

# Algorithms imaging tests comparison following the first febrile urinary tract infection in children

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## ABSTRACT

**Objectives.** To compare the diagnostic sensitivity, costs and radiation doses of imaging tests algorithms developed by the Argentine Society of Pediatrics in 2003 and 2015, against British and American guidelines after the first febrile urinary tract infection (UTI).

**Population and Methods.** Inclusion criteria: children  $\leq 2$  years old with their first febrile UTI and normal ultrasound, voiding cystourethrography and dimercaptosuccinic acid scintigraphy, according to the algorithm established by the Argentine Society of Pediatrics in 2003, treated between 2003 and 2010. The comparisons between algorithms were carried out through retrospective simulation.

**Results.** Eighty (80) patients met the inclusion criteria; 51 (63%) had vesicoureteral reflux (VUR); 6% of the cases were severe. Renal scarring was observed in 6 patients (7.5%). Cost: ARS 404,000. Radiation: 160 millisieverts. With the Argentine Society of Pediatrics' algorithm developed in 2015, the diagnosis of 4 VURs and 2 cases of renal scarring would have been missed. The cost of this omission would have been ARS 301,800 and 124 millisieverts of radiation. British and American guidelines would have missed the diagnosis of all VURs and all cases of renal scarring, with a related cost of ARS 23,000 and ARS 40,000, respectively and 0 radiation.

**Conclusion.** Intensive protocols are highly sensitive to VUR and renal scarring, but they imply high costs and doses of radiation, and result in questionable benefits.

**Key words:** urinary tract infections, algorithms, diagnostic imaging, vesicoureteral reflux, renal scarring.

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## INTRODUCTION

There is no consensus on the optimal imaging strategy after the first febrile urinary tract infection (UTI). In part, this is due to the lack of certainties about the long-term clinical significance of vesicoureteral reflux (VUR) and UTI-associated renal scarring. Currently, we know that in a high percentage of children with renal compromise previously attributed to pyelonephritis and VUR, this condition is actually congenital. Moreover, after their first febrile UTI episode, most children have a good prognosis.<sup>1-4</sup>

In the last decade, there has been a proliferation of algorithms that coincided in a drastic reduction of imaging studies. There is a marked variability as regards sensitivity and specificity for the detection of abnormalities, as well as a great difference in health-related costs and radiation exposure.<sup>5-7</sup> In Argentina, the algorithm by the Argentine Society of Pediatrics (SAP) in 2003, recommending an ultrasound, a voiding cystourethrography (VCUG) and a late dimercaptosuccinic acid (DMSA) scintigraphy for all children  $\leq 2$  after the first febrile UTI, was reviewed.<sup>8</sup> In the most recent consensus by SAP in 2015, it was decided that, after the first febrile UTI with normal kidney and bladder ultrasound scans, the VCUG would be restricted to children  $\leq 1$  and the DMSA to patients with VUR, six months after the UTI.<sup>9</sup>

## OBJECTIVES

To compare the diagnostic sensitivity, health-related costs and radiation doses of SAP algorithms from 2003 and 2015, against the British guidelines by the National Institute for Clinical Excellence (NICE) and the current American guidelines after the first febrile UTI.

## POPULATION AND METHODS

Observational and retrospective study. The study analyzed case records from UTI patients treated between 2003 and 2010 at the Unit of Pediatric Nephrology and the Service of Radiology of Hospital Dr. José Penna in Bahía Blanca, Province of Buenos Aires, Argentina.

Inclusion criteria:  $\leq 2$  years old with their first febrile UTI episode, with normal kidney

and bladder ultrasound scans, good response to treatment, assessed by VCUG and late DMSA.

The percentage of detected VURs and their severity was assessed according to the international classification –Grades I, II (low), III (moderate), IV-V (severe)–.<sup>10</sup> DMSAs were considered abnormal if they showed scarring (areas without uptake). The scarring was classified as mild or significant, based on the differential renal function (> or ≤ 45%, respectively).<sup>11</sup> Health-related costs were estimated based on average local costs: ultrasound, ARS 550; VCUG, ARS 1500; DMSA, ARS 3000 (1 dollar: ARS 14,50, September 2016).

The radiation dose was reported in millisieverts (mSv), a unit that represents the harmful effect of the exposure to radiation on organs and tissue. The

calculation was 1 mSv for each VCUG and DMSA.<sup>12</sup>

The comparison of diagnostic sensitivity, health-related costs and radiation dose among the different protocols was carried out through retrospective simulation. *Table 1* compares the imaging strategies to be evaluated. NICE guidelines describe UTIs in terms of typical (good response within 48 h of treatment) and atypical (no response to antibiotic treatment).<sup>6</sup> The guidelines of the American Academy of Pediatrics (AAP) recommend a VCUG in cases of recurrent UTI, pathological ultrasound and atypical UTI.<sup>7</sup> This study only compared the recommendations for typical UTIs. The authorization of the internal Research and Ethics Committees was requested to review case records. Since this was a retrospective study, no informed consent was obtained.

TABLE 1. Comparison of the indication of imaging studies after the first febrile urinary tract infection in children

Guidelines	Ultrasound	VCUG	Late DMSA
SAP (2003) ≤ 2 years	Yes	Yes	Yes
SAP (2015) ≤ 1 year	Yes	Yes	Performed if VUR is detected
> 1 year old	Yes	No	No
NICE ≤ 6 m.o.	Yes	Performed if the ultrasound is pathologic	No
> 6 m.o.	No	No	No
AAP 2 m.o. to ≤ 24 m.o.	Yes	Performed if the ultrasound is pathologic	No

VCUG: voiding cystourethrography; DMSA: dimercaptosuccinic acid; SAP: Argentine Society of Pediatrics; NICE: British guidelines from the National Institute for Clinical Excellence; AAP: guidelines from the American Academy of Pediatrics; VUR: vesicoureteral reflux.

TABLE 2. Comparative chart: direct costs, radiation doses, diagnoses and omissions with the implementation of the different imaging guideline. N: 80

Guidelines	Direct costs	Radiation dose (mSv)	Diagnoses	Diagnostic omission
SAP (2003)	ARS 404,000	160	VUR: 51 patients 20: Grades I-II 26: Grade III 5: Grade IV Scarring: 6 5 pequeñas 1 significativa	0
SAP (2015)	ARS 301,800	124	VUR: 47 patients 19: Grades I-II 24: Grade III 4: Grade IV Scarring: 4 2 small 1 significant	VUR: 4 patients 1: Grade II 2: Grade III 1: Grade IV 1: Grade IV Scarring: 2 small
NICE (2007)	ARS 23,000	0	No VUR or scarring	All VURs and scarrings
AAP (2011)	ARS 40,000	0	No VUR or scarring	All VURs and scarrings

SAP: Argentine Society of Pediatrics; NICE: British guidelines from the National Institute for Clinical Excellence; AAP: guidelines from the American Academy of Pediatrics; VUR: vesicoureteral reflux.

The differences in costs and radiation doses were analyzed through Friedman and Wilcoxon tests with Bonferroni correction, using SPSS software, version 22.

## RESULTS

Out of the 188 patients treated for UTI, 80 met the inclusion criteria; 40 of them were female; 46 were younger than 6 months old; 30 were between 7-12 months old; and 4 were older than 12 months old. VUR was detected in 51 patients (63%); 47 of them < 1 year old. Only 10% of the VURs were severe. Six patients showed abnormalities in the DMSA (7.5%); only 1 had significant renal scarring. *Table 2* compares the costs, radiation doses, diagnoses and omissions with the implementation of each guideline.

The greatest differences in costs and radiation are seen between the Argentine and NICE-American guidelines. The difference between the 2003 and 2015 SAP guidelines, as regards costs and radiation doses, reached statistical significance (*Table 3*).

Average follow-up of patients with VUR and scarring was 67 months. All 6 patients with scarring had normal growth, blood pressure and renal function, without proteinuria.

## DISCUSSION

The different algorithms showed marked differences as regards the diagnostic sensitivity. By comparing health-related costs and the doses of radiation between the guidelines, statistically significant differences were found.

*Diagnostic sensitivity.* The significance of VUR and renal scarring, as well as the importance of their diagnosis, has been a controversial

issue. For years, VUR was considered to be the greatest factor in UTI-associated damage, and a significant cause of chronic kidney disease (CKD). Currently, we know that most patients who develop CKD are born with associated kidney dysplasia (non-preventable congenital damage). As a consequence, the stringent screening for VUR in the last 40 years has not changed CKD prevalence levels. There is also evidence that acquired kidney damage is related more to the UTI than to the VUR.<sup>4,6</sup>

Under the 2003 SAP algorithm, no VUR or scarring diagnosis was missed. With the 2015 recommendations, 4 VURs (1 grade II, 2 grade III and 1 grade IV) and 2 cases of small scarring would have gone undiagnosed. By implementing the NICE and American guidelines, all the diagnoses would have been missed.

In our group, a high percentage of VUR was detected which could be explained by the referral of previously diagnosed patients to the nephrology office. However, 90% of these cases were low grade (only 6% of VURs were grade IV). Our data is consistent with the results of a recent systematic revision which showed that, after the first febrile UTI, only 2.5% of VURs were grade IV-V showing the high percentage of children that are subjected to unnecessary tests.<sup>1</sup> The clinical significance of grades I-III VURs is controversial because VURs have a tendency to resolve spontaneously and there is no evidence that surgery and prophylactic antibiotics can reduce the development of scarring.<sup>13</sup>

The percentage of scarring in our group was lower than that published in other series, probably because only patients with their first UTI and normal ultrasound scans were included. Long-term prognosis seems to be good, with a low risk of hypertension and/or CKD.<sup>4</sup> Early diagnosis and treatment of UTIs is the strategy that has the highest impact on the prevention of renal scarring.

*Health-related costs.* Our investigation was limited because only costs of imaging studies, known as "direct health-related costs," could be estimated. It was not possible to determine non healthcare-related costs (transportation of patients, unnecessary use of time and space), indirect costs (absenteeism, productivity loss) or intangible costs, which are difficult to assess (pain, stress, exposure to radiation by technical and medical staff).

Although costs under the NICE and American guidelines are much lower, diagnostic omission

TABLE 3. Comparison between the costs and radiation of the different imaging guidelines

Paired guidelines Wilcoxon test	Factor			
	Cost		Radiation	
	z value	variation	z value	variation
AAP (2011)-NICE (2007)	17.50	-5.831 <sup>b</sup>	0.00	0.000 <sup>a</sup>
SAP (2015)-NICE (2007)	40.50	-7.843 <sup>b</sup>	38.50	-7.871 <sup>b</sup>
SAP (2003)-NICE (2007)	40.50	-8.037 <sup>b</sup>	40.50	-8.944 <sup>b</sup>
SAP (2015)-AAP (2011)	38.50	-7.871 <sup>b</sup>	38.50	-7.871 <sup>b</sup>
SAP (2003)-AAP (2011)	40.50	-8.944 <sup>b</sup>	40.50	-8.944 <sup>b</sup>
SAP (2003)-SAP (2015)	16.50	-5.387 <sup>b</sup>	16.50	-5.387 <sup>b</sup>

<sup>a</sup> There are no statistical differences between the guidelines.

<sup>b</sup> There are highly significant differences between the paired imaging guidelines.

AAP: Guidelines from the American Academy of Pediatrics; NICE: British guidelines from the National Institute for Clinical Excellence; SAP: Argentine Society of Pediatrics.

error is significant. It was recently reported that the implementation of NICE guidelines reduced imaging studies by 77%, but it missed 58% of abnormalities. Therefore, the authors recommended ultrasound scans in children < 1 year old.<sup>14</sup>

In Argentina, 750,000 children are born every year, and UTI incidence in children < 2 years old is 8% in girls and 2% in boys.<sup>15</sup> If we estimate only the cost of tests after the first febrile UTI in children < 2 years old, according to the 2003 SAP algorithm, the cost would amount to USD 378,750,000. By implementing the new 2015 SAP recommendations, this cost would fall to USD 126,112,500 per year.

**Radiation dose.** Less intensive protocols imply a lower radiation exposure. In Argentina, the annual dose limit for patients is 1 mSv, and there is a recommendation not to exceed 5 mSv in 5 years. Large campaigns are being conducted to raise awareness about the rational use of radiation in children, with a high level of compliance among Argentine pediatric radiologists. The adequate selection of diagnostic methods is promoted, targeting populations at risk, with the aim of minimizing invasive procedures that imply radiation exposure, while maintaining an acceptable sensitivity to detect significant abnormalities. It is important to highlight the importance of ultrasound scans to determine the need for additional tests.

Our data supports the new national consensus. By implementing these guidelines, DMSAs would have been reduced by 56%, VCUG by 25%, radiation dose by 25% and costs by 27%, with little significant kidney damage and few diagnostic omission errors of VUR.

## CONCLUSION

More intensive protocols have a high sensitivity to detect VUR and renal scarring, but they are related to high healthcare-related costs and considerable doses of radiation resulting in a doubtful benefit. ■

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