Prevention of febrile urinary tract infections in children: assessment of the impact of the latest guidelines from the American Academy of Pediatrics

A thesis submitted in fulfillment of the requirements for the degree of Master of Science in Medical Research Methodology

By

Vasileios Liakos

Thessaloniki, May, 2019
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Abbreviations

AAP: American Academy of Pediatrics

AUTH: Aristotle University of Thessaloniki

BBD: bowel/bladder dysfunction

CAP: continuous antimicrobial prophylaxis

CFUs/mL: colony-forming units per mL

CI: confidence interval

CPG: clinical practice guideline

DMSA scan: dimercaptosuccinic acid scan

IQR: interquartile range

RBUS: renal and bladder ultrasonography

RCT: randomized controlled trial

RIVUR: Randomized Intervention for children with Vesicoureteral Reflux

RR: risk ratio

SD: standard deviation

UTI: urinary tract infection

VCUG: voiding cystourethrography

VUR: vesicoureteral reflux

Keywords

antimicrobial prophylaxis, children, DMSA scan, *Escherichia coli*, infants, renal and bladder ultrasonography, urinary tract infection, vesicoureteral reflux, voiding cystourethrography
Abstract

The first guidelines of the American Academy of Pediatrics (AAP) regarding the evaluation of the first febrile urinary tract infection in children aged 2 to 24 months were published in 1999 and suggested renal and bladder ultrasonography (RBUS), voiding cystourethrography (VCUG) and dimercaptosuccinic acid scan (DMSA) in all patients, along with continuous antimicrobial prophylaxis (CAP) if vesicoureteral reflux (VUR) was detected. The 2011 revision suggests initial evaluation only with RBUS and reserving VCUG, DMSA and CAP for selected patients.

Aim of this retrospective cohort study is to assess the impact of the revised AAP guidelines in a Greek pediatric population. The study cohort comprised of children hospitalized in the 3rd Pediatric Department of "Hippokration" Hospital, Thessaloniki, Greece, for a first febrile UTI episode and managed either with the old or the revised approach. We compared the two exposure groups in terms of UTI recurrences, VCUGs performed, presence of VUR, CAP utilization, time-to-first recurrence and patient visits per month. All data became available via search of medical records or telephone communication.

We found no difference in rates of UTI recurrence (8/44 vs 5/24, P=1) or patients positive for VUR (19/52 vs 4/14, P=0.75) among children evaluated with the old and new guidelines respectively, while VCUGs decreased by 51.7% (P<0.001) and CAP utilization by 86.2% (P<0.001). Most recurrences occurred within a 6-month period from the first episode and patient visits substantially diminished from 11.5 to 4 per month. Subgroup analyses according to age yielded similar results.

We concluded that the new simplified UTI evaluation strategy did not compromise the prognosis of Greek children hospitalized for a first febrile UTI, which is in accordance with evidence from other healthcare settings. The 2011 AAP revision effectively tackles bacterial resistance, healthcare system overload and patient discomfort, without posing a detrimental impact on children’s health.
Introduction

The urinary tract is one of the most common sites of infection in the pediatric population. The prevalence of urinary tract infections is estimated to be approximately 5% in the age groups of infants and young children (1), while symptoms can be obscure, varying from nothing but fever or few recognizable signs to rather classic symptoms such as increased frequency of urination and dysuria. UTIs in children can also lead to various short-term and long-term complications, including bacteremia, hypertension and a higher potential for renal damage. The challenging diagnostic path to overcome their nonspecific clinical presentation and the higher risk of complications in children are the motivational basis of all research efforts exploring different diagnostic and therapeutic modalities for UTIs in the pediatric field.

Initial attempts to frame universal guidelines for the diagnosis and treatment of UTIs in children were made in 1973 (2), but showed considerable variation. Since then several changes were proposed, which led to the next landmark guideline published in 1999 by the American Academy of Pediatrics (AAP) (3) (Committee on Quality Improvement, Subcommittee on Urinary Tract Infection). The guideline’s recommendations covered the evaluation of children 2 to 24 months of age after their first episode of febrile UTI and were widely implemented until the last decade. Specifically, subsequent management in all patients with a first febrile UTI included renal and bladder ultrasonography (RBUS), voiding cystourethrography (VCUG) and dimercaptosuccinic acid scan (DMSA), in order to assess the risk of recurrence and the presence of renal scars. In addition, children with any degree of vesicoureteral reflux (VUR) diagnosed during their first episode were started on continuous antimicrobial prophylaxis (CAP), in order to prevent recurrences and, ultimately, renal scar formation. However, a number of well-designed randomized controlled trials (4–9) thereof demonstrated no significant benefits with this approach and highlighted the problems of bacterial resistance, healthcare system overload and patient discomfort.

The above strategy was revised by the AAP in 2011 (10), which led to a new set of clinical practice guidelines based on a thorough literature search and incorporation of all data made available since the last version of published recommendations. Similarly to the 1999 practice parameter, the revision focused specifically on the diagnosis and management of the first febrile UTI episode in all children 2 to 24 months of age. Exclusion of lower and higher age groups reflected either insufficiency of generated evidence or data inconsistency. The main principles driving the need for this revision were to reestablish the diagnostic criteria of UTIs and to reconsider the need for imaging along the whole evaluation process. As a result, AAP
adopted a more simplified approach, suggesting only RBUS as a routine scan in all children after their first febrile UTI whilst reserving VCUG, DMSA scan and chemoprophylaxis only for selected patients. Based on RBUS findings, indications for more sophisticated imaging modalities, such as VCUG and DMSA, were hydronephrosis, scarring, high grade VUR, obstructive uropathy, a recurrent episode of febrile UTI and other atypical or complex circumstances (e.g. isolation of non-E. coli uropathogens). In addition, well-conducted RCTs questioned the benefits of CAP on UTI prevention in the pediatric population, abolishing this practice in children with VUR grades I-III (4–9).

A recently published randomized, double-blind, placebo-controlled trial ["Randomized Intervention for Children with Vesicoureteral Reflux" (RIVUR study) (11)] explored the efficacy of long-term chemoprophylaxis with trimethoprim-sulfamethoxazole on the prevention of UTI recurrences and renal scar formation. Based on this trial findings, risk of febrile or symptomatic UTI recurrences was halved for children receiving CAP compared to those allocated to the placebo arm, nevertheless the two groups were comparable in terms of renal scarring.

The established policy of the AAP and its Subcommittee on Urinary Tract Infection to reassess existing clinical practice guidelines every 5 years in conjunction with concurrent generated evidence by the RIVUR trial led to the reaffirmation of the 2011 recommendations. In 2016 (12), AAP reiterated the key aspects of the previously suggested diagnostic path and evaluation process regarding the first febrile UTI episode in children.

The proposed simplified management approach by the AAP for children ≥2 months old with UTI, initially drafted in 2011 and reaffirmed in 2016, has been also widely adopted by Greek pediatric hospital units over the last 4-5 years. Regarding infants <2 months of age, most physicians still perform VCUG in all cases of a first febrile UTI episode; however, the use of chemoprophylaxis in this age group tends to be limited to infants with significant VUR (usually ≥IV grade) similarly to recommendations for older patients. Despite the accumulation of high quality evidence supporting the adopted simplified approach, its implementation on Greek pediatric population has not yet been fully assessed. The aim of this study was to investigate the impact of the latest AAP UTI guidelines on patient-important outcomes in a Greek tertiary pediatric department.
Methods

Study design & setting

The present work was a retrospective cohort study conducted in the 3rd Pediatric Department of "Hippokration" Hospital, a tertiary care general hospital in Thessaloniki, Northern Greece. Along the whole process of conduction and dissemination of our work, we tried to endorse the STROBE international statement for observational studies (13). We searched for subjects diagnosed with the disease and exposed to two different management strategies, for whom we evaluated certain outcomes after a chosen follow-up period. Specifically, patients included in the study were children aged up to 4 years who were hospitalized for their first episode of febrile UTI, divided into two exposure groups: the first group comprised those managed according to the old guidelines of the AAP (1999) (3), while the second group consisted of those evaluated with the simplified approach suggested in the revised guidelines (2011) (10). The two groups of children, namely those who followed the old and the revised instructions respectively, were formed after manually scanning medical records from the Infectious Diseases Outpatient Clinic and the electronic medical records of patients hospitalized in the 3rd Pediatric Department of Aristotle University of Thessaloniki and, finally, selecting all children up to 4 years old with a first episode of febrile UTI.

Subjects

Regarding the first group of patients, we decided to manually search for and include children strictly managed in compliance with the 1999 clinical practice guidelines. For sample size increment purposes of this group, we also utilized the database of a crossover randomized controlled trial with similar eligibility criteria (14), a kind offer from Dr Charalampos Antachopoulos. All included children were hospitalized during the time period October 2002 - April 2011. The lower cut-off was chosen based on available data in the Infectious Diseases Outpatient Clinic and the electronic medical records, whereas the upper cut-off corresponds to the time period when the AAP officially published the new approach regarding management of pediatric UTIs. Duplicates among individuals of the hospital's database and patients included in the aforementioned RCT were removed.

As far as the second group of children was concerned, we included children hospitalized from July 2014 to November 2017. We electively decided to allow a 3-year period (2011 - 2014) for endorsement of the revised AAP guidelines by the majority of Greek pediatric hospital units. We chose November 2017 as the upper cut-off, in order to ensure a minimum follow-up period.
of 12 months (up to December 2018, when the study’s protocol was initially drafted). A one-year follow-up period was set because current bibliography (14) suggests that most recurrences occur during the first 6-month period after the initial febrile UTI episode.

**Diagnosis of UTI**

The diagnosis of UTI was based on finding significant bacteriuria [growth of at least \(10^5\) colony-forming units per mL (CFUs/mL)] of a single urinary pathogen, cultured from a urine specimen obtained through a sterile bag or a clean catch, or \(10^4\) CFUs/mL in specimens obtained through bladder catheterization or any growth in specimens collected via suprapubic aspiration. Patients that met these laboratory conditions were also expected to have accompanying fever (axillary temperature \(\geq 38^\circ\text{C}\)). Patients could optionally exhibit any other signs or symptoms compatible with UTI except fever, such as foul-smelling urine, altered voiding pattern, lethargy, irritability, poor feeding, vomiting, failure to thrive, frequency of urination, urgency, dysuria, abdominal pain or loin tenderness.

**Eligibility criteria**

The inclusion criteria for all patients are outlined below:

- Age up to 4 years
- Presence of fever
- Confirmation of urinary tract infection with urine culture
- First episode of urinary tract infection
- Conduction of RBUS with normal findings (evaluation of children with abnormal RBUS findings does not differ between the 1999 and 2011 guidelines; however, the recommendation for VCUG in children with normal RBUS has been abolished in the 2011 guidelines)
- Conduction of VCUG (if deemed necessary) with available findings
- Available written information regarding recurrences or feasible communication with children’s parents

We also followed the following exclusion criteria for all eligible participants in the study:

- Age over 4 years
- Absence of information regarding the presence of fever or no fever
- Lack of confirmation of bacterial growth with urine culture
• An infection non-related to the urinary tract
• Known clinical background of urinary tract infections (recurrent episodes)
• Failure to conduct RBUS or RBUS with any abnormal findings
• Known VUR (e.g. antenatal hydronephrosis)
• Anatomical abnormalities of the genitourinary system (e.g. posterior urethral valves, renal agenesis, kidney dysplasia)
• Functional abnormalities of the genitourinary system (e.g. neurogenic bladder)
• Known syndromes (e.g. central diabetes insipidus, Lesch - Nyhan syndrome)
• Inability to maintain follow-up (either due to missing records or failure to communicate with children’s parents)

Total number of children considered eligible to enter our study were subsequently divided into two groups according to exposure in each management strategy. Specifically, the first group of patients consisted of those managed in full compliance with the 1999 guidelines, whereas the second group consisted of those evaluated with the revised and simplified 2011 approach. As a result, taking also into account the corresponding time period when clinicians followed each strategy, the first group sustained a hospitalization date from October 2002 to April 2011 and the second group from July 2014 to November 2017.

Data collection

After filtering all eligible patients against the inclusion and exclusion criteria, we started recording their personal data. For each child enrolled in the study we recorded the following parameters: sex, age, diagnosis upon admission, time period of hospitalization, availability of corresponding discharge summary, presence of pyuria/bacteriuria, urine culture results (CFUs/mL and uropathogen), method used to obtain urine specimen, results of RBUS, VCUG and DMSA scan during the first febrile UTI and during recurrences (if any), the need for chemoprophylaxis after the first febrile UTI and after recurrences (if any), total follow-up duration, total number of recurrent episodes of febrile UTIs and any other information deemed relevant by their parents. In addition, we measured the number of patient visits for UTI follow-up at the Infectious Diseases Outpatient Clinic over several arbitrarily chosen months during the time periods when the corresponding guidelines were implemented (10/2002 - 04/2011 and 07/2014 - 11/2017).

The follow-up of children managed with the 1999 approach and all relevant data about their outcomes under investigation were extracted from medical records of the Infectious Diseases
Outpatient Clinic and the electronic medical records of hospitalized patients. The outcomes of all patients evaluated with the 2011 guidelines were obtained via telephone communication with their family and the voluntary provision of information by their parents. For each participant, maximum number of attempts to communicate with family were three, while answers were obtained with the parents’ or legal guardians’ informed consent.

Outcomes compared among the two exposure groups were: total number of children that sustained recurrent episodes of febrile UTIs, total number of VCUGs requested by treating physicians, VUR presence (if any), the need for long-lasting chemoprophylaxis with antibiotics, time interval between first febrile UTI and first recurrence (if any) and total number of patient visits per month for UTI follow-up in the Infectious Diseases Outpatient Clinic before and after the implementation of the new guidelines (as an indicator of health services’ workload). The terms "recurrences" and "breakthrough UTIs" refer to children with at least one recurrent episode of febrile UTI and not the total number of recurrences among all children. Positive urine cultures accompanied with no clinical signs or symptoms (routine check-up) were not counted as recurrences. The primary endpoint was the total number of children with febrile UTI recurrences. Secondary endpoints were total number of performed VCUGs, presence of VUR, utilization of chemoprophylaxis, time-to-first recurrence and total number of patient visits per month for UTI follow-up in the Infectious Diseases Outpatient Clinic.

The main investigator, Dr Vasileios Liakos, was responsible for the whole process of data collection with no involvement of the three-member committee or any other researcher from the cooperating hospital. In particular, Dr Liakos performed the filtering of eligible patients according to strict inclusion and exclusion criteria, distribution of individuals in the two exposure groups, recording of relevant data and conduction of follow-up with the second group of patients (children evaluated with the revised guidelines) through telephone communication with their parents. As already mentioned, follow-up of children managed with the old approach was sustained through screening their visits in medical records of the Infectious Diseases Outpatient Clinic. Moreover, Dr Liakos performed statistical analysis of recorded data and ultimately drafted the report of the study. The data extraction form utilized for all required parameters was created using a data processing sheet in Microsoft Excel (see Appendix).
Data analysis

Statistical analysis

The study consists of individuals evaluated with two different management approaches; hence, each patient can belong in only one group. The summary measures we used for baseline characteristics were percentages for categorical data, means and SDs for normally distributed continuous variables and medians and IQRs for continuous variables with skewed distributions. If a continuous variable sustained a skewed distribution in at least one exposure group, we used medians and IQRs for both groups. Differences among categorical variables were assessed with $\chi^2$ test or Fisher’s exact test depending on expected frequencies. If at least 80% of expected counts were over 5 we used $\chi^2$ test, otherwise we preferred Fisher’s exact test. Differences among continuous variables were assessed with either Student’s t test or Mann-Whitney U test depending on variable’s normality. Parametric or non-parametric analysis was chosen after checking distributions with the utilization of Kolmogorov-Smirnov or Shapiro-Wilk tests (for total number of observations under 50), while homogeneity of variances assumption was checked with Levene’s test.

The endpoints of children with breakthrough UTIs, VCUGs performed, VUR findings and antibiotic utilization were all considered dichotomous variables. To summarize between group differences we used risks and corresponding risk ratios, while exploiting again $\chi^2$ test or Fisher’s exact test to assess them. The remaining outcomes, namely the time interval between the first episode of febrile UTI and first recurrence and number of patient visits per month in the Infectious Diseases Outpatient Clinic, were evaluated qualitatively with no further statistical testing.

Statistical package used for all aforementioned analyses was RStudio (Version 1.1.442) and p values of <0.05 were considered to be significant.

Subgroup analyses

Upon planning the study, we decided to execute a subgroup analysis measuring primary and secondary endpoints depending on age variable. Since the latest guidelines from the AAP refer to children aged 2 to 24 months, we divided all participants into two age subgroups, children up to 2 months (<2 months) and over 2 months (≥2 months) of age. In the first age subgroup (<2 months), where we continue to perform VCUG in all cases (with limited exceptions), we collectively analyzed VCUGs and subsequent VUR findings from patients with normal RBUS of both study periods merged (10/2002 - 04/2011 and 07/2014 - 11/2017), so
that possible inferences can be drawn regarding the need to undergo VCUG in infants with a first febrile UTI and normal RBUS at this age; the remaining primary and secondary endpoints mentioned above were compared separately between the two study periods. Primary and secondary outcomes for patients of the second age subgroup (≥2 months) were compared between the two exposure groups as stated in primary analysis.

**Sample size estimation**

The study is original among Greek population and, as a result, there was no data available for approximating a sample size that would detect potential statistical differences, if any, with the necessary study power. This is also clearly stated in the limitations section accompanying this research project.

**Ethical approval**

The study was approved by the AUTh Ethics Committee (Decision Protocol No. 2.66/27/02/2019) and parents or legal guardians of all children provided oral consent before enrollment.
Results

Baseline characteristics

Total study population eventually included 81 individuals, recorded sequentially via an ID number.

In the first group of patients, including those evaluated with the old management strategy, a total of 52 children (54% males, 46% females) who met the eligibility criteria were finally enrolled in the study. Median age of this group was 3.3 months (IQR: 4.5 months) and median follow-up duration was 5.3 months (IQR: 7.8 months).

In the second group of patients, including those managed with the new simplified management strategy, a total of 482 hospitalized children were initially evaluated for eligibility according to electronic records. After filtering those against the eligibility criteria, a total of 29 children (52% males, 48% females) were finally enrolled in the study. Median age of this group was 7 months (IQR: 8.5 months) and median follow-up duration was 26 months (IQR: 22 months).

Baseline characteristics of all participants in the study are summarized in Table 1.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>52</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>28 (54%)</td>
<td>15 (52%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>24 (46%)</td>
<td>14 (48%)</td>
<td></td>
</tr>
<tr>
<td>Median age in months (IQR)</td>
<td>3.3 (2, 6.5)</td>
<td>7 (1.5, 10)</td>
<td>0.43</td>
</tr>
<tr>
<td>Median follow-up in months (IQR)</td>
<td>5.3 (2.5, 10.25)</td>
<td>26 (20, 42)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1. Baseline sample characteristics of all participants

Primary analyses

Recurrences

To assess whether exposure to each management strategy affected the probability of UTI recurrence, we utilized the following variables: guideline group (independent variable) and total number of children with recurrences (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in
contingency Table 2, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Guideline group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of children</td>
<td>Old</td>
</tr>
<tr>
<td>No recurrences</td>
<td>44 (84.6%)</td>
<td>24 (82.8%)</td>
</tr>
<tr>
<td>With recurrences</td>
<td>8 (15.4%)</td>
<td>5 (17.2%)</td>
</tr>
<tr>
<td>Column Total</td>
<td>52</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 2. Contingency table of children with breakthrough UTIs among all participants

Visualization of comparing column percentages between each guideline group against total number of children with recurrences can be obtained through the following clustered bar chart (Figure 1).

![Comparison of UTI recurrence rate among each guideline group](image)

Figure 1. Clustered bar chart between children with recurrences and guideline group (all participants)

The null hypothesis (H₀) suggested that there was no association between recurrence rate and the management strategy used and the alternative hypothesis (Hₐ) that such an
association did exist. Expected frequencies indicated the use of Fisher’s exact test, showing a p-value of 1. The p-value obtained was higher than 0.05 (level of significance) and confidence interval (CI) for risk ratio included 1, so we could not reject the null hypothesis. There was no significant difference (1.8% increase) in the probability of recurrence in a child managed with the new guidelines (17.2%) compared to a child managed with the old guidelines (15.4%).

When examining gender, breakthrough febrile UTIs in the first group of children occurred in five males and three females, while in the second group all five recurrences were observed in females. Uropathogens responsible for recurrent episodes in the first group were *Escherichia coli* (N=3), *Pseudomonas* (N=2), *Klebsiella* (N=1) and unspecified species (N=2), while in the second group we found *Escherichia coli* (N=3), *Klebsiella* (N=1) and unspecified species (N=1). Among children with recurrences, median numbers of total recurrent episodes per child were 1 (IQR: 0) and 1 (IQR: 1) in the two groups respectively (P=0.13).

**Voiding cystourethrographies**

Regarding total number of VCUGs performed in each group of children, we had to assess whether exposure to each management strategy affected this number, so two variables were under examination: guideline group (independent variable) and total number of VCUGs performed (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 3, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Guideline group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Old</td>
<td>New</td>
</tr>
<tr>
<td><strong>Number of children with</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCUG performed</td>
<td></td>
<td>Old</td>
<td>New</td>
</tr>
<tr>
<td>No VCUG performed</td>
<td>0 (0%)</td>
<td>15 (51.7%)</td>
<td></td>
</tr>
<tr>
<td>VCUG performed</td>
<td>52 (100%)</td>
<td>14 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>Column Total</td>
<td>52</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Ratio</strong></td>
<td></td>
<td></td>
<td>0.48 (95% CI: 0.33 to 0.70)</td>
</tr>
</tbody>
</table>

**Table 3.** Contingency table of VCUGs performed among all participants
We concluded that the risk (probability) of VCUG performance was 2.07 times lower in the second guideline group than in the first group.

Visualization of comparing total number of VCUGs performed in each guideline group can be obtained through the following clustered bar chart (Figure 2).

![Comparison of total VCUGs performed among each guideline group](image)

**Figure 2.** Clustered bar chart between VCUGs performed and guideline group (all participants)

The null hypothesis ($H_0$) suggested that there was no association between VCUGs performed and the management strategy used and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of $x^2$ test, showing a p-value of <0.001. The p-value obtained was lower than 0.05 (level of significance) and confidence interval (CI) for risk ratio did not include 1, so we could reject the null hypothesis and accept the alternative one. There was a significant difference (51.7% decrease) in the probability of VCUG performance in a child managed with the new guidelines (48.3%) compared to a child managed with the old guidelines (100%).

When examining VCUGs’ time of performance, all 52 children evaluated with the old guidelines underwent VCUG during their first febrile UTI episode. In the second group of children, 10/14 of VCUGs were performed during the first febrile UTI and 4/14 after the first recurrent episode.
Vesicoureteral reflux

Regarding VUR findings in the VCUGs performed, we had to assess whether exposure to each management strategy affected the probability of diagnosing VUR, so two variables were under examination: guideline group (independent variable) and VUR presence (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 4, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Guideline group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VUR presence (in VCUGs performed)</td>
<td>Old</td>
<td>New</td>
</tr>
<tr>
<td>No VUR</td>
<td>33 (63.5%)</td>
<td>10 (71.4%)</td>
</tr>
<tr>
<td>VUR (of any grade)</td>
<td>19 (36.5%)</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td>Column Total</td>
<td>52</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 4. Contingency table of VUR presence among all participants

Visualization of comparing column percentages between each guideline group against total number of VUR cases can be obtained through the following clustered bar chart (Figure 3).

Figure 3. Clustered bar chart between VUR findings and guideline group (all participants)
The null hypothesis ($H_0$) suggested that there was no association between VUR presence and the management strategy used and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of Fisher’s exact test, showing a p-value of 0.75. The p-value obtained was higher than 0.05 (level of significance) and confidence interval (CI) for risk ratio included 1, so we could not reject the null hypothesis. There was no significant difference (7.9% decrease) in the probability of VUR presence in a child managed with the new guidelines (28.6%) compared to a child managed with the old guidelines (36.5%), where VCUG was performed for any reason.

When examining gender, VUR presence in the first group of children was observed in 15 males and 4 females, while in the second group in 2 males and 2 females. When measuring grade of VUR found, all 19 cases of VUR in the first group were up to III grade, while out of 4 VUR cases in the second group, 2 were up to III grade and 2 were IV grade. These IV grade cases of VUR were diagnosed during the first febrile UTI episode.

Chemoprophylaxis

To assess whether exposure to each management strategy affected the probability of receiving chemoprophylaxis, we utilized the following variables: guideline group (independent variable) and total number of children that received CAP (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 5, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Guideline group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of children</td>
<td>Old</td>
</tr>
<tr>
<td>No CAP</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>With CAP</td>
<td>52 (100%)</td>
</tr>
<tr>
<td>Column Total</td>
<td>52</td>
</tr>
</tbody>
</table>

| Risk Ratio | 0.14 (95% CI: 0.06 to 0.34) |

Table 5. Contingency table of children receiving CAP among all participants
We concluded that the risk (probability) of receiving CAP was 7.25 times lower in the second group than in the first group.

Visualization of comparing column percentages between each guideline group against total number of children receiving CAP can be obtained through the following clustered bar chart (Figure 4).

![Comparison of CAP utilization among each guideline group](Figure 4)

**Figure 4.** Clustered bar chart between CAP utilization and guideline group (all participants)

The null hypothesis (H₀) suggested that there was no association between the probability of receiving CAP and the management strategy used and the alternative hypothesis (Hₐ) that such an association did exist. Expected frequencies indicated the use of $x^2$ test, showing a p-value of <0.001. The p-value obtained was lower than 0.05 (level of significance) and confidence interval (CI) for risk ratio did not include 1, so we could reject the null hypothesis and accept the alternative one. There was a significant difference (86.2% decrease) in CAP utilization in children managed with the new guidelines (13.8%) compared to children managed with the old guidelines (100%).

All 52 children of the first group received antimicrobial prophylaxis after their first febrile UTI episode. On the contrary, out of 29 children in the second group, only 3 of them received prophylaxis after their first episode (1 because of III grade VUR and 2 because of IV grade VUR), while 1 child was initiated on prophylaxis after a recurrence (III grade VUR findings on VCUG).
**Time-to-first recurrence**

In the first group, median time-to-first recurrence was 3.8 months (IQR: 2.3 months) and all recurrences were observed within 6 months from the diagnosis of the first febrile UTI episode, except for one (10-month interval). Similarly, median time-to-first recurrence in the second group was 3 months (IQR: 2 months) and all recurrent episodes occurred within 3 months from the first episode, except for one (16-month interval). Time-to-first recurrence did not differ in the two exposure groups (P=0.40).

**Healthcare services’ workload**

The last secondary endpoint was the number of patient visits per month recorded in the Infectious Diseases Outpatient Clinic for UTI follow-up as a measure of health services’ utilization. We measured 11.5 and 4 mean patient visits per month (~65% decrease) along the time periods 2003 - 2010 and 2014 - 2017 respectively, which possibly indicates a significant reduction in healthcare facilities’ utilization.

**Subgroup analyses**

**Children ≥2 months**

In the first group of patients, including those evaluated with the old management strategy, a total of 41 children (46% males, 54% females) who met the eligibility criteria were finally enrolled in the study. Median age of this group was 4 months (IQR: 4 months) and median follow-up duration was 5.5 months (IQR: 7.5 months).

In the second group of patients, including those evaluated with the new simplified management strategy, a total of 18 children (22% males, 78% females) were finally enrolled in the study. Median age of this group was 10 months (IQR: 5.1 months) and median follow-up duration was 26 months (IQR: 23.5 months).

Baseline characteristics of this age subgroup are summarized in Table 6.
---|---|---|---
Total, n | 41 | 18 | 0.08
Males, n (%) | 19 (46%) | 4 (22%) | 0.08
Females, n (%) | 22 (54%) | 14 (78%) | 0.08
Median age in months (IQR) | 4 (3, 7) | 10 (7.6, 12.8) | <0.001
Median follow-up in months (IQR) | 5.5 (2.5, 10) | 26 (21, 44.5) | <0.001

Table 6. Baseline sample characteristics of children ≥2 months

Recurrences

To assess whether exposure to each management strategy affected the probability of UTI recurrence, we utilized the following variables: guideline group (independent variable) and total number of children with recurrences (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 7, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

| ≥2 Months | Guideline group |
| --- | --- | --- |
| Total number of children | Old | New | Row Total |
| No recurrences | 36 (87.8%) | 13 (72.2%) | 49 |
| With recurrences | 5 (12.2%) | 5 (27.8%) | 10 |
| Column Total | 41 | 18 | 59 |

Risk Ratio | 2.28 (95% CI: 0.75 to 6.90)

Table 7. Contingency table of children ≥2 months with breakthrough UTIs
Visualization of comparing column percentages between each guideline group against total number of children with recurrences can be obtained through the following clustered bar chart (Figure 5).

![Comparison of UTI recurrence rate among each guideline group](image)

**Figure 5.** Clustered bar chart between children with recurrences and guideline group (children ≥2 months)

The null hypothesis ($H_0$) suggested that there was no association between recurrence rate and the management strategy used and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of Fisher’s exact test, showing a p-value of 0.26. The p-value obtained was higher than 0.05 (level of significance) and confidence interval (CI) for risk ratio included 1, so we could not reject the null hypothesis. There was no significant difference (15.6% increase) in the probability of recurrence in a child managed with the new guidelines (27.8%) compared to a child managed with the old guidelines (12.2%).

When examining gender, breakthrough febrile UTIs in the first group of children occurred in three males and two females, while in the second group all five recurrences were observed in females. Uropathogens responsible for recurrent episodes in the first group were *Pseudomonas* (N=2), *Klebsiella* (N=1) and unspecified species (N=2), while in the second group we found *Escherichia Coli* (N=3), *Klebsiella* (N=1) and unspecified species (N=1). Among children with recurrences, median numbers of total recurrent episodes per child were 1 (IQR: 0) and 1 (IQR: 1) in the two groups respectively (P=0.44).
Voiding cystourethrographies

Regarding total number of VCUGs performed in each group of children, we had to assess whether exposure to each management strategy affected this number, so two variables were under examination: guideline group (independent variable) and total number of VCUGs performed (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 8, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th>≥2 Months</th>
<th>Guideline group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No VCUG performed</td>
<td>Old</td>
<td>New</td>
<td>Row Total</td>
<td></td>
</tr>
<tr>
<td>No VCUG performed</td>
<td>0 (0%)</td>
<td>11 (61.1%)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>VCUG performed</td>
<td>41 (100%)</td>
<td>7 (38.9%)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Column Total</td>
<td>41</td>
<td>18</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Contingency table of VCUGs performed among children ≥2 months

We concluded that the risk (probability) of VCUG performance was 2.57 times lower in the second guideline group than in the first group.

Visualization of comparing total number of VCUGs performed in each guideline group can be obtained through the following clustered bar chart (Figure 6).

Figure 6. Clustered bar chart between VCUGs performed and guideline group (children ≥2 months)
We formed the null hypothesis ($H_0$) that there was no association between VCUGs performed and the treatment strategy used and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of Fisher’s exact test showing a p-value of <0.001. The p-value obtained was lower than 0.05 (level of significance) and confidence interval (CI) for risk ratio did not include 1, so we could reject the null hypothesis and accept the alternative one. There was a significant difference (61.1% decrease) in the probability of VCUG performance in a child managed with the new guidelines (38.9%) compared to a child managed with the old guidelines (100%).

When examining VCUGs' time of performance, all 41 children evaluated with the old guidelines underwent VCUG during their first febrile UTI episode. In the second group, 3/7 of VCUGs were performed during the first febrile UTI and 4/7 after the first recurrent episode.

**Vesicoureteral reflux**

Regarding VUR findings in the VCUGs performed, we had to assess whether exposure to each management strategy affected the probability of diagnosing VUR, so two variables were under examination: guideline group (independent variable) and VUR presence (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 9 where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th>≥2 Months</th>
<th>Guideline group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VUR presence (in VCUGs performed)</td>
<td>Old</td>
</tr>
<tr>
<td>No VUR</td>
<td>26 (63.4%)</td>
</tr>
<tr>
<td>VUR (of any grade)</td>
<td>15 (36.6%)</td>
</tr>
<tr>
<td>Column Total</td>
<td>41</td>
</tr>
<tr>
<td>Risk Ratio</td>
<td>1.17 (95% CI: 0.46 to 3.02)</td>
</tr>
</tbody>
</table>

**Table 9.** Contingency table of VUR presence among children ≥2 months
Visualization of comparing column percentages between each guideline group against total number of VUR cases can be obtained through the following clustered bar chart (Figure 7).

**Figure 7.** Clustered bar chart between VUR findings and guideline group (children ≥2 months)

The null hypothesis ($H_0$) suggested that there was no association between VUR presence and the management strategy used and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of Fisher’s exact test, showing a $p$-value of 1. The $p$-value obtained was higher than 0.05 (level of significance) and confidence interval (CI) for risk ratio included 1, so we could not reject the null hypothesis. There was no significant difference (6.3% increase) in the probability of VUR presence in a child managed with the new guidelines (42.9%) compared to a child managed with the old guidelines (36.6%), where VCUG was performed for any reason.

When examining gender, VUR presence in the first group of children was observed in 11 males and 4 females, while in the second group in 1 male and 2 females. When measuring grade of VUR found, all 15 cases of VUR in the first group were up to III grade, while out of 3 VUR cases in the second group, 2 were up to III grade and 1 was IV grade. This IV grade case of VUR was diagnosed during the first febrile UTI episode.
Chemoprophylaxis

To assess whether exposure to each management strategy affected the probability of receiving chemoprophylaxis, we utilized the following variables: guideline group (independent variable) and total number of children that received CAP (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 10, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<table>
<thead>
<tr>
<th>≥2 Months</th>
<th>Guideline group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of children</td>
<td>Old</td>
</tr>
<tr>
<td>No CAP</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>With CAP</td>
<td>41 (100%)</td>
</tr>
<tr>
<td>Column Total</td>
<td>41</td>
</tr>
</tbody>
</table>

Risk Ratio | 0.17 (95% CI: 0.06 to 0.47)

Table 10. Contingency table of children ≥2 months receiving CAP

We concluded that the risk (probability) of receiving CAP was 6 times lower in the second group than in the first group.

Visualization of comparing column percentages between each guideline group against total number of children receiving CAP can be obtained through the following clustered bar chart (Figure 8).

Figure 8. Clustered bar chart between CAP utilization and guideline group (children ≥2 months)
The null hypothesis ($H_0$) suggested that there was no association between the probability of receiving CAP and the management strategy used and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of Fisher’s exact test, showing a p-value of <0.001. The p-value obtained was lower than 0.05 (level of significance) and confidence interval (CI) for risk ratio did not include 1, so we could reject the null hypothesis and accept the alternative one. There was a significant difference (83.3% decrease) in CAP utilization in children managed with the new guidelines (16.7%) compared to children managed with the old guidelines (100%).

All 41 children of the first group received antimicrobial prophylaxis after their first febrile UTI episode. On the contrary, out of 18 children in the second group, only 2 of them received prophylaxis after their first episode (1 because of III grade VUR and 1 because of IV grade VUR), while 1 child was initiated on prophylaxis after a recurrence (III grade VUR findings on VCUG).

**Time-to-first recurrence**

In the first group, median time-to-first recurrence was 5 months (IQR: 3 months) and all recurrences were observed within 6 months from the diagnosis of the first febrile UTI episode, except for one (10-month interval). Similarly, median time-to-first recurrence in the second group was 3 months (IQR: 3 months) and all recurrent episodes occurred within 3 months from the first episode, except for one (16-month interval). Time-to-first recurrence did not differ in the two exposure groups (P=0.52).

**Children <2 months**

In the first group of patients, including those evaluated during the time period 10/2002 - 04/2011, a total of 11 children (82% males, 18% females) who met the eligibility criteria were finally enrolled in the study. Median age of this group was 40 months (IQR: 12 months) and median follow-up duration was 3 months (IQR: 9.8 months).

In the second group of patients, including those evaluated during the time period 07/2014 - 11/2017, a total of 11 children (100% males) were finally enrolled in the study. Median age of this group was 32 months (IQR: 28.5 months) and median follow-up duration was 24 months (IQR: 15 months). No recurrences were observed in this group of patients.

Baseline characteristics of this age subgroup are summarized in Table 11.
<2 Months | Time periods | p-value
--- | --- | ---
Total, n | 11 | 11 |
Males, n (%) | 9 (82%) | 11 (100%) |
Females, n (%) | 2 (18%) | 0 (0%) |
Median age in months (IQR) | 40 (32.5, 44.5) | 32 (17, 45.5) |
Median follow-up in months (IQR) | 3 (2.3, 12) | 24 (19, 34) |

Table 11. Baseline sample characteristics of children <2 months

Recurrences

To assess whether exposure to each time period of management affected the probability of UTI recurrence, we utilized the following variables: time period (independent variable) and total number of children with recurrences (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 12, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.

<2 Months | Time period
--- | ---
Total number of children | | | 19
No recurrences | 8 (72.7%) | 11 (100%) |
With recurrences | 3 (27.3%) | 0 (0%) |
Column Total | 11 | 11 |
Risk Ratio | 0.14 (95% CI: 0.008 to 2.48)

Table 12. Contingency table of children <2 months with breakthrough UTIs

Visualization of comparing column percentages between each time period against total number of children with recurrences can be obtained through the following clustered bar chart (Figure 9).
The null hypothesis ($H_0$) suggested that there was no association between recurrence rate and the time period of management and the alternative hypothesis ($H_a$) that such an association did exist. Expected frequencies indicated the use of Fisher’s exact test, showing a p-value of 0.21. The p-value obtained was higher than 0.05 (level of significance) and confidence interval (CI) for risk ratio included 1, so we could not reject the null hypothesis. There was no significant difference (27.3% decrease) in the probability of recurrence in a child managed during the second time period (0%) compared to a child managed during the first time period (27.3%).

When examining gender, breakthrough febrile UTIs in the first group of children occurred in two males and one female, while in the second group no recurrences were observed. Uropathogens responsible for recurrent episodes in the first group were *Escherichia Coli* (N=2) and unspecified species (N=1). Among children with recurrences in the first group, all of them suffered only one recurrent episode.

**Voiding cystourethrogramies**

Lack of evidence regarding the need for VCUG performance in children aged <2 months after their first febrile UTI with normal RBUS findings resulted in merging all children managed during the two time periods together. A total of 81.8% (18/22) of children with normal RBUS
findings in this age subgroup were evaluated with VCUG and all 18 VCUGs were performed during the first febrile UTI episode.

**Vesicoureteral reflux**

Regarding VUR presence in the VCUGs performed, confirmation of VUR was established in 27.8% (5/18) of cases. When examining gender, all five VUR cases were diagnosed in males. When measuring grade of VUR found, four cases were up to III grade and one was IV grade. This IV grade case of VUR was diagnosed during the first febrile UTI episode.

Visualization of all VUR cases can be obtained through the following bar chart (Figure 10).

**Chemoprophylaxis**

To assess whether exposure to each time period of management affected the probability of receiving chemoprophylaxis, we utilized the following variables: time period (independent variable) and total number of children that received CAP (dependent variable). Both variables constitute dichotomous variables and their combined descriptive statistics are summarized in contingency Table 13, where observed absolute frequencies, risks, marginal totals and the corresponding risk ratio are presented.
We concluded that the risk (probability) of receiving CAP was 11 times lower in the second time period than in the first time period.

Visualization of comparing column percentages between each time period against total number of children receiving CAP can be obtained through the following clustered bar chart (Figure 11).

The null hypothesis ($H_0$) suggested that there was no association between the probability of receiving CAP and the time period of management and the alternative hypothesis ($H_a$) that
such an association did exist. Expected frequencies indicated the use of \( \chi^2 \) test, showing a p-value of <0.001. The p-value obtained was lower than 0.05 (level of significance) and confidence interval (CI) for risk ratio did not include 1, so we could reject the null hypothesis and accept the alternative one. There was a significant difference (90.9% decrease) in CAP utilization in children managed during the second time period (9.1%) compared to children managed during the first time period (100%).

All 11 children of the first time period received antimicrobial prophylaxis after their first febrile UTI episode. On the contrary, out of 11 children in the second time period, only 1 of them received prophylaxis after the first episode (IV grade VUR findings on VCUG).

**Time-to-first recurrence**

During the first time period, median time-to-first recurrence was 3 months (IQR: 0.8 months) and all recurrences were observed within 6 months from the diagnosis of the first febrile UTI episode, while no recurrences were observed during the second time period.
Discussion

Main findings

Regarding our primary analyses, baseline characteristics of all 81 individuals included were comparable in terms of gender and age, but differed in follow-up duration (P<0.001). Median follow-up duration of patients managed according to the 1999 guidelines was 5.3 months, achieved through manually scanning the available patient revisit intervals recorded in the Infectious Diseases Outpatient Clinic and the electronic database of hospitalized patients, while the corresponding median follow-up for patients evaluated with the revised 2011 guidelines was 26 months, achieved via telephone communication. Theoretically, the above difference could introduce bias, but current bibliography (14) suggests that the vast majority of breakthrough UTIs occur within the first 6-month period after the initial febrile episode, rendering the follow-up duration of the first group clinically sufficient to assess recurrences.

When examining the primary endpoint, number of children with breakthrough UTIs, we observed no difference between the two exposure groups. In children with a first febrile UTI episode, applying one of the two management strategies, meaning the old and the new simplified policy, does not affect the rate of recurrence. In a similar manner, we found a 51.7% absolute decrease (P<0.001) in the number of VCUGs performed after the implementation of the revised approach, reinforcing the argument that the new approach can possibly reduce health services' overload and patient discomfort. Furthermore, we showed no difference in the probability of finding VUR of any grade in a child managed with the new guidelines compared to a child managed with the old guidelines, where VCUG was performed for any reason. This finding proves of vital importance with serious implications regarding the need to reduce patient and parental anxiety throughout the evaluation process. In terms of CAP utilization, total number of children prescribed antibiotic prophylaxis sustained an absolute reduction of 86.2% (P<0.001) after the implementation of the simplified approach, minimizing the drawbacks of bacterial resistance and antibiotics' adverse effects. Finally yet importantly, all UTI recurrences among the two groups were observed within a 6-month period after the initial episode except for one in each group, so the error introduced because of different follow-up duration of the two proves clinically non-significant.

Another interesting endpoint was the number of patient visits per month for UTI follow-up in the Infectious Diseases Outpatient Clinic, in order to assess the impact of the implementation of the 2011 revision on health services’ utilization. We observed that patient visits were markedly reduced during the time period 2014 - 2017 compared to the time period 2003 - 2010.
(4 vs 11.5 visits per month). This adds up to all aforementioned results, suggesting a beneficial effect on healthcare facility utilization, economic costs and possibly on parental absence from work, patient anxiety and discomfort.

Subgroup analyses according to age were conducted based on the fact that the 2011 revision proposed by the AAP included children 2 to 24 months of age. As a result, we chose to examine all primary and secondary endpoints among children ≥2 months and <2 months. Baseline characteristics of the age subgroup ≥2 months were comparable in terms of gender, but differed in age and follow-up duration (P<0.001). Similarly to reasons expressed in our primary analyses, follow-up duration of the two groups were probably clinically sufficient to detect recurrences, although different. Comparison of UTI recurrence rate among each guideline group showed a 15.6% absolute increase in the probability of recurrence in children evaluated with the new approach (P=0.26). Similar results were highlighted in the RIVUR trial (11), where antibiotic prophylaxis halved the risk of recurrences compared to children who received placebo. This notwithstanding, the occurrence of renal scarring in the RIVUR trial did not differ in the two arms, children under antibiotics vs children under placebo, questioning the clinical significance of preventing recurrences when juxtaposed with the issues of bacterial resistance and patient discomfort. In addition, among children who suffered a recurrent episode, we observed a median number of one recurrence per child in both exposure groups (P=0.44). As a result, even if children with recurrences may slightly be increased in the new guideline group, we almost miss one recurrent episode per child, a finding consistent with the RIVUR trial. Regarding our secondary endpoints, we observed a 61.1% absolute decrease (P<0.001) in the number of VCUGs performed after the implementation of the new guidelines and no difference in the probability of detecting VUR among patients of the two groups, with obvious impact on healthcare services’ utilization and patient’s family discomfort. In terms of CAP utilization, total number of children prescribed antibiotic prophylaxis sustained an absolute reduction of 83.3% (P<0.001), while all recurrences occurred again within a 6-month period after the first episode, addressing a positive impact on bacterial resistance and any bias introduced due to different follow-up intervals of the two groups.

There is currently no evidence regarding proper management and evaluation of children <2 months of age with a first febrile UTI episode. These patients are likely to undergo RBUS, VCUG and DMSA scan after their initial episode, but CAP utilization is generally adopted in high-grade VUR patients (grades >III). As a result, we chose to collectively merge all children <2 months in terms of VCUGs performed and subsequent VUR findings, while recurrences and CAP utilization were examined separately between the two time periods. We found that
the policy of non-prescribing CAP in such infants in the absence of significant VUR does not seem to be associated with a significant increase in UTI recurrences, while CAP sustained an absolute 90.9% decrease. In addition, 18 children were evaluated with VCUG and VUR was established in 5 of them. When measuring grade of VUR found, four cases were up to III grade and one was IV grade. The IV grade VUR case was diagnosed during the first febrile UTI episode (with normal RBUS findings), so no VUR patients were missed. Consequently, the approach of VCUG performance in this age subgroup during the evaluation of the first UTI episode led to only one high-grade VUR patient missing CAP. These findings question the policy of performing VCUG in all infants <2 months of age with normal RBUS, addressing the need for further investigation in larger patient sample sizes. Taken together, the results of our subgroup analyses point towards a possible extension of the pediatric population for which the simplified 2011 guidelines could be endorsed.

**Comparison with literature**

With the present study, we attempted to assess the impact of the AAP guidelines regarding the first febrile UTI episode in children. This notwithstanding, several associations and societies suggest different approaches in terms of imaging and CAP utilization during the whole evaluation process of the first episode, mainly due to evidence inconsistency.

The National Institute for Health and Care Excellence (NICE) (15) suggests RBUS conduction in all infants <6 months old and children >6 months with atypical UTI. VCUG conduction is recommended in all infants <6 months old with abnormal RBUS findings or atypical UTI and strongly considered in children >6 months with hydronephrosis, oliguria, non- E. coli isolates or family history of VUR. DMSA scan is suggested in children <3 years old with atypical UTI, while CAP utilization is not recommended. As a result, NICE also heads towards simplifying the management of the first UTI episode, with RBUS being the main imaging tool, VCUG and DMSA utilization in specific circumstances and omitting CAP.

The European Association of Urology (EAU) in collaboration with the European Society for Pediatric Urology (ESPU) have also provided recommendations (16) for children presenting with UTI. During the first febrile episode, RBUS is recommended in all children, while VCUG and DMSA are reserved for cases of female infants, suspicion of VUR, pyelonephritis, upper tract dilatation or recurrent episodes. Diagnosis of VUR is established with two available approaches: the bottom-up method (VCUG and, if positive, DMSA scan) or the top-down method (DMSA scan and, if positive, VCUG). Recommendations also suggest that antibacterial prophylaxis is beneficial, particularly in females with ≥III grade VUR. In this way,
patient discomfort seems markedly reduced along the whole imaging process, but CAP utilization is not abolished.

In addition, a working group of the Italian Society of Pediatric Nephrology (ISPN) formed clinical practice guidelines concerning UTI management in children 2 months to 3 years of age (17). Conduction of RBUS is indicated in all children after the first febrile episode, reserving further imaging techniques for patients with abnormal RBUS findings, risk factors or recurrences. Antimicrobial prophylaxis is considered only in children awaiting VCUG performance, sustaining ≥III grade VUR or suffering a recurrence. Among other trials, guidelines regarding CAP were also based on the Swedish reflux trial (9), a well-designed RCT including children aged 1-2 years with VUR grade ≥III. Prophylaxis seemed to reduce recurrences in females, while males did not benefit from this approach.

Overall, our study and current generated data share the common characteristic of pointing towards the need for simplification of the imaging evaluation in pediatric UTIs. Total risks and benefits indicate the significance of RBUS conduction during the first episode, but a personalized management will assess the need for further imaging modalities. On the other hand, there seems to be no consensus in prophylaxis’ efficacy and, consequently, additional research efforts on the subject are expected.

**Strengths and limitations**

A retrospective cohort study is suitable for the clinical question we addressed (prevention of UTIs in children) and seemed feasible, since there was an organized database of children in the 3rd Pediatric Department of "Hippokration" Hospital treated for urinary tract infections with all their basic characteristics extensively recorded, while the outcomes under question were adequately expected to be recorded through our communication with their family members. In addition, the impact of the new simplified approach for UTIs in children was never assessed in a Greek pediatric population until now. Cohort studies allow us to calculate the incidence of a disease (UTI recurrence) in exposure groups (patients evaluated either with the old or the revised management strategy), so we were able to measure absolute risks, relative risks and risk differences. The retrospective characteristic overpassed the drawbacks of time restriction, cost effectiveness and availability of specific medical infrastructures, rendering the adoption of a retrospective cohort design a good choice in terms of maximizing the credibility of our findings.
This notwithstanding, the selection of a retrospective cohort study design is accompanied by a series of methodological issues and constraints. The study is original to the population of Greece and, consequently, there was no data available to approximate a sample size that would allow for detection of statistical differences, if any, with the necessary study power. Moreover, introduction of serious selection and information bias could not be avoided. During the formation of the two exposure groups, our initial step was to scan the hospital’s hand-written database for children hospitalized with the diagnosis of febrile UTI and subsequently search the corresponding discharge summaries in the hospital’s electronic database. Missing data (urine culture results, telephone numbers etc) was observed throughout the whole process with an unpredictable impact on our results. Questionable adherence of clinicians to the AAP guidelines and arbitrary selection of children’s hospitalization time period possibly magnify the aforementioned bias. In addition, the main investigator, Dr Liakos, was solely responsible for data collection with no involvement of the three-member committee or any other researcher from the cooperating hospital, making the absence of double-checking another possible limitation. Answers of study participants’ family members differed in terms of accuracy and completeness, highlighting the limitation of recall bias. Last but not least, potential confounding factors affecting both the incidence as well as the accuracy of diagnosis of UTI recurrences, such as parental awareness and quality of primary health care, were not assessed.

**Implications for clinical practice or research**

Admitting possible limitations of our work, it is obviously advisable that further research needs to be encouraged regarding febrile UTI management in the pediatric population. A well-designed randomized controlled trial could overcome our study’s restrictions and provide Greek scientific community with quality data on the matter, minimizing bias and maximizing the internal and external validity of generated evidence. In addition, current literature examined the evaluation approach of the first febrile UTI episode in children 2 to 24 months of age, because of UTI’s prevalence in these age subgroups. However, systematically omitting individuals under 2 months of age and older than 24 months results in uncertain clinical decisions in everyday practice. Although we tried to include children aged up to 4 years in our study, CPGs regarding certain age subgroups need to be established. Another issue to be examined is the optimal duration of antibiotic treatment in UTIs (currently 7-14 days of therapy is recommended) (18), in order to limit antimicrobial exposure and reduce adverse effects and antimicrobial resistance. Finally, human and bacterial genome characteristics seem to play a major role in introducing UTI risk factors in children (19,20), while equally important attention
is called to bowel and bladder dysfunction (BBD) (21), which is believed to correlate with UTI recurrences, but these remain to be assessed. The results of our study may also encourage similar research efforts towards revision or simplification of common infections' treatment strategies in the pediatric field, anticipating massive benefits.
Conclusion

In the present study, we attempted to examine the impact of the new simplified approach proposed by AAP in 2011 in a Greek pediatric population, reiterating key steps throughout the algorithm of preventing febrile UTIs in this age subgroup. All children continue to undergo RBUS after their first UTI, but the need for VCUG, DMSA scan and long-term antibiotic chemoprophylaxis has been strongly questioned and stringent indications for these have been determined in the 2011 guidelines. In full concordance with existing evidence, our study showed that recurrence rates in children evaluated with the new strategy (2011) did not differ compared to children managed with the older approach (1999). Health services' overload and patient morbidity and discomfort can be significantly decreased, since total number of VCUGs performed was substantially diminished with the new approach. Similar reduction was observed in the number of patient visits per month in the Infectious Diseases Outpatient Clinic. Administration of antimicrobial prophylaxis was also markedly reduced following the implementation of the new guidelines in children of Northern Greece, with a potentially beneficial effect on socioeconomic costs and bacterial resistance. These findings are believed to expand existing medical evidence on this subject and encourage similar innovative research efforts to cover knowledge gaps, such as proper evaluation of children aged <2 months and >24 months after their first febrile UTI episode.
References


Appendix

Data dictionary

<table>
<thead>
<tr>
<th>ID</th>
<th>A unique number for each participant in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full name</td>
<td>Surname, Name</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Age</td>
<td>Age in months or years</td>
</tr>
<tr>
<td>Father’s name</td>
<td>Surname, Name</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Possible diagnosis upon admission</td>
</tr>
<tr>
<td>Hospitalization period</td>
<td>Date of admission and discharge (dd/mm/yyyy)</td>
</tr>
<tr>
<td>Contact number</td>
<td>A 10-digit telephone number</td>
</tr>
<tr>
<td>Discharge summary</td>
<td>Availability of discharge summary (Yes/No)</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Yes/No (if No, reasons mentioned)</td>
</tr>
<tr>
<td>Pyuria/bacteriuria</td>
<td>Presence of pyuria or bacteriuria (Yes/No)</td>
</tr>
<tr>
<td>Uropathogen</td>
<td>Name of the exact isolate from urine culture</td>
</tr>
<tr>
<td>CFUs/mL</td>
<td>Amount of colony - forming units per mL of the uropathogen in urine culture</td>
</tr>
<tr>
<td>Urine specimen</td>
<td>Method used to obtain urine specimen</td>
</tr>
<tr>
<td>RBUS</td>
<td>Full RBUS findings (1st episode, recurrences)</td>
</tr>
<tr>
<td>VCUG</td>
<td>Full VCUG findings (1st episode, recurrences)</td>
</tr>
<tr>
<td>DMSA</td>
<td>Full DMSA findings (1st episode, recurrences)</td>
</tr>
<tr>
<td>CAP</td>
<td>Yes/No (if Yes, name of antibiotic utilized)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Total follow-up duration in months</td>
</tr>
<tr>
<td>Recurrences</td>
<td>Total number of recurrent episodes per child</td>
</tr>
<tr>
<td>Other information</td>
<td>Any additional information provided by children’s families or legal guardians</td>
</tr>
<tr>
<td>Contact date</td>
<td>dd/mm/yyyy</td>
</tr>
<tr>
<td>Contact clinician</td>
<td>Surname, Name</td>
</tr>
</tbody>
</table>

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