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# Different Guidelines for Imaging After First UTI in Febrile Infants: Yield, Cost, and Radiation

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## KEY WORDS

urinary tract infection, guidelines, vesicoureteral reflux, voiding cystourethrography, renal DMSA scan

## ABBREVIATIONS

AAP—American Academy of Pediatrics  
 CI—confidence interval  
 DMSA—technetium<sup>99m</sup>dimercaptosuccinic acid  
 IRIS1—Italian Renal Infection Study 1  
 ISPN—Italian Society of Pediatric Nephrology  
 LR+—positive likelihood ratio  
 LR—negative likelihood ratio  
 NICE—National Institute of Clinical Excellence  
 NPV—negative predictive value  
 PPV—positive predictive value  
 RCH—Royal Children's Hospital of Melbourne  
 TDA—top down approach  
 UTI—urinary tract infection  
 VCUG—voiding cystourethrography  
 VUR—vesicoureteral reflux

All authors contributed substantially to the conception and design of the study; Drs De Mutiis and Puccio performed the data analysis; all authors were involved in the interpretation of the data; Drs La Scola, De Mutiis, Hewitt, and Montini prepared the first draft of the manuscript; and all authors participated in revising the article and approved the final version of the manuscript.

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**WHAT'S KNOWN ON THIS SUBJECT:** There is a lack of consensus regarding the optimal investigative approach after a first febrile urinary tract infection. This is because of uncertainty regarding the long-term clinical significance of vesicoureteral reflux and urinary tract infection–related renal scarring.



**WHAT THIS STUDY ADDS:** No ideal diagnostic algorithm exists. We found marked variability in sensitivity and specificity for detection of abnormalities using current protocols. We also highlight the considerable cost differences, both financially and in terms of radiation dose, of different protocols.

## abstract



**OBJECTIVE:** To evaluate the yield, economic, and radiation costs of 5 diagnostic algorithms compared with a protocol where all tests are performed (ultrasonography scan, cystography, and late technetium<sup>99m</sup> dimercaptosuccinic acid scan) in children after the first febrile urinary tract infections.

**METHODS:** A total of 304 children, 2 to 36 months of age, who completed the diagnostic follow-up (ultrasonography, cystourethrography, and acute and late technetium<sup>99m</sup> dimercaptosuccinic acid scans) of a randomized controlled trial (Italian Renal Infection Study 1) were eligible. The guidelines applied to this cohort in a retrospective simulation were: Melbourne Royal Children's Hospital, National Institute of Clinical Excellence (NICE), top down approach, American Academy of Pediatrics (AAP), and Italian Society of Pediatric Nephrology. Primary outcomes were the yield of abnormal tests for each diagnostic protocol; secondary outcomes were the economic and radiation costs.

**RESULTS:** Vesicoureteral reflux (VUR) was identified in 66 (22%) children and a parenchymal scarring was identified in 45 (15%). For detection of VUR (47/66) and scarring (45/45), the top down approach showed the highest sensitivity (76% and 100%, respectively) but also the highest economic and radiation costs (€52 268. 624 mSv). NICE (19/66) and AAP (18/66) had the highest specificities for VUR (90%) and the Italian Society of Pediatric Nephrology had the highest specificity (20/45) for scars (86%). NICE would have been the least costly (€26 838) and AAP would have resulted in the least radiation exposure (42 mSv).

**CONCLUSIONS:** There is no ideal diagnostic protocol following a first febrile urinary tract infection. An aggressive protocol has a high sensitivity for detecting VUR and scarring but carries high financial and radiation costs with questionable benefit. *Pediatrics* 2013;131:e665–e671

The investigative approach after a first febrile urinary tract infection (UTI) is being questioned, with a lack of consensus as to the optimal protocol. This lack of consensus is because of the uncertainty regarding the long-term clinical significance of vesicoureteral reflux (VUR) and UTI-related renal scarring.<sup>1–3</sup> Furthermore, renal damage previously attributed to acquired pyelonephritic scarring is now recognized as being more commonly congenital in nature,<sup>1,4–8</sup> and recent studies have cast doubt on the efficacy of antibiotic prophylaxis after a febrile UTI.<sup>9–14</sup> The core imaging modalities advocated after a UTI have been ultrasonography, voiding cystourethrography (VCUG), and technetium<sup>99m</sup>dimercaptosuccinic acid (DMSA) scan renal scintigraphy. The reason for imaging is to detect obstructive malformations, VUR, and renal parenchymal damage; however, there is no consensus as to the nature of the malformations, severity of reflux, or degree of damage that warrants detection.<sup>15</sup> Whereas an intensive approach was recommended by some,<sup>16</sup> there has been a proliferation of guidelines that have proposed different diagnostic algorithms, with the expectation of minimizing invasive procedures while maintaining an acceptable sensitivity and specificity for the detection of abnormalities.<sup>17–21</sup>

The aim of this article is to evaluate current diagnostic algorithms for their ability to detect VUR and permanent scarring and to determine the economic and radiation costs incurred by the different protocols in children at the time of the first febrile UTI.

## METHODS

### Patients

Data collected from the Italian Renal Infection Study 1 (IRIS1), a multicenter prospective controlled trial involving 502 children, 1 month to 7 years of age, after an uncomplicated first febrile UTI

and with a normal antenatal ultrasonography, were used for this study.<sup>22</sup> Children with severe clinical sepsis, dehydration and vomiting, and creatinine clearance (Schwartz formula)<sup>23</sup>  $\leq 70$  mL/min/1.73 m<sup>2</sup> were excluded from the trial. The 304 children from IRIS1 between 2 and 36 months of age who completed the diagnostic follow-up were eligible. All children underwent a comprehensive evaluation, including renal tract ultrasonography and DMSA renal scintigraphy during the acute phase (within 10 days of the UTI), VCUG within 2 months, and a DMSA study 12 months later when the acute study was positive to detect scarring at the site of original pyelonephritis, as previously recommended.<sup>24</sup> Details of the diagnostic protocol are available in the original article.<sup>22</sup>

### Diagnostic Guidelines

Diagnostic algorithms of guidelines published after 2006, were considered, and their application to eligible children from the IRIS1 study was retrospectively simulated (Supplemental Fig 2). The Royal Children's Hospital of Melbourne (RCH 2006),<sup>17</sup> the National Institute of Clinical Excellence (NICE 2007),<sup>18</sup> the top down approach (TDA 2007),<sup>19</sup> the American Academy of Pediatrics (AAP 2011),<sup>20</sup> and the Italian Society of

Pediatric Nephrology (ISPN 2011)<sup>21</sup> were studied for their ability to detect the children with VUR or scarring, determining also the individual and total economic and radiation costs. As reference, we used the "all tests performed" protocol, where ultrasonography, VCUG, and late DMSA scan are theoretically performed on all children. Details of the algorithms are summarized in Table 1 and are available as referenced.<sup>17–21</sup>

### Costs

The costs that would have been incurred for the different algorithms were calculated. Because the IRIS1 study was conducted in 3 Italian regions, Alto Adige, Emilia Romagna, and Veneto, the costing was the mean of those reimbursements of the health systems of each region: renal ultrasonography (€82), VCUG (€83), and DMSA renal scintigraphy (€84).

### Radiation Dose

The radiation dose for DMSA scintigraphy has been estimated as 1 mSv, regardless of the child's age, by using the dose recommendations of the European Pediatric Task Group.<sup>25</sup> Greater variability exists in the reported radiation dose associated with the VCUG (from 0.5 to 3.2 mSv), with 1 mSv being the most

**TABLE 1** Summary of the 5 Imaging Recommendations Evaluated in This Article<sup>17–21</sup>

Guidelines	Ultrasound	Voiding Cystogram	Late DMSA Scan
RCH <sup>17</sup>	Yes	If boys <6 mo and/or positive ultrasonography	No
NICE <sup>18</sup>			
<6 mo	Yes	If positive ultrasonography and/or atypical UTI <sup>a</sup>	If atypical UTI <sup>a</sup>
≥6 mo	If atypical UTI <sup>a</sup>	If children with risk factors <sup>b</sup>	If atypical UTI <sup>a</sup>
TDA <sup>19</sup>	No	If positive acute DMSA	If positive acute DMSA
AAP <sup>20</sup>	Yes	If positive ultrasonography	No
ISPN <sup>21</sup>	Yes	If positive ultrasonography and/or children with risk factors <sup>c</sup>	If positive ultrasonography and/or VUR

<sup>a</sup> Seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, septicemia, failure to respond to correct antibiotic treatment within 48 hours, or infection with non-*Escherichia coli* organisms.

<sup>b</sup> Dilatation on ultrasonography, poor urine flow, non-*E. coli* infection, or family history of VUR.

<sup>c</sup> Abnormal prenatal ultrasonography of the urinary tract, family history of VUR, septicemia, renal failure, age <6 months in a male infant, likely noncompliance of the family, abnormal bladder emptying, no clinical response to correct antibiotic treatment within 72 h, or non-*E. coli* infection.

commonly accepted value.<sup>26</sup> For the purposes of this study, we assessed the radiation exposure as 1 mSv for both imaging procedures.

### Outcomes

Primary outcomes were the yield of abnormal tests (all grades of reflux, grades III–V reflux, and UTI related renal scarring) for each diagnostic protocol evaluated, using as comparison the all tests performed protocol. The prediction is based on what would be known at the time of the first UTI.

Secondary outcomes were the economic cost and the total radiation dose that each guideline would have incurred.

### Statistics

Statistics were performed by open source statistical software R (version 2.13.1; <http://www.r-project.org/>).

Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), positive and negative likelihood ratio (LR+ and LR–, respectively), and corresponding 95% confidence intervals (95% CIs) of each algorithm to identify children with VUR and scars were calculated against the all tests performed protocol.

## RESULTS

### Participant Characteristics

A total of 304 children (median age, 7.7 months; 64% girls) were eligible (Fig 1). Demographic and clinical characteristics of the patients are listed in Table 2. Fourteen percent of patients (42/304) had an abnormal finding at ultrasonography, and 53% had signs of acute pyelonephritis (160/304) at an acute DMSA scan. VUR was identified in 22% of children (66/304), of whom 8.5% (26/304) had grades III–V, whereas

a parenchymal scar was present in 15% (45/304) on a late DMSA study.

### Primary Outcomes

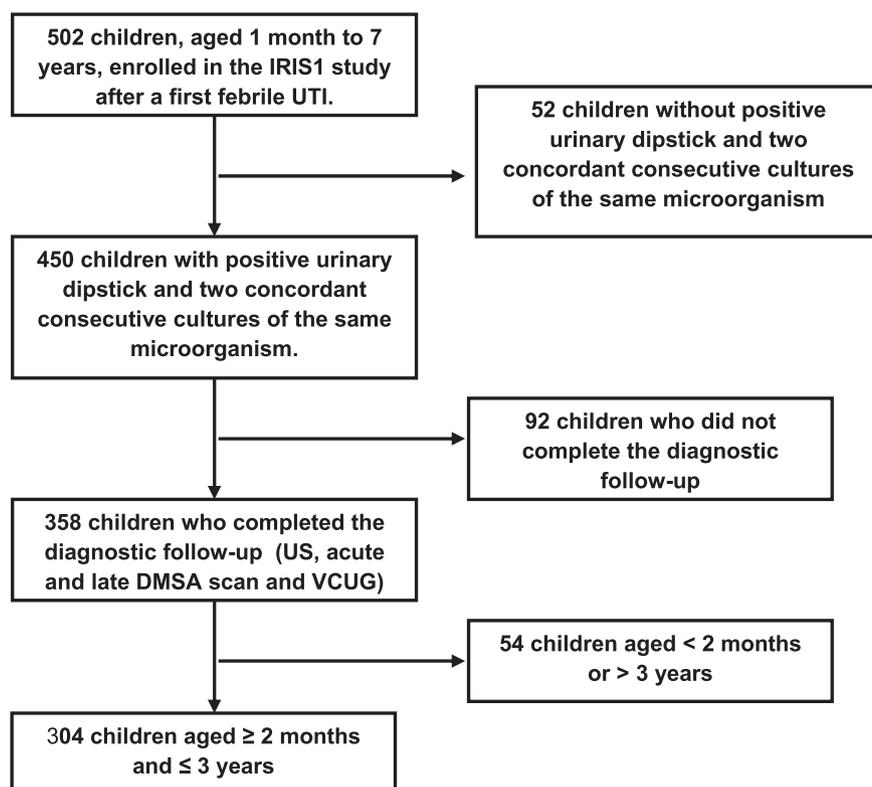
All 5 selective protocols missed a variable proportion of reflux and scars (with the exception of the TDA protocol, which detected 100% of the scars), and none would have diagnosed all the nephrologic abnormalities (Table 3).

#### VUR I–V

The diagnostic ability of different guidelines in identifying children with VUR grades I–V is reported in Table 4. The TDA yielded 47/66 (76%) VUR grades I–V, with the highest sensitivity and NPV (76% and 89%, respectively) but the lowest specificity (54%). Conversely, NICE detecting 19/66 (29%) VURs and AAP 18/66 (27%) had higher specificities (91% and 90% respectively), but very low sensitivities (29% and 27% respectively).

#### VUR III–V

The diagnostic ability of different guidelines in identifying VUR grades III–V is listed in Table 5. The TDA, detecting 22/26 (85%) of VUR grades III–V, had the highest sensitivity (85%); however, this was combined with a relatively low specificity (50%). In contrast, both NICE and AAP detected a minority of the cases (13/26 and 10/26, respectively) and had lower sensitivities (50% and 38%, respectively) combined with higher specificity (90% and 88%, respectively).



**FIGURE 1**

Flow of patients throughout the study and adherence to protocol.

**TABLE 2** Demographic and Clinical Characteristics of the 304 Children Included in the Protocol

Age, median (range), mo	7.7 (2–36)
Females (%)	193/304 (64)
Positive ultrasonography (%)	42/304 (14)
VUR III–V (%)	26/304 (8.5)
VUR I–V (%)	66/304 (22)
Pyelonephritis (%) <sup>a</sup>	160/304 (53)
Scars (%) <sup>b</sup>	45/304 (15)

<sup>a</sup> At acute DMSA.

<sup>b</sup> At late DMSA scan.

**TABLE 3** Economic and Radiation Costs and Rate of Missed Reflux and Scars of the 6 Imaging Recommendations Evaluated in This Article

	All Tests Performed <sup>a</sup>	RCH	NICE	TDA	AAP	ISPN
Total costs, €	75 696	32 743	26 838	52 268	28 457	44 139
Cost/patient, €	249	108	88	172	94	145
Total radiation, mSv	608	92	156	624	42	228
Radiation/patient, mSv	2	0.3	0.5	2.05	0.14	0.75
Number VURs I–V missed (%)	0/66 (0)	40/66 (61)	47/66 (71)	16/66 (24)	48/66 (73)	34/66 (51)
Number VURs I–II missed (%)	0/40 (0)	28/40 (70)	34/40 (85)	12/40 (30)	32/40 (80)	27/40 (68)
Number VURs III–V missed (%)	0/26 (0)	12/26 (46)	13/26 (50)	4/26 (15)	16/26 (61)	7/26 (27)
Number of scars missed (%)	0/45 (0)	45/45 (100)	28/45 (62)	0/45 (0)	45/45 (100)	25/45 (53)

<sup>a</sup> Ultrasonography, cystography, and late DMSA scan.

**TABLE 4** Diagnostic Ability of the 5 Guidelines as Predictors of VUR Grades I–V Based on Cystography

Guidelines	VUR I–V Detected			Percent (95% CI)			
	n (%)	Sensitivity	Specificity	PPV	NPV	LR +	LR –
RCH	26/66 (39)	39 (28–51)	72 (67–78)	28 (19–37)	81 (76–86)	1.4 (1.1–1.8)	0.8 (0.6–1.1)
NICE	19/66 (29)	29 (18–40)	91 (88–95)	47 (32–63)	82 (78–87)	3.3 (2.7–3.8)	0.8 (0.6–0.9)
TDA	47/66 (76)	76 (65–86)	54 (47–60)	31 (24–38)	89 (84–94)	1.6 (1.4–1.8)	0.4 (0.01–0.9)
AAP	18/66 (27)	27 (17–38)	90 (86–94)	43 (28–59)	82 (77–86)	2.7 (2.2–3.2)	0.8 (0.7–1)
ISPN	32/66 (49)	48 (36–60)	65 (59–71)	28 (19–36)	82 (76–87)	1.4 (1.1–1.7)	0.8 (0.5–1.1)

### Scars at Late DMSA

The diagnostic ability of different guidelines in identifying UTI-related renal scars is listed in Table 6. The TDA detected 45/45 scars and had the highest sensitivity (100%), because a late DMSA study was recommended in all cases after pyelonephritis. NICE and ISPN recommended a late DMSA to detect scarring in selected circumstances, detecting 17/45 (38%) and 20/45 (47%) scars, respectively, with a comparable sensitivity (38% and 44%, respectively) and specificity (84% and 86%, respectively). The RCH and AAP protocols did not recommend a late DMSA to detect scarring.

### Secondary Outcomes

The all tests protocol resulted in the highest procedural costs (€75 696), and the TDA resulted in the highest radiation dose (624 mSv). The NICE guidelines were the least costly (€26 838), whereas the AAP guidelines resulted in the least radiation exposure (42 mSv), demonstrating an almost threefold difference in expenditure and 15-fold difference in radiation (Table 3).

### DISCUSSION

The 5 diagnostic protocols evaluated approach the investigation of children

at the time of the first febrile UTI in different ways.<sup>17–21</sup> Whereas the all tests protocol would perform ultrasonography, VCUG, and DMSA scan in all children and would not miss any reflux or scar, the 5 guidelines formulated algorithms with the aim of identifying a high-risk population for VUR or scarring. To this population, they apply the definitive diagnostic tests of VCUG for VUR and DMSA for UTI-related renal scars, missing a variable proportion of reflux or scars but at the same time decreasing economic costs and radiation burden, as well as physical and psychological stress. A less aggressive approach is finding increasing favor, given that renal damage previously attributed to acquired pyelonephritic scarring is now recognized as being more commonly congenital in nature.<sup>4–8</sup> A recent article underlined that, in the absence of major congenital nephrological abnormalities, the etiologic fraction of recurrent UTIs as a cause of chronic kidney disease appears to be minimal.<sup>1</sup> Furthermore, the efficacy of surgical<sup>27</sup> or medical treatment of VUR, especially low grades, has been reevaluated.<sup>9–15</sup>

Our study cohort is representative of the general population of children with a first febrile UTI, for whom the diagnostic algorithms are recommended. The prevalence of VUR (22% and 8.5% for reflux grades I–V and III–V, respectively), pyelonephritis on an acute DMSA scan (53%), and scarring on the late DMSA study (15%) in our cohort is similar to that reported by most clinical studies.<sup>28–31</sup>

**TABLE 5** Diagnostic Ability of the 5 Guidelines as Predictors of VUR Grades III–V Based on Cystography

Guidelines	VUR III–V Detected			Percent (95% CI)			
	n (%)	Sensitivity	Specificity	PPV	NPV	LR+	LR–
RCH	14/26 (54)	54 (35 to 73)	72 (67 to 77)	15 (8 to 23)	94 (91 to 97)	1.9 (1.5 to 2.3)	0.6 (0.2 to 1.1)
NICE	13/26 (50)	50 (31 to 69)	90 (87 to 94)	32 (18 to 47)	95 (92 to 98)	5.1 (4.6 to 5.7)	0.5 (0.2 to 0.9)
TDA	22/26 (85)	85 (71 to 99)	50 (45 to 56)	14 (8 to 19)	97 (94 to 100)	1.7 (1.5 to 1.9)	0.3 (–0.6 to 1.2)
AAP	10/26 (39)	38 (20 to 57)	88 (85 to 92)	24 (11 to 37)	94 (91 to 97)	3.3 (2.8 to 3.9)	0.7 (0.4 to 1)
ISPN	19/26 (73)	73 (56 to 90)	65 (59 to 71)	16 (10 to 23)	96 (94 to 99)	2.1 (1.8 to 2.4)	0.4 (–0.2 to 1)

**TABLE 6** Diagnostic Ability of 5 Guidelines as Predictors of Parenchymal Renal Damage Based on Late DMSA Scan

Guidelines	Scars Detected			Percent (95% CI)			
	n (%)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
RCH	0/45 (0)	NA	NA	NA	NA	NA	NA
NICE	17/45 (38)	38 (24–52)	84 (80–89)	29 (18–41)	89 (85–93)	2.4 (1.9–2.8)	0.7 (0.5–1)
TDA	45/45 (100)	100	56 (49–62)	28 (21–35)	100	2.2 (2.1–2.4)	0
AAP	0/45 (0)	NA	NA	NA	NA	NA	NA
ISPN	20/45 (47)	44 (30–59)	86 (82–90)	36 (23–48)	90 (86–94)	3.2 (2.7–3.6)	0.6 (0.4–0.9)

NA, not applicable.

### Primary Outcome: VUR

The 5 protocols detected reflux grades I–V (from 76% for TDA to 27% for AAP) and reflux grades III–V (from 85% for TDA to 39% for AAP) in varying degrees (Tables 4 and 5). The TDA, which uses the result of the acute DMSA scan as the first step of the algorithm, demonstrates the highest sensitivity and NPV (sensitivity, 76% and 85%, and NPV, 89% and 97%, respectively, for reflux grades I–V or III–V). In contrast, it has a low specificity (~50%), resulting in a low LR+ (~1.6). The remaining 4 selective guidelines consider the results of ultrasonography (AAP) or the presence of risk factors together with the results of ultrasonography (RCH, NICE, and ISPN) as the first step in the selection of children for further imaging. This approach would fail to detect all children with reflux, because it is well known that ultrasonography, after an initial febrile UTI, is not able to reliably identify changes associated with reflux or subsequent renal damage.<sup>28,32,33</sup> Adding risks factors increases the probability of detecting nephro-urologic malformations but also increases the number of subsequent investigations. These 4 protocols demonstrate a lack of ability to reliably detect all children with VUR grades III–V. When the ability to identify any grade of VUR was assessed, these protocols prove even more limited. These considerations are echoed by the low likelihood ratios for the different guidelines, with the highest being the NICE, with 3.3 and 5.1 for reflux grades I–V and III–V, respectively. It is

important to underline that the likelihood ratio is considered the most concise clinical determinant for assessing an outcome, with values >10 allowing one to rule in a disorder in a significant way.

### Primary Outcome: Scar

The TDA is the only guideline that recommends a DMSA scan during the acute phase of the infection, not taking into consideration the execution of ultrasonography. A late DMSA scan is recommended when the acute study is positive, allowing a sensitivity of 100% (Table 6). The NICE and ISPN guidelines recommend performance of late DMSA scans in selected circumstances, such that each would have identified less than half of the children with scars (Table 3). The RCH and AAP protocols fail to detect any children with scarring, because they do not advocate a late DMSA scan.

### Secondary Outcomes

Compared with the all tests performed protocol, the 5 guidelines reduced the economic and radiation cost in various degrees, except for the TDA, which has a high economic price (€52 268) and radiation burden (624 mSv) (Table 3). The latter is even higher than the all tests performed protocol (608 mSv) and is 15 times higher than the AAP (42 mSv), because of the need to repeat a late DMSA scan in those children with signs of acute pyelonephritis at early scintigraphy. Radiation risks associated with radiographic and scintigraphic

imaging may not be trivial.<sup>34</sup> A recent article on the risk of childhood cancer associated with exposure to diagnostic radiation in early infancy showed an increased risk of lymphoma (odds ratio, 5.14; 95% CI, 1.27–20.78).<sup>35</sup> Therefore, such procedures have to be adequately justified against alternative diagnostic procedures,<sup>34</sup> according to the risk-benefit philosophy of medical radiation exposure and to the uncertainty of benefits for the patients of certain findings such as grades I–II reflux and minor parenchymal scars.

### Limitations

A possible limitation of our analysis, which mainly applies to the NICE and ISPN guidelines, stems from the selection criteria for the IRIS1 study, whereby those reported to have an abnormal antenatal renal ultrasound and abnormal postnatal renal function were excluded, together with severe clinical sepsis, dehydration, and vomiting, which precluded administration of oral antibiotics.<sup>11</sup> These children are uncommon in everyday clinical practice and therefore unlikely to affect our data significantly, whereas the children with prenatally identified nephro-urologic abnormalities would presumably have been investigated and followed.

A further limitation is represented by the fact that the simulation of diagnostic algorithms was carried out at the time of the first UTI, not considering children who would have had a second UTI (data not available). Performing further radiological exams in children with recurrent UTIs, as recommended by some of the protocols, would have resulted in an even greater number of findings for these approaches but also in an increase in costs and radiation burden.

### CONCLUSIONS

Lack of unified agreement exists regarding the optimal diagnostic protocol at the time of an uncomplicated first

febrile UTI, and it remains open to discussion the benefit of identifying minor abnormalities.

Our analysis highlights the effectiveness or lack thereof of 6 readily available protocols in detecting VUR and scarring and at the same time examined the cost

and radiation impact of the different approaches. This study may be useful in helping the practicing clinician decide which algorithm is most applicable for any given patient and family, considering multiple variables: socioeconomic, cultural, and geographical. However, no

perfect diagnostic algorithm exists at the present time. An aggressive protocol has a high sensitivity for detecting abnormalities, which in some cases could be of questionable benefit to the infants, and it is burdened with high financial and radiation costs.

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## Different Guidelines for Imaging After First UTI in Febrile Infants: Yield, Cost, and Radiation

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