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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Role of dexamethasone in controlling the proinflammatory cytokine cascade in the first episode of paediatric acute pyelonephritis

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Abstract

Aim: Febrile urinary tract infection is a common bacterial infection in childhood. The kidney damage after acute pyelonephritis (APN) could be related to the stimulation of the proinflammatory response. We aimed to investigate the role of inflammatory cytokines and the effect of dexamethasone after a first episode of APN.

Methods: Subanalysis of the DEXCAR RCT in which children with confirmed APN (1 month–14 years) were randomly assigned to receive a 3 days course of either intravenous dexamethasone or placebo. Urinary cytokine levels at diagnosis and after 72 h of treatment were measured.

Results: Ninety-two patients were recruited. Younger patients, males and those with abnormalities in the ultrasound study or vesicoureteral reflux showed higher values of urinary cytokines. Patients with severe APN had higher Tumour Necrosis Factor (TNF)α levels (81.0 ± 75.8 vs. 33.6 ± 48.5 pg/mg creatinine, $p = 0.015$). Both intervention groups showed similar basal clinical characteristics, including urinary cytokine levels. Treatment reduced urinary cytokine levels irrespective of dexamethasone administration. Neither the intervention group nor the urinary cytokine levels modulated the development of kidney scars.

Conclusion: Basal urinary cytokines were associated with age, abnormal ultrasound and vesicoureteral reflux. Patients with severe APN had higher TNFa urinary levels. Administration of dexamethasone in children with APN does not improve the control of the proinflammatory cytokine cascade.

KEYWORDS
acute pyelonephritis, corticosteroids, cytokines, kidney scarring

Abbreviations: APN, Acute pyelonephritis; AUC, Area Under the Curve; CAKUT, Congenital anomalies of the kidney and urinary tract; CRP, C-reactive protein; DMSA, Technetium 99 m-dimercaptosuric acid renal scintigraphy; E, Specificity; IL, Interleukin; IQR, interquartile range; KIM, Kidney Injury Molecule; MMP9, Matrix metalloproteinase; NGAL/Lipocalin-2, Neutrophil gelatinase-associated lipocalin-2; NPV, Negative Predictive Value; PCT, Procalcitonin; RCT, Randomised Clinical Trial; REDSS, Renal Damage Severity Score; ROC, Receiver operating curve; S, Sensitivity; SD, Standard deviation; TIMP-1, Tissue inhibitor of metalloproteinase-1; TNF, Tumour Necrosis Factor; UTD, urinary tract dilatation; UTI, urinary tract infection; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux.

The DEXCAR Study Group presented in Acknowledgements section.

1 | INTRODUCTION

Urinary tract infection (UTI) is one of the most frequent bacterial infections in childhood, with incidences between 8%–10% in girls and 2%–3% in boys, in children younger than 7 years.[1,2]

A prevalence of 50%–80% of acute pyelonephritis (APN) is estimated in patients with febrile UTI.[3] The incidence of permanent kidney scarring after APN is variable (10%–60%)[3–6] and is associated with further development of complications such as arterial hypertension, proteinuria, preeclampsia and chronic renal failure in adulthood.[7] Some studies have evaluated the benefit of antimicrobial prophylaxis to reduce the appearance of kidney scar, especially in children with vesicoureteral reflux (VUR), with inconclusive results.[8,9]

The exact pathogenesis of kidney scarring development after an episode of APN is not well understood. However, it is postulated that the inflammatory and immunological response, triggered to eradicate the infecting bacteria, may play a role.[10] When pathogens are recognised by the toll-like receptors in the urothelium, these trigger a production of inflammatory mediators with chemotactic effects. The inflammatory process is not only responsible for clearance of bacteria during infection, but it may also produce early kidney injury. Thus, even after adequate antimicrobial management, in some cases, the inflammatory process will lead to kidney scarring due to the robust immune response after the stimulation of proinflammatory cytokines.[10] The analysis of serum and urine cytokines, mainly interleukin (IL) 6 and IL8, and other biomarkers like neutrophil gelatinase-associated lipocalin-2 (NGAL/Lipocalin-2), is emerging in the literature, showing higher levels of these proteins in children and adults with UTI and kidney damage.[11–20] Considering this hypothesis, the role of anti-inflammatory treatment has been assessed as a potential control of cytokine cascade. *Sharifian* et al[21] demonstrated in 54 children with a first episode of APN that coadjuvant treatment with dexamethasone enhanced the decrease in urinary IL6 and IL8 compared with children who received only the usual antimicrobial treatment. Potentially, limiting not softening the inflammatory response could be a key strategy for the management of urinary infection and the risk of permanent kidney damage. Recent studies, as well as a metanalysis, analysed the role of anti-inflammatory treatment in kidney scarring prevention after APN in children, with contradictory results.[22–27]

Thus, the objective of our study was to analyse the role of urine inflammatory biomarkers in technetium 99 m-dimercaptosuric acid renal scintigraphy (DMSA) scan-proven APN, as well as the therapeutic use of dexamethasone to reduce risk of develop kidney scarring.

Key Notes

- Our study shows that concomitant administration of dexamethasone in children with acute pyelonephritis (APN) does not improve the control of the proinflammatory cytokine cascade.
- Thus, dexamethasone's benefit in reducing the risk of kidney scarring has not been demonstrated.
- Further studies may reveal the role of biomarkers such as urinary Tumour Necrosis Factor (TNF)α or Kidney Injury Molecule (KIM)1 in identifying those patients with conditions related to high-risk adverse events after APN.

2 | PATIENTS AND METHODS

We performed a subanalysis from DEXCAR,[25] a phase III, double-blind, placebo-controlled, multicentric Randomised Clinical Trial (RCT) in children aged from 1 month to 14 years with a first episode of APN, which was confirmed by urine culture and DMSA. Participants with endocrinological disease, immunosuppression condition, cancer or known uropathy, as well as those who developed a second UTI during follow-up, were excluded. Details of the DEXCAR study were published elsewhere.[25]Intervention was randomly assigned in blocs of four in a 1:1 ratio to receive a 3 days course of either intravenous corticosteroid (dexamethasone 0.30 mg/kg, twice daily) or placebo (sodium chloride 0.9% with the same volume and administration regimen). All patients received antibiotic therapy according to each centre's protocol for seven to 10 days. Briefly, 34% gentamicin therapy (19% ampicillin associated regimen), 33% amoxicillin-clavulanate therapy and 33% 3rd generation cephalosporin. DMSA was performed in all participants within the first 72 h of treatment to confirm APN, as well as after at least 6 months to evaluate the presence of kidney scar. A blinded centralised nuclear medicine physician performed the DMSA assessment. Based on the Randomised Intervention for Children with Vesicoureteral Reflux (RIVUR) study,[28] we defined a renal damage severity score (REDSS) considering the affected areas of each kidney.[25] The REDSS score ranged from 0 points (no injuries on the DMSA) to a hypothetical 8-point score for a global diffuse photopenia in both kidneys. If the REDSS score was≥3 points, we considered global damage as severe.

The local radiologist at each centre, who was blinded to the treatment, performed abdominal ultrasound in the acute phase. The results were classified as a normal ultrasound, congenital anomalies of the kidney and urinary tract (CAKUT) or urinary tract dilatation (UTD) according to the last multidisciplinary consensus UTD classification system.[29,30] Voiding cystourethrography (VCUG) was performed 2–4 weeks after APN diagnosis. Vesicoureteral reflux (VUR) was graded I–V according to the US International Study Committee on Vesicoureteral Reflux in Children.[31] VUR was defined as nondilated VUR (grades I and II) and dilated VUR (grades III–V).

At admission, a blood test (haemogram, C-reactive protein (CRP), procalcitonin (PCT), ionogram, urea, creatinine and blood culture) and urine analysis, including urine culture (urine was collected by clean catch in continent children [positive culture if >100 000 CFU/mL] and catheterisation in non-continent children [positive if >10 000 CFU/mL]), were performed following routine centre laboratory protocols.

Urine sample aliquots for cytokine and other biomarkers analysis (hereafter biomarkers) were collected at admission and after 72 h of treatment. Samples were kept frozen at −80°C until analysis. Creatinine as well as nine biomarkers were analysed in each urine sample. The biomarkers IL1β, IL6, IL8, tumour necrosis factor (TNF) α, kidney injury molecule (KIM)1, tissue inhibitor of metalloproteinase-1 (TIMP1), NGAL/Lipocalin-2 and cystatin C were analysed by multiplex sandwich immunoassay using Luminex 200™ following the manufacturer's instructions. Briefly, IL1β, IL6, IL8 and TNFα were analysed together using the human high-sensitivity T-cell magnetic bead panel. TIMP1 and KIM1 were analysed together using the Human Kidney Injury magnetic bead Panel 1, and NGAL/Lipocalin-2 and cystatin C were analysed together using the Human Kidney Injury Magnetic Bead Panel 2. In all cases, a first test to determine whether sample dilution was necessary was performed with1/2, 1/10, 1/100 and 1/200 diluted samples. The results showed that sample dilution was not necessary in any of the cases. The experiment was performed using the manufacturer's instructions, and plates were read in the Bio-Plex™ 200 System. Matrix metalloproteinase-9 (MMP-9) was analysed by ELISA using Human MMP-9 ELISA Kit from Sigma-Merk. The results of each biomarker were divided by urine creatinine, measured with the Jaffe method using a kinetic colorimetric assay for normalisation.[32] These biomarkers were selected according to previous literature and the technical possibility to be detected altogether in a multiplex analysis.[9,10,12–16,25–30]

2.1 | Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 27.0; IBM Corp.,). Quantitative variables are shown as the means (± SD) or medians (interquartile ranges) after assessing the normal distribution of variables with a Kolmogorov–Smirnov test. Categorical variables are shown as n and percentage (%). *T* tests or Mann–Whitney *U* tests were used for statistical comparisons during the cross-sectional analysis between groups. Pearson's chi-squared test was used for the statistical comparison of the categorical data. Correlations between quantitative variables were performed by Pearson or Spearman tests as appropriate. Diagnostic accuracy for certain urine cytokine levels and conditions were calculated with a receiver operating curve (ROC) method. Longitudinal evolution of urinary biomarkers levels was analysed by two-way ANOVA for repeated measures. We performed a logistic regression analysis to assess the effect of the intervention and urinary biomarkers on later kidney scar presence, adjusting for relevant confounders (vesicoureteral reflux, germ, age, sex and REDSS). Statistical significance was accepted at $p < 0.05$. As this is a secondary analysis from a previous RCT, details of the sample size calculation can be found elsewhere.[25] However, a power analysis was performed for a better understanding of the results.

2.2 | Legal and ethical considerations

The clinical trial, registered at Clinicaltrials.gov as NCT02034851, fulfilled the principles of the Declaration of Helsinki and all the legal requirements of regulatory national agencies.

3 | RESULTS

From the 184 children recruited by the DEXCAR study, ninety-two patients with the first episode of APN, confirmed by DMSA, completed the acute urinary biomarkers study (Figure 1). The basal characteristics of the sample are shown in Table 1. The median age was 8 months (IQR 4–20.5), 91.8% were younger than 2 years, and 66% were younger than 1 year. Seventy-five percent were females. As expected, 95.6% of infections were caused by *Escherichia coli*. None of the patients had associated bacteraemia or other complications, including infection by resistant microorganisms. Abdominal ultrasound was abnormal in 13 patients (14.1%) (11 UTDs and 2 CAKUTs [double ureteral system in one patient and renal ectopy in the other]). None of the patients with any UTD were classified in the high-risk group according to the new consensus classification[30] (6 cases low risk and 5 moderate). Vesicoureteral reflux was confirmed in 14 patients (16.7% among the 84 who completed the VCUG assessment) and bilateral in three. All patients showed a coincidence of the APN with the side of VUR. Reflux severity was classified as dilated (grades III-V) in 4 patients. Almost 33% of patients were classified as severe REDSS according to our DMSA severity score.

3.1 | Biomarkers values related to clinical parameters

Basal urinary biomarkers values were correlated with some clinical and analytical parameters. Younger patients presented higher values of MMP9 ($r = -0.29$, $p = 0.03$), IL6 ($r = -0.26$, $p = 0.02$), TNFα ($r = -0.29$, $p = 0.03$), TIMP1 ($r = -0.28$, $p = 0.008$) and NGAL/Lipocalin-2 ($r = -0.31$, $p = 0.006$). Males presented higher values of IL6 and NGAL/Lipocalin-2 (IL6: 396.44 ± 455.14vs. 249.14 ± 325.29 pg/mg creatinine, $p = 0.017$; NGAL/Lipocalin-2: 78.856.98 vs. 44.00 ± 47.42 pg/mg creatinine, $p = 0.007$ in males and females, respectively). Basal urinary biomarkers were not associated with fever duration or with any of the inflammatory blood test parameters.

3.2 | Biomarkers values related to structural anomalies

Patients with an abnormal ultrasound study showed a higher value of basal urinary biomarkers, although statistical significance was observed only in the MMP9 analysis (78.9 ± 57.0 vs. 41.1 ± 40.0 pg/mg creatinine, $p = 0.014$) (Figure 2A). Patients with VUR presented

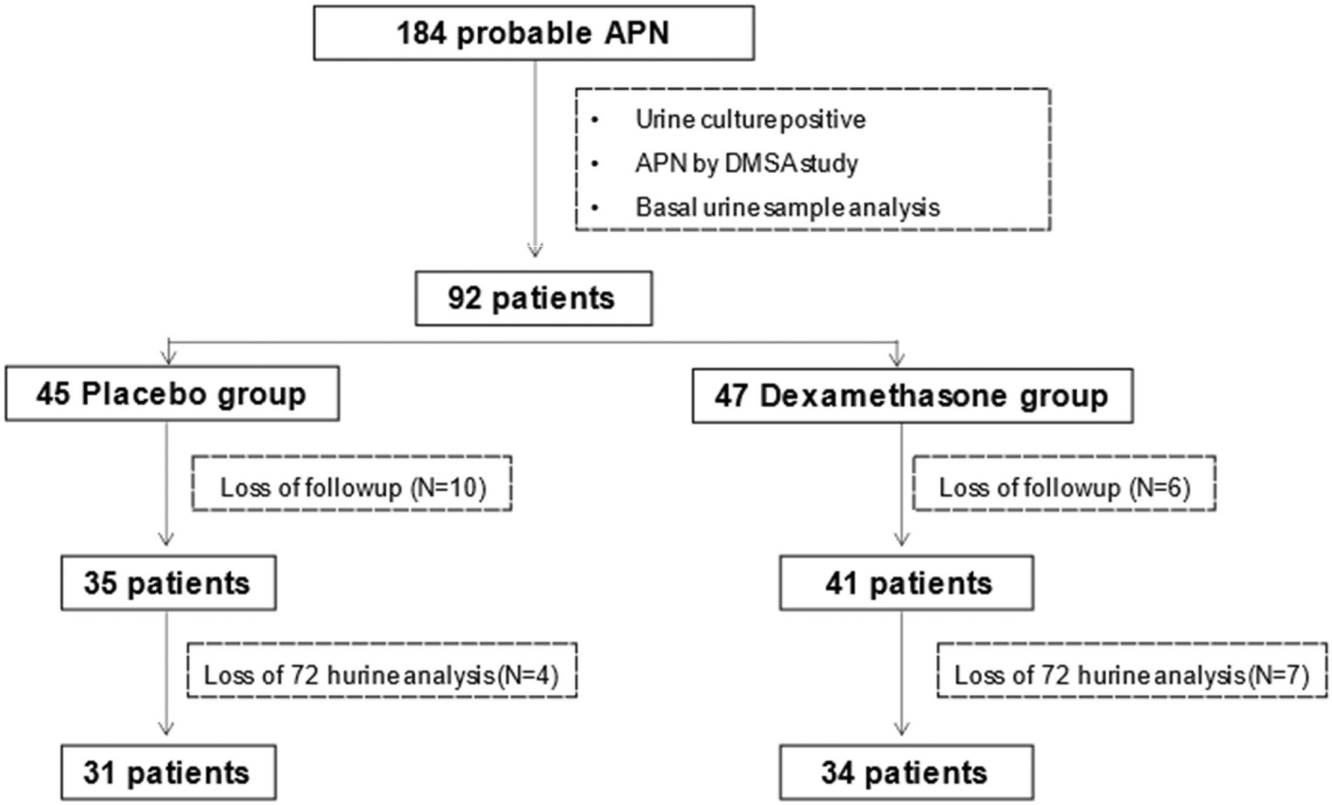

FIGURE 1 Flow chart.

TABLE 1 Sample clinical characteristics.

	Whole sample ($n=92$)	Placebo group ($n=45$)	Dexamethasone group ($n=47$)
Age (months)	8 (4,20.5)	9 (4,16)	8 (4,21)
Gender (n, % females)	69%, 75%	33%, 73.3%	36%, 76.6%
Preadmission fever (days)	2.5 ± 2.2	3.0 ± 2.6	2.1 ± 1.6*
Leucocytes ($mm^3 x 10^3$)	20.2 ± 6.7	19.7 ± 6.7	20.6 ± 6.6
Neutrophiles ($mm^3 x 10^3$)	12.1 ± 5.2	12.1 ± 5.4	12.2 ± 5.1
CRP (mg/dl)	13.1 ± 8.3	13.5 ± 9.5	12.6 ± 6.9
PCT (ng/ml)	7.7 ± 13.0	9.3 ± 16.1	5.7 ± 7.8
US (n, % of abnormal)	13, 14.1%	8, 17.8%	5, 10.6%
VUR (n, % positive)#	14, 16.7%	7, 17.9%	7, 15.6%
Early REDSS (score)	2.2 ± 0.9	2.3 ± 0.8	2.2 ± 1.0
Early severe REDSS (≥3) (n, %)	3, 32.8%	13, 39.4%	8, 25.8%

Note: Results of numeric variables are represented as mean ± standard deviation or median (95% IQR) as appropriate.

Abbreviations: CRP: C-reactive protein; PCT: procalcitonin protein; REDSS: Renal Damage Severity Score; US: ultrasound Study; VUR: vesicoureteral reflux.

*$p=0.04$ vs Placebo group.

#6 and 2 patients in the placebo and dexamethasone group, respectively, did not perform the VUR assessment.

higher concentrations of urinary biomarkers, except for IL6 and NGAL/Lipocalin-2, reaching statistical significance in KIM1 (7.87 ± 4.78 vs. 4.68 ± 2.95 ng/mg creatinine, $p=0.029$) (Figure 2B). The benefit of KIM1 concentration for discriminating between patients with VUR was tested by ROC analysis. The area under the curve (AUC) was 0.68, and KIM1 values below 1.56 ng/mg creatinine had 100% sensitivity (S) and negative predictive value (NPV), while KIM1 values above 9.4 ng/mg creatinine showed a specificity (E) of 90.8% and a positive likelihood ratio of 4.64. The results of most biomarkers were 2–3 times higher in patients with dilated VUR than

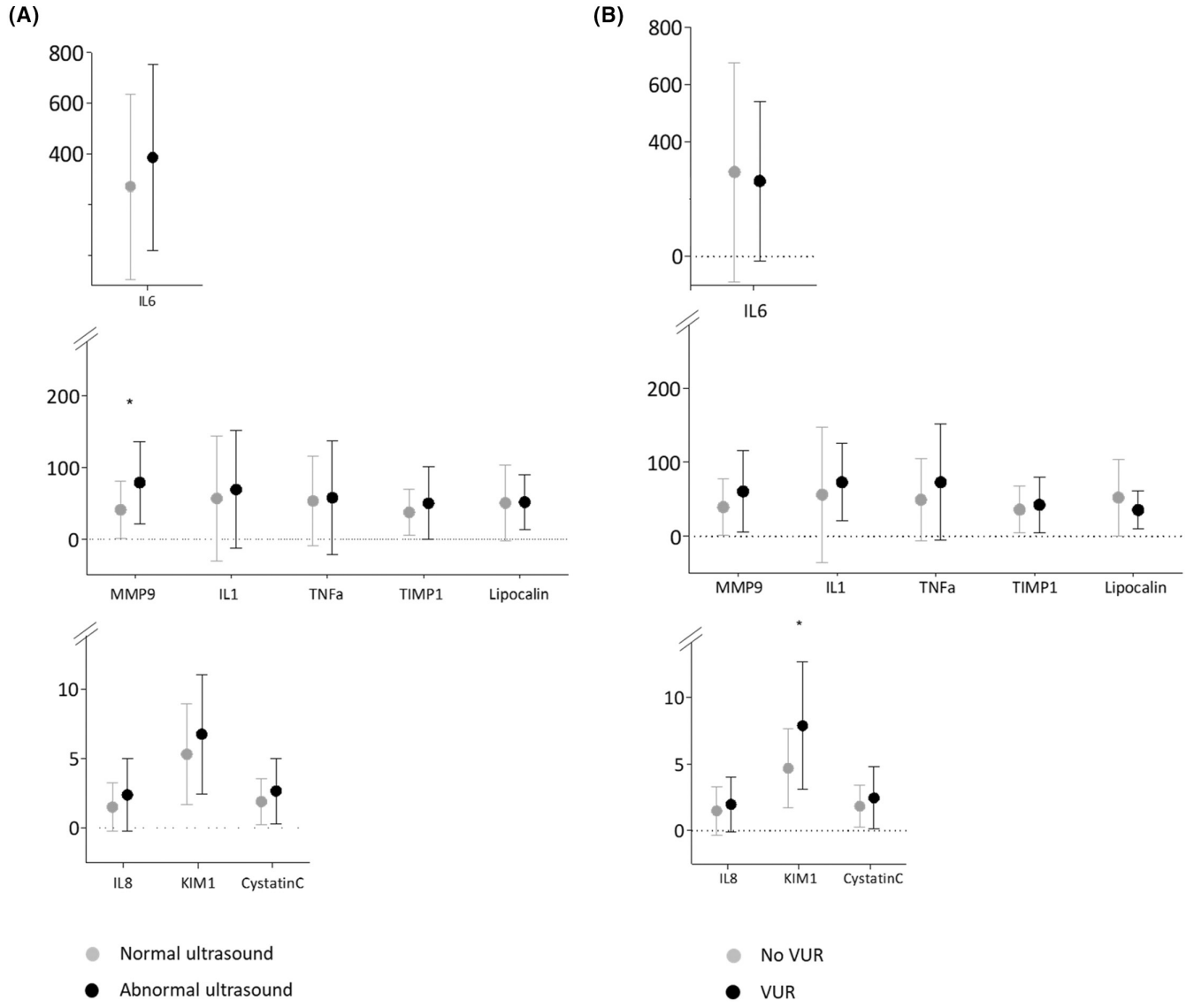

FIGURE 2 Basal urinary cytokines and biomarkers concentrations by ultrasound abnormality (A) or vesicoureteral reflux (B) presence. Cytokine and biomarker concentrations are presented as pg/mg creatinine for IL1, IL6 and TNFα, and as ng/mg creatinine for MMP9, IL8, TIMP1, KIM1, NGAL/Lipocalin-2 and cystatin C. Lipocalin: NGAL/Lipocalin-2.

in those with nondilated VUR, although those differences did not reach statistical significance, probably due to the small sample size (data not shown).

3.3 | Biomarkers values related to kidney damage

Basal urinary biomarkers concentrations were analysed according to the presence of acute severe REDSS score (REDSS ≥3) and we found that TNFα was higher in case of severe parenchymal lesion (81.0 ± 75.8 vs. 33.6 ± 48.5 pg/mg creatinine, $p = 0.015$). Benefit of TNFα for discriminating between those cases of severe parenchymal lesion was tested by ROC analysis. We observed that urine TNFα cut off value of 20.3 pg/mg creatinine is a good predictor of severe APN (AUC 0.74, S 76.9%, E 61.5%, positive predictive values 50%, NPV 84.21%, positive likelihood ratio 2, negative likelihood ratio 0.37).

3.4 | Effect of intervention on biomarkers values

The baseline characteristics of the participants according to the intervention group were similar regarding all studied parameters except for fever before admission (3.0 ± 2.6 vs. 2.1 ± 1.6, $p = 0.04$ days in the placebo and dexamethasone groups, respectively) (Table 1). The basal urinary biomarkers concentrations were also similar in both study Groups (Table S1).

Urinary biomarkers showed a significant decrease after 72 h of treatment except in the case of MMP9 and cystatin C, regardless of treatment performed. This effect was maintained in each

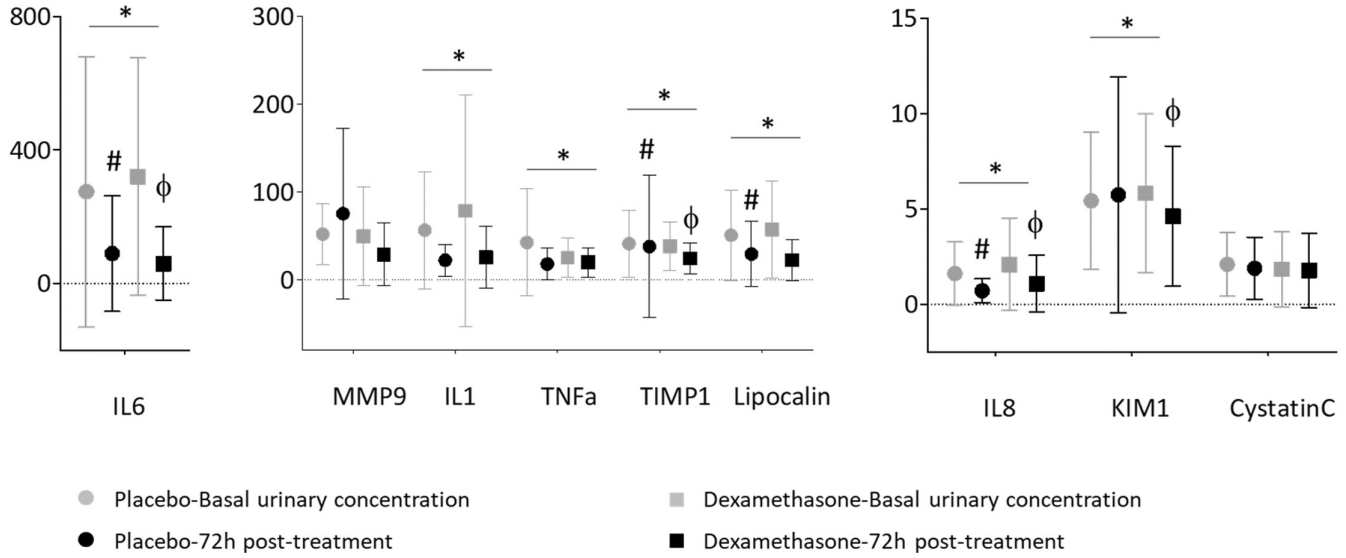

FIGURE 3 Longitudinal change of urinary biomarkers concentrations by treatment group. Grey and black objects represent basal and 72 h post-treatment urinary biomarkers, respectively. Circles shown placebo group concentrations and squares those from Dexamethasone group.*: differences between basal and 72 h post-treatment in the whole sample; #: $p < 0.05$ vs basal concentration in placebo group; ϕ: $p < 0.05$ vs basal concentration in dexamethasone group. Cytokine and biomarker concentrations are presented as pg/mg creatinine for IL1, IL6 and TNFα, and as ng/mg creatinine for MMP9, IL8, TIMP1, KIM1, NGAL/Lipocalin-2 and cystatin C. Lipocalin: NGAL/Lipocalin-2.

intervention group separately. The magnitude of the decrease was somewhat higher in the group treated with dexamethasone, but without reaching statistical significance (Figure 3).

3.5 | Effect of biomarkers on kidney scarring

After a follow-up of at least 6 months (medium 8 months, range from 6 to 15), 76 participants underwent the late DMSA assessment, and 18 kidney scars were observed. To assess the effect of different variables on the development of kidney scars, we performed binary logistic regressions. The results showed that neither the intervention group (*p* values 0.876) nor the basal urinary biomarkers concentrations (with p values ranging from 0.158 to 0.997) or decline in concentration after 72 h of treatment (with p values ranging from 0.125 to 0.982) modulated the development of kidney scars (Table S2).

4 | DISCUSSION

Experimental studies in mice showed how the inflammatory response during the development of APN is essential in the elimination of bacteria but is also responsible for tissue damage.[33] Control of this inflammatory cascade could reduce the risk of scarring after an episode of APN, thus reducing the subsequent risk of long-term complications. Accordingly, the role of different biomarkers in the study and prognosis of patients with urinary tract infection has been investigated in both serum and urine samples.[11–21,34] In our study, we evaluated the urinary concentrations of different biomarkers in 92 paediatric patients with DMSA-confirmed APN.

We observed how urinary biomarkers were modulated by age and sex. Our data differ from previous published studies regarding IL6 concentrations, such as Benson et al., who observed higher IL6 levels in girls and in older patients.[34] In contrast, other authors did not find differences according to age and sex in the serum or urinary concentrations of these different biomarkers.[11,21] The value of urinary biomarkers was not correlated with the duration of fever or acute phase reactants in serum, as described previously.[11,12]

We found higher urinary biomarkers concentrations in patients with malformations or urinary tract dilation, as well as in cases of VUR. The prevalence of VUR among children with UTI ranges between 30%–50%[15,16] and was lower in our population study (16.7%). A nonnegligible percentage of these patients will present long-term chronic kidney damage (8%–18%), so early diagnosis and management could improve their prognosis. The increased urinary excretion of cytokines and other biomarkers occurs secondary to tubular damage and interstitial fibrosis in patients with VUR[16]; therefore, the study of biomarkers, such as IL6 and IL8, has been proposed as an alternative to more invasive classical methods (i.e. VCUG).[15,16] Previous studies have evaluated the association of proinflammatory cytokines, mainly IL6 and IL8, in children with VUR, with mixed results. Gokce et al. and Nickavar et al. demonstrated higher urinary IL6 concentrations in patients with reflux associated neprhopathy,[15,16] in a baseline clinical condition. Moreover, Jauntausch et al. and Renata et al. did not observe significant differences in urinary proinflammatory cytokines in patients with UTI according to VUR presence or severity.[11,12] Our results showed that patients with VUR tended to show higher cytokine and biomarker concentrations, although only KIM1 reached statistical significance. The KIM1 glycoprotein is expressed by the proximal tubular epithelium in occurrences of renal damage, not expressed in healthy population. Thus,

the KIM1 glycoprotein has been proposed as a biomarker of kidney damage.[35] Some studies have evaluated the role of KIM1 in the diagnosis of kidney scars in children with VUR.[36] Pharmakiz et al, in a population of 123 children with VUR and 30 healthy children, do not demonstrated differences in urinary KIM1 concentrations between groups. On the contrary, we demonstrated significantly higher KIM1 levels in patients with VUR, suggesting their potential usefulness as an early diagnosis biomarker of VUR in patients with UTI.

The identification of biomarkers that could predict the patients who are at a higher risk of developing long-term complications during an APN episode will help to optimise follow-up efforts and minimise unnecessary studies and treatments. In a previous study, we observed that patients with greater severity of APN, defined by the REDSS score, presented a higher risk of kidney scarring.[25] The current study demonstrates that the basal TNFα concentration is higher among patients with more severe APN. These results could provide a new strategy to identify patients with a higher risk of kidney scarring after an APN episode if their urinary TNFα concentrations exceed certain levels (i.e. 20 pg/mg creatinine).

Several authors evaluated the role of cytokines and other biomarkers in the risk of kidney scarring progression. Three different studies involving a total of 155 patients with acute pyelonephritis showed higher IL8 concentrations in those who developed scars.[12,14,15] These data contradict the results obtained in the present study, where no significant differences in urinary biomarkers among patients with kidney scarring were observed. In addition, the evolution of serum and urinary biomarkers after APN treatment establishment has also been investigated.[11–13] There is compelling evidence, confirmed by our study, that treatment is associated with a decrease in urinary cytokines and other biomarkers. However, our results did not find a relationship between biomarkers reduction and further development of kidney scarring.

Considering the role of the inflammatory cascade in the progression of kidney damage, the therapeutic use of corticosteroids in their prevention was investigated by different authors with contradictory results.[22–26] Some clinical trials showed promising results,[22] whereas the present study and others did not find positive results.[23–26] Using all this studies, Gkiourtzis et al. recently performed a metanalysis concluding that corticosteroid treatment could reduce kidney scarring risk.[28] Nevertheless, the different clinical trials had non-verifiable designs since they were carried out on very different populations. Some patients had APN confirmed by DMSA, and others had simple febrile UTIs. The dose and route of administration of corticosteroids also differ. Thus, there is still no strong evidence to recommend the use of corticosteroid as coadjuvant treatment in patients with APN.

Considering the results of DEXCAR RCT,[25] the lack of effect of dexamethasone treatment observed is in accordance with the present results showing no significant reduction in proinflammatory cytokines and other biomarkers in our sample. Similar results were found by Ghaffari et al., who observed no differences in urinary cytokines regardless of the administration of dexamethasone or placebo.[23]

One of the limitations of our study is that it is a secondary analysis from a RCT. In addition, we did not reach the desired number of patients, and therefore, we were underpowered. With a sample size of 65 patients (which completed the follow-up in our study) we had a power of 80%to find differences of 0.7 SD in urine cytokines, whereas the power to detect differences of 0.5 SD was 52.2%. Reasons for this loss of participants were mainly the exclusion of normal acute DMSA scans or patients with previous uropathy, as well as, the lack of images to perform the centralised assessment of DMSA scans. These limitations resulted in some loss of data but could also be a goodness due to reduce interobserver discrepancies between centres, as well as to ensure our participants are a homogeneous and previously kidney healthy population. Moreover, we lost additional data due to urine sample availability. However, despite these limitations, our study is the largest one that analysed the benefit of corticosteroids controlling the cytokine cascade and their role in the risk of kidney scar in children with the first episode of APN.

In summary, our study shows that concomitant administration of dexamethasone in children with APN does not improve the control of the proinflammatory cytokine cascade. Thus, its benefit in reducing the risk of kidney scarring has not been demonstrated. Further studies may reveal the benefit of biomarkers such as urinary TNFα or KIM1 to identify the patients with specific conditions that confer a higher risk of long-term consequences after APN.

AUTHOR CONTRIBUTIONS

Neus Rius-Gordillo: Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; formal analysis. **Natàlia Ferré:** Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; formal analysis; funding acquisition; supervision. **Juan David Gonzàlez:** Investigation. **Zaira Ibars:** Investigation. **Ester Parada-Ricart:** Investigation. **Joaquin Escribano:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; writing – review and editing; formal analysis; supervision.

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CONFLICT OF INTERESTS STEMENT

The authors declare no competing interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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