez les enfants. Le recours aux corticostéroïdes, de concert avec la thérapie standard pour une pyélonéphrite aiguë, s'est révélé prometteur. Par ailleurs, les données probantes sont très limitées et il ne faudrait pas offrir les corticostéroïdes sur une base habituelle comme adjuvant au traitement.

Pediatric urinary tract infections (UTIs) result in more than 1.1 million (0.7%) physician office visits by children annually in North America.¹ A 2008 meta-analysis² found that the prevalence of UTIs is 7% among febrile infants younger than 24 months of age and 7.8% among children younger than 19 years of age with urinary symptoms, with or without fever. Circumcision reduces the prevalence of UTIs in male infants, especially during the first 3 months of life (prevalence of 2.4% in circumcised and 20.1% in uncircumcised boys). Nevertheless, in boys 6 to 12 months old, the prevalence rates decline to 0.3% and 7.3% in circumcised and uncircumcised boys, respectively.² This large difference might possibly be due to sampling error, associated with difficulty in obtaining a clean sample owing to foreskin retraction.³ Prevalence among girls varies with age (Table 1).² *Escherichia coli* is the most common bacteria responsible for pediatric UTIs (80% of cases).⁴

Acute pyelonephritis is an infection of the upper urinary tract that might lead to renal scarring potentially followed by hypertension and renal function impairment.⁵ The overall incidence of renal scarring is estimated at 42% (26.5% in Australia to 49.0% in Asia).⁶

Renal scarring is reported to be a result of renal parenchymal inflammation. Bacterial infection activates neutrophils and macrophages, and those migrate to the inflammation site. Phagocytosis leads to release of cytokines like interleukins (1, 6, and 8), metabolites of arachidonic acid, and noxious inflammatory mediators such as oxygen radicals and lysosomal enzymes. This results in tissue damage and scar formation.⁷ Renal scarring can be detected by dimercaptosuccinic acid (DMSA) renal scintigraphy several weeks to months after the infection.⁸

Conflicting findings have been published in regard to the value of antibiotics, an important treatment for

Table 1. Prevalence rates of UTIs in female infants younger than 24 months old

AGE, MO	PREVALENCE RATES, %
0-3	7.5
3-6	5.7
6-12	7.3
12-24	2.1

UTI—urinary tract infection.
Data from Shaikh et al.²

pyelonephritis, when evaluating their contribution to prevent scarring in children.⁹⁻¹² A recent study from Greece provided confirmation that delay in treatment initiation of 72 hours or more is a risk factor for permanent renal scar formation in children with febrile UTI.¹³

Corticosteroids,^{14,15} nonsteroidal anti-inflammatory drugs,¹⁶ vitamin A,¹⁷ vitamin E,¹⁸ combination of vitamin C and E,¹⁹ melatonin,²⁰ mesenchymal stem cells,²¹ and montelukast²² were all studied in both animals and humans as potential therapies to reduce renal inflammation and scar formation, with limited success.

Corticosteroids for renal scar prevention

A rat study from Turkey illustrated that the combination of ceftriaxone with either a nonsteroidal anti-inflammatory drug (eg, ketoprofen) or a corticosteroid (eg, methylprednisolone) in acute pyelonephritis decreased subsequent renal scar formation diagnosed by both follow-up DMSA scan and histopathologic evaluation.¹⁴ This positive finding was also seen in a human study that assigned 84 Taiwanese children younger than 16 years of age, with a first episode of acute pyelonephritis, to receive either an antibiotic with oral methylprednisolone for 3 days or antibiotics with placebo.¹⁵ A DMSA scan 6 months later revealed a lower percentage of children who had renal scarring in the treatment group compared with the placebo group (33% vs 60%, respectively; $P < .05$). The median cortical defect volume was also decreased in the treatment group compared with placebo (0 vs 1.5 mL, respectively; $P < .01$).

Finally, as cytokines play a considerable role in renal scar formation following acute pyelonephritis, previous studies have demonstrated that subsequent formation of renal scarring after acute pyelonephritis can be predicted by measuring urine cytokine levels.²³ Sharifian et al⁷ concluded that dexamethasone, in conjunction with antibiotics, significantly ($P < .05$) reduced urine cytokines (interleukins 6 and 8) and serum creatinine ratios at presentation and at 72 hours following treatment in children aged 3 months to 10 years with acute pyelonephritis admitted to a children's hospital. Thirty-four children were treated with ceftriaxone in combination with dexamethasone for 3 days, compared with 20 children in a control group that received ceftriaxone alone. The difference between cytokine-creatinine ratios in initial and follow-up urine samples was significant in the case group ($P < .001$) but not in the control group. This result suggests that dexamethasone use in acute pyelonephritis might have a role in preventing renal scarring by reducing urine cytokines concentrations.

Conclusion

Corticosteroids are effective as an adjunctive therapy in addition to standard treatment of children with acute pyelonephritis, in order to prevent subsequent renal scarring. However, research is extremely limited, especially in

children, and more studies are needed to confirm these findings before steroids can be used in practice as an acceptable treatment to reduce risk of scarring. 

Competing interests

None declared

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References

- Freedman AL. Urologic Diseases in North America Project: trends in resource utilization for urinary tract infections in children. *J Urol* 2005;173(3):949-54.
- Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J* 2008;27(4):302-8.
- Robinson JL, Finlay JC, Lang ME, Bortolussi R, Canadian Paediatric Society, Infectious Diseases and Immunization Committee, Community Paediatrics Committee. Urinary tract infections in infants and children: diagnosis and management. *Paediatr Child Health* 2014;19(6):315-25.
- Edlin RS, Shapiro DJ, Hersh AL, Copp HL. Antibiotic resistance patterns of outpatient pediatric urinary tract infections. *J Urol* 2013;190(1):222-7. Epub 2013 Jan 28.
- Vachvanichsanong P. Urinary tract infection: one lingering effect of childhood kidney diseases—review of the literature. *J Nephrol* 2007;20(1):21-8.
- Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. *J Urol* 2009;181(11):290-7. Epub 2008 Nov 14.
- Sharifian M, Anvaripour N, Karimi A, Fahimzad A, Mohkam M, Dalirani R, et al. The role of dexamethasone on decreasing urinary cytokines in children with acute pyelonephritis. *Pediatr Nephrol* 2008;23(9):1511-6. Epub 2008 Jun 13.
- Roupakias S, Sinopidis X, Tsikopoulos G, Spyridakis I, Karatza A, Varvarigou A. Vesicoureteral reflux and renal scarring investigation and management. *Minerva Urol Nefrol* 2017;69(2):144-152. Epub 2016 Jun 29.
- Oh MM, Kim JW, Park MG, Kim JJ, Yoo KH, Moon du G. The impact of therapeutic delay time on acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI. *Eur J Pediatr* 2012;171(3):565-70. Epub 2011 Nov 3.
- Coulthard MG, Lambert HJ, Vernon SJ, Hunter EW, Keir MJ, Matthews JN. Does prompt treatment of urinary tract infection in preschool children prevent renal scarring: mixed retrospective and prospective audits. *Arch Dis Child* 2014;99(4):342-7. Epub 2013 Dec 18.
- Doganis D, Sifas K, Mavrikou M, Issaris G, Martirosova A, Perperidis G, et al. Does early treatment of urinary tract infection prevent renal damage? *Pediatrics* 2007;120(4):e922-8. Epub 2007 Sep 17.
- Hewitt IK, Zucchetto P, Rigon L, Maschio F, Molinari PP, Tomasi L, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. *Pediatrics* 2008;122(3):486-90.
- Karavanaki KA, Soldatou A, Koufadaki AM, Tsentidis C, Haliotis FA, Stefanidis CJ. Delayed treatment of the first febrile urinary tract infection in early childhood increased the risk of renal scarring. *Acta Paediatr* 2017;106(11):149-154. Epub 2016 Nov 17.
- Bahat Özdoğan E, Özdemir T, Arslansoyu Çamlar S, İmamoglu M, Çobanoğlu Ü, Sönmez B, et al. Could pyelonephritic scarring be prevented by anti-inflammatory treatment? An experimental model of acute pyelonephritis. *Biomed Res Int* 2014;2014:134940.
- Huang YY, Chen MJ, Chiu NT, Chou HH, Lin KY, Chiou YY. Adjunctive oral methylprednisolone in pediatric acute pyelonephritis alleviates renal scarring. *Pediatrics* 2011;128(3):e496-504. Epub 2011 Aug 15.
- Gurocak S, Ure I, Cumaoglu A, Gonul II, Sen I, Tan O, et al. Renal tissue damage after experimental pyelonephritis: role of antioxidants and selective cyclooxygenase-2 inhibitors. *Urology* 2010;76(2):508.e1-5. Epub 2010 May 26.
- Zhang GQ, Chen JL, Zhao Y. The effect of vitamin A on renal damage following acute pyelonephritis in children: a meta-analysis of randomized controlled trials. *Pediatr Nephrol* 2016;31(3):373-9. Epub 2015 May 19.
- Yousefchajjan P, Kabhazi M, Rasti S, Rafeie M, Sharafkhan M. Vitamin E as adjuvant treatment for urinary tract infection in girls with acute pyelonephritis. *Iran J Kidney Dis* 2015;9(2):97-104.
- Emamghorashi F, Owji SM, Motamedifar M. Evaluation of effectiveness of vitamins C and E on prevention of renal scar due to pyelonephritis in rat. *Adv Urol* 2011;2011:489496. Epub 2010 Dec 12.
- İmamoglu M, Cay A, Cobanoğlu U, Bahat E, Karahan C, Tosun I, et al. Effects of melatonin on suppression of renal scarring in experimental model of pyelonephritis. *Urology* 2006;67(6):1315-9. Epub 2006 May 12.
- Soylu A, Demirci T, Finnci F, Bağrıyanık A, Demir BK, Atmaca S, et al. Mesenchymal stem cells ameliorate postpyelonephritic renal scarring in rats. *Urology* 2012;80(5):1161.e7-12. Epub 2012 Aug 24.
- Tugtepe H, Sener G, Cetinel S, Velioglu-Ogünç A, Yeğen BC. Oxidative renal damage in pyelonephritic rats is ameliorated by montelukast, a selective leukotriene CysLT1 receptor antagonist. *Eur J Pharmacol* 2007;557(1):69-75. Epub 2006 Nov 10.
- Renata Y, Jassar H, Katz R, Hochberg A, Nir RR, Klein-Kremer A. Urinary concentration of cytokines in children with acute pyelonephritis. *Eur J Pediatr* 2013;172(6):769-74. Epub 2013 Feb 7.



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