New Criteria for Renal Scintigraphy After Urinary Tract Infection: Are those Adequate?

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Abstract

Introduction: Criteria for imagiological studies following urinary tract infections (UTI) are frequently updated, including for renal scintigraphy with dimercaptosuccinic acid (DMSA), the gold standard method for renal scars detection. Until 2020, in the authors' hospital, every patient with febrile UTI underwent follow-up scintigraphy. This study aims to analyze the results of post-UTI DMSA scintigraphy based on current performance criteria, which are atypical UTI below three years old, recurrent UTI and altered renal and bladder ultrasound (RBUS).

Methods: Retrospective analysis of patients under 16 years of age who underwent post-UTI DMSA scintigraphy between 2011 and 2020. Demographical, clinical, analytical and imagiological data were collected.

Results: Of the 231 patients considered, 60% were female, and the median age was 14 months. *Escherichia coli* was the most commonly identified bacteria. Atypical UTI under three years old occurred in 28 patients (12%), recurrent UTI in 50 (22%) and RBUS abnormalities in 18 (7%). Altered DMSA scintigraphy was identified in 39 patients (17%), with these alterations correlating with the new criteria (odds ratio 2.7 (1.3-5.4)). Altered DMSA scintigraphy was more frequent in patients with recurrent UTI or altered RBUS, but not with atypical UTI under three years old. Alterations in DMSA scintigraphy were found in 18 patients who did not meet new criteria (12%).

Conclusion: The new criteria are associated with a higher incidence of altered DMSA scintigraphy but also lead to unidentified alterations. Follow-up studies are necessary to understand the clinical consequences for patients who, under the new criteria, would not undergo DMSA scintigraphy.

Keywords: Child; Radionuclide Imaging; Technetium Tc 99m Dimercaptosuccinic Acid; Urinary Tract Infections/complications; Urinary Tract Infections/diagnostic imaging

INTRODUCTION

Urinary tract infections (UTI) are defined by the presence of a pathogenic microorganism in the urinary tract, leading to a symptomatic inflammatory response. These infections are prevalent in children and exhibit three incidence peaks: infancy, toddlerhood and adolescence.[1] While UTI are equally common in boys and girls during the first year of life, they become more frequent in girls thereafter.[2,3]

UTI can be categorized into two types: cystitis, characterized by inflammation confined to the bladder, and pyelonephritis, where the renal parenchyma is affected, often presenting with fever or lumbar pain.[1]

Although diagnostic and treatment guidelines for UTI generally show minor variations, recommendations regarding follow-up imaging after pyelonephritis in children remain a highly debated topic.[4]

One of the imaging studies performed in children after UTI is renal scintigraphy with dimercaptosuccinic acid (DMSA). This exam is the preferred method for detecting renal scars as it provides insight into renal morphology, structure and function, using a radioactive isotope, which is absorbed by the renal parenchyma, identifying areas with decreased uptake, indicative of kidney damage.[5] Renal scars may occur in 10% to 40% of children following an acute pyelonephritis.[1]

While it was previously advocated to use DMSA scintigraphy after the initial episode of pyelonephritis, in order to promptly identify renal scarring and/or anatomical and functional abnormalities that may predispose individuals to recurrent infections, most recent guidelines are opposed to this approach. Some examples are: the 2018 and 2022 National Institute for Health and Care Excellence

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(NICE) guidelines that recommend DMSA scintigraphy four to six months after the acute infection but only in the cases of recurrent UTI or atypical UTI in patients under three years of age[5,6] and the Italian Society of Pediatric Nephrology guidelines that have evolved over time - in 2012 they recommended using DMSA scintigraphy in recurrent UTI, altered renal and bladder ultrasound (RBUS) or vesicoureteral reflux (VUR)[7] however, since 2020, they only recommend it for documented VUR grade IV or V.[8]

The rationale behind these limitations lies on the fact that, although renal scars have been associated with hypertension, proteinuria and progression to renal failure, many post pyelonephritis exams show normal results and DMSA scans are associated with elevated costs, radiation exposure and need for patient sedation.[2] Nonetheless, concerns persist as it can result in undiagnosed renal scarring. In the authors' pediatric service, the standard practice until 2020 dictated that in every first pyelonephritis, the child would undergo a RBUS and a DMSA scintigraphy six months after the acute episode. In 2020, the pediatric service adopted a new approach in alignment with the latest NICE criteria for DMSA scintigraphy,[5] associated with its performance in case of abnormal RBUS.[7] This approach was also aligned with the pediatric nephrology unit of the referral hospital.

The objective of this study is to access the impact of these practice changes. The specific aims are: i) to define the sensitivity and specificity of the new criteria to diagnose renal scars after UTI; ii) to identify in how many patients the diagnosis of renal scarring would be missed according to the updated criteria; iii) to study whether RBUS would avoid missing renal scarring in patients that did not meet the NICE criteria.

MATERIAL AND METHODS

A retrospective study was performed including every patient under 16 years old who underwent post-UTI DMSA scintigraphy between 2011 and 2020.

UTI was considered when bacteriuria accompanied by compatible symptoms was identified. Bacteriuria was defined as proliferation of a single bacterial strain in urine obtained from supra-pubic bladder aspiration, growth of 10 000 colony-forming units per ml in urine collected from bladder catheterization, and over 100 000 colony-forming units per ml in midstream urine sample. When fever and/or lumbar pain or tenderness occurred concomitantly, the episode was considered as pyelonephritis while when only lower urinary tract symptoms occurred, it was defined as cystitis.[6]

According to the NICE guidelines, atypical UTI was considered when one of the following situations was documented: infection with non-*Escherichia coli* organisms, poor urine flow, seriously ill/sepsis, abdominal or bladder mass, elevated creatinine or failure to respond to treatment with suitable antibiotics within 48 hours. Recurrent UTI was defined as the occurrence of at least two episodes of UTI, with one being pyelonephritis, or the occurrence of at least three episodes of cystitis.[6]

RBUS was conducted after every febrile UTI and was considered abnormal in case of kidney size asymmetry (10 mm or more), renal hypoplasia, solitary kidney, absence of cortico-medullary differentiation, decreased kidney parenchymal thickness, dilation of renal pelvis (maximum anteroposterior diameter equal to or superior to 10 mm), calyx or ureter, ectopic ureter, ureterocele, bladder wall thickening, bladder diverticulum or posterior urethral dilation.

DMSA scintigraphy was performed at least six months after the UTI and was considered altered in case of renal asymmetry (differential renal quantitative activity equal to or superior to 10%) or in case of renal scar (focal or generalized area of diminished radioisotope uptake).

The criteria used to consider that the DMSA scintigraphy was adequately performed were atypical UTI below 3 years of age, recurrent UTI or abnormalities in the RBUS.

Demographical, clinical, analytical, and imagological data were systematically collected.

Statistical analysis was performed using SPSS® 26.0. Numerical variables were presented as mean and standard deviation in case of normal distribution and as median and interquartile range in case of non-normal distribution. Comparative analysis utilized the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables with non-normal distribution.

RESULTS

In the analysed period, 240 DMSA renal scintigraphies were performed. From those, nine were excluded, eight for being follow-up scans after previously identified alterations and one due to a previous heminephrectomy, resulting in 231 results considered.

The median age of the included patients was 14 months (5-35 months) and there was a female predominance (60%).

Antenatal ultrasound changes were presented in eight patients: five pelvic and calyceal dilation, two hydronephrosis and one renal dysplasia and ureterocele. After birth investigation was performed in seven of them (one missed the appointment): one of the patients with hydronephrosis in the antenatal ultrasound had VUR and surgery was necessary.

The most common microorganism identified in the urine culture of the last UTI before the DMSA scintigraphy was *Eschericia coli* (192 cases, 83%), followed by *Proteus mirabilis* (21 cases, 9%) (Table 1).

Table 1. Isolated microorganisms in the urine culture

Microorganism	Frequency (%)
Escherichia coli	83.1%
Proteus mirabilis	9.1%
Klebsiella pneumoniae	4.8%
Enterococcus faecalis	1.3%
Morganella morganii	0.9%
Citrobacter koseri	0.4%
Enterobacter cloacae	0.4%

In 198 patients (86%) targeted antibiotic therapy was initiated in the first 72 hours of symptoms. In the remaining ones, 17 patients were firstly evaluated after this timing; in six of them resistance to empiric treatment initiated was identified and in 10 patients there is no available data.
Atypical UTI in children under 3 years old was identified in 28 children (12%), all of them due to non-*Eschericia coli* infections, one of the cases with concomitant sepsis.
Recurrent UTI was identified in 50 children (22%).
RBUS was performed in most cases during the acute episode (74%), with the remaining being done within the next 6 weeks in 24% of cases and 2% after more than 2 months.
When alterations were identified in the RBUS performed in the acute episode, it was repeated at least 6 weeks after to confirm the findings. Abnormal findings were identified in 18 RBUS (7%), with four patients presenting more than one alteration. The most common alterations were pelvic and/or calyceal dilation of 10 mm or more which was identified in nine patients (50%), followed by decreased kidney parenchymal thickness in four cases (22%) (Table 2).

Table 2. Identified alterations in renal and bladder ultrasound

Alterations identified in RBUS	Frequency
Pelvic and/or calyceal dilation ≥ 10 mm	9 (50%)
Decreased kidney parenchymal thickness	4 (22%)
Ureter dilation	3 (17%)
Kidney size assimetry	2 (11%)
Renal hypoplasia	2 (11%)
Ureterocele	2 (11%)

RBUS: renal and bladder ultrasound

In nine patients VUR was identified in the follow-up imagological studies after pyelonephritis, one of them corresponding to the patient with antenatal ultrasound changes that missed follow-up.
Alterations were identified in 39 DMSA scintigraphy (17%): in 15 (38%) there was a difference in renal quantitative activity equal to or superior to 10%, in 12 (31%) renal scars were identified and in 12 (31%) both alterations were identified.
When analysing gender distribution, no statistically significant differences were observed between altered or non-altered DMSA scintigraphy (male 33%/female 67% in altered DMSA RS group *vs* male 41%/female 59% in non-altered RS group, p=0.364).
Regarding age distribution, the group with identified alterations in DMSA scintigraphy had younger median age than those with normal results (13 *vs* 14 months), although this difference was not statistically significant (p=0.384).
Infection by *Eschericia coli* was more frequently associated with alteration in DMSA scintigraphy, but without statistical significance (19% *vs* 10%, p=0.201).
According to the new criteria for DMSA scintigraphy, only 79 of the 231 would have been performed (34%). Among these 79, 21 (27%) showed alterations. However, out of the 152 DMSA scintigraphies that would not have been performed based on the new criteria, 18 (12%) exams with alterations would have been missed.
When analysing atypical UTI below 3 years old, three patients presented alterations in the DMSA scintigraphy, being this incidence inferior than in the non-atypical UTI (11% *vs* 18%, p=0.432). Regarding recurrent UTI, 13 patients had altered DMSA scintigraphy, being more frequent than in the non-recurrent UTI group, but without statistically significant difference (26% *vs* 14%, p=0.052).
From the patients with documented alterations in the RBUS, 11 had alterations in DMSA scintigraphy, being statistically significant more frequent than in the group with normal RBUS (61% *vs* 13%, p<0.001).
When considering only the 72 patients that met the criteria defined by NICE guidelines, 21 presented alterations in the DMSA scintigraphy, being more frequent than in the group that did not meet these criteria, but without statistically significant difference (21% *vs* 15%, p=0.281).
When considering the new criteria defined in their hospital, the authors identified a tendency to alter results in the group that met those, with a statistically significant difference (27% *vs* 12%, p=0.005), yielding an odds ratio of 2.7 (1.3-5.4) (Table 3).
Regarding the sensitivity and specificity of the new criteria, applying NICE criteria isolated conferred a sensitivity of 39% for DMSA scintigraphy alterations and a specificity of 70%. When considering the altered RBUS as an additional criterion, sensitivity increases to 54%, without reducing specificity (70%) (Table 4).

Table 3. Frequency and odds ratio for altered scintigraphy according to new criteria

	Present	Absent	*p* value	Odds ratio
Authors' hospital criteria	27%	12%	0.005	2.70 (1.34-5.43)
NICE guidelines criteria	21%	15%	0.281	1.30 (0.82-2.03)
Atypical UTI <3 years old	11%	18%	0.432	0.56 (0.16-1.94)
Recurrent UTI	26%	14%	0.052	2.10 (0.98-4.46)
Altered RBUS	61%	13%	0.001	10.36 (3.71-29.01)

NICE: National Institute for Health and Care; RBUS: renal and bladder ultrasound; RS: renal scintigraphy; UTI: urinary tract infection

Table 4. Accuracy of criteria for detection of scintigraphy alterations

	Sensitivity	Specificity	PPV	NPV
Authors' hospital criteria	54%	70%	27%	88%
NICE guidelines criteria	39%	70%	21%	85%
Atypical UTI <3 years old	8%	87%	11%	82%
Recurrent UTI	33%	81%	26%	86%
Altered RBUS	28%	96%	61%	87%

NPV: negative predictive value; PPV: positive predictive value; NICE: National Institute for Health and Care; RBUS: renal and bladder ultrasound; UTI: urinary tract infection

From the 18 patients that would not perform DMSA scintigraphy according to new criteria, 8 presented differential renal quantitative activity between 10% and 20%, five presented renal scar and five presented association both renal scar and differential renal quantitative activity superior to 10% (ranging from 18% to 40%).

The patients with alterations in DMSA scintigraphy have been followed during a median of 6 years (3.5-8 years), with 19 still being followed. During this time, no hypertension, persistent proteinuria or decreased renal function has been identified. In 11 cases (28% of the patients with altered DMSA scintigraphy) loss of follow-up occurred due to missed appointments.

DISCUSSION

The demographic data identified in our study were consistent with the literature, showing higher prevalence of UTI in females and *Escherichia coli* as the most frequent pathogen.[1]

No statistically significant differences were found in altered DMSA scintigraphy when considering gender or age differences, aligning with findings from other studies.[9,10]

In our study, *Escherichia coli* was associated with an increased incidence of DMSA scintigraphy alterations, although without statistical significance, contrarily to evidence from literature.[9,11-13]

In this sample, both recurrent UTI[11,12,14,15] and alterations in RBUS[9,11-15] showed a positive correlation with alterations in DMSA scan, accordingly to the existing literature, although atypical UTI did not demonstrate this correlation, contrary to what is suggested by literature.[11,15] The presence of criteria defined by NICE guidelines has also a positive correlation with an increased risk of alterations, but the addition of alterations in RBUS as a criterion led to a result with statistically significant impact, supporting its addition in our clinical practice.

Applying these criteria presented a positive impact avoiding the realization of a significant number of unjustified DMSA scans. Although, some alterations would have been missed and further studies are necessary to clarify the impact of these lesions on children's long-term renal function with a larger sample. The high percentage of loss of follow-up due to missing appointments reinforces the need to sensitize both the patients and their parents for the importance of this follow-up for an early identification of renal function impairment.

Our study reinforces the controversy surrounding the different guidelines of imaging follow-up after an UTI episode. An algorithm considering demographical, clinical, and analytical data is essential to optimize the use of imagiological exams after UTI.

As strengths of this study, we highlight that data were collected from a single centre with an organized strategy for managing children with UTI, microbiological data was available for all samples and RBUS and DMSA scan was performed to every patient at the appropriate timings. However, the authors recognize some limitations, including the retrospective nature of the study, the sample size, and the lack of complete follow-up information on patients with altered DMSA scan results.

Prizes and Previous Presentations

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MMC: Study design, data collection and analysis, writing the original draft.

TAL and MFS: Data collection and analysis, reviewing and editing the original draft.

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CN: Study design, reviewing of the manuscript.

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