Review Article

Imaging investigation after urinary tract infection in childhood: narrative review of current recommendations

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Background and Objective: Urinary tract infections (UTIs) are one of the most common bacterial infections in children. The imaging exams that take place after the occurrence of UTI have the main goal of detecting congenital anomalies of the kidney and urinary tract (CAKUT). The value of imaging investigation relies on guiding the management of the patient and directing measures to prevent recurrent infections and to avoid possible kidney scars. Currently, there has been a general trend to restrict the number of imaging tests performed in clinical practice as can be seen in the most important guidelines regarding the management of patients with febrile UTI. The guidelines from the American Association of Pediatrics (AAP), the National Institute for Health and Care Excellence (NICE), and the European Association of Urology (EAU)/European Society for All Pediatric Urology (ESPU) made recommendations in this regard. We believe that the critical discussion about the advantages and disadvantages of the different guidelines and protocols proposed is important for pediatricians and nephrologists and helps to define the best approach for patients. In this matter, this review aimed to provide a critical view of imaging investigation methods and guidelines after UTIs in pediatric patients.

Methods: The authors performed a non-systematic search in PubMed, Cochrane, Scopus, SciELO and in renowned books from the subjects of pediatric nephrology and pediatric urology published up to August 5th, 2021, and critically selected and independently reviewed articles written mainly in English or Portuguese to produce this narrative review.

Key Content and Findings: In this narrative review, shortcomings of different imaging guidelines and examinations after urinary tract infections in children are explored, while the principles and advantages of distinct imaging methods are highlighted. We find that, while an initial renal and bladder ultrasonography is of great value, more invasive exams need to be carefully selected to identify patients at risk for further complications whilst minimizing distress and other consequences to the child.

Conclusions: A renal ultrasonography with good quality of images and examined by an expert is generally recommended as initial screening after UTI. Additional imaging exams depend on findings provided by renal ultrasonography.

Keywords: Urinary tract infection (UTI); congenital anomalies of the kidney and urinary tract (CAKUT); renal ultrasonography; voiding cystourethrography (VCUG); renal scintigraphy

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Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections among children. UTIs have a prevalence of 7.0% among infants with fever (1) and of 7.9% in patients aged less than 19 years old and that present with fever or urinary symptoms. In children, the rate of UTI recurrence can reach values of approximately 30% to 50% (2), and the number of ambulatory visits for this age group approaches 1.5 million every year in the USA (3). This epidemiological data shows the relevance of this clinical condition to public health, with elevated morbidity, especially among infants.

The imaging exams that take place in the occurrence of UTIs have the main goal of detecting congenital anomalies of the kidney and urinary tract (CAKUT). Through imaging, it is possible to detect kidney scars, obstructive lesions, and vesicoureteral reflux (VUR), which can contribute to the development of late complications such as arterial hypertension and chronic kidney disease (CKD). A variable percentage of 10% to 30% of children with UTI develop kidney scars. UTIs can be the first symptom of CAKUT in about 30% of infants (4,5). With this in mind, the value of imaging investigation resides upon the relevance of the findings to the clinical management of the patient, directing measures to be taken to reduce possible complications or to prevent recurring infections. These measures consist mainly of treatment followed by prophylaxis with low-dose antibiotics. Other recommendations such as immunostimulating agents, probiotics, and circumcision have also been investigated (6).

In this context, the most commonly used imaging methods after UTIs are renal and bladder ultrasound (RBUS), voiding cystourethrography (VCUG), and dimercaptosuccinic acid (DMSA) static renal scintigraphy. The RBUS is a practical and accessible exam, capable of providing a wide range of information about the anatomy of the urinary tract, although highly reliant on equipment quality and the operator's expertise. It is also insufficient for the diagnosis of kidney scars or VUR. The VCUG is the gold standard for the diagnosis of VUR, but it requires urethral catheterization, use of contrast media, exposure to ionizing radiation, and public micturition, factors that result in an invasive and distressing procedure for parents and patients. The static renal scintigraphy with DMSA is efficient in the detection of cortical damage or kidney scars, but it is also associated with radiation exposure, as it requires the venous administration of radiopharmaceuticals. With this in mind, a general trend that points towards restricting the number of imaging exams performed in clinical practice can be observed in the most important guidelines regarding the approach of the patient with a febrile UTI, which include the guidelines from the American Association of Pediatrics (AAP), the National Institute for Health and Care Excellence (NICE), and the European Association of Urology (EAU)/European Society for Pediatric Urology (ESPU). These recommendations question the validity of performing a routine VCUG and static renal scintigraphy after the first episode of UTI. The recent literature also questions the role of imaging exams in establishing the patient's prognosis. These questionings mainly rely upon the controversial effectiveness of antibiotic prophylaxis in preventing the recurrence of UTIs or the occurrence of kidney scars and upon the low frequency of detection of high-grade VUR.

The routine use of antibiotic prophylaxis has been broadly debated and questioned by systematic reviews and randomized controlled trials (RCTs) (7-10) that indicate the chances of drug resistance and lead to the conclusion that low-dose antibiotics should only be indicated to patients that present severe malformations or with a higher risk for recurring infections (11). There are, on the other side, studies that suggest beneficial effects on the use of prophylaxis, demonstrating that this research field is still highly controversial (12).

Similarly, a large amount of studies has taken place intending to test the relevance of the diagnosis of VUR for the patient's prognosis, challenging the validity of VCUG as a routine exam. Even though divergences exist, the literature suggests that grades I–III reflux have a high ratio of spontaneous resolution with time (13), and, especially for grades I–II, there is no sufficient evidence to support its association with the development of kidney scars (14). Given the lower prevalence of grades IV–V VUR, the performance of routine VCUG has, therefore, seen progressively lower sustenance.

Considering the controversies and different guidelines on imaging investigation after UTI, we believe that a narrative review that discusses the advantages and disadvantages of each imaging method and current guidelines is of interest to pediatricians and pediatric nephrologists. Therefore, the main objective of this review is to provide a critical overview of the main

Table 1 The search strategy summary

Items	Specification
Date of search	July 3rd, 2021 to August 5th, 2021
Databases and other sources searched	PubMed, Cochrane, Scopus, SciELO, and in renowned books from the subjects of pediatric nephrology and pediatric urology
Search terms used	"Urinary tract infection", "Renal and Bladder Ultrasound", "Voiding Cystourethrography", "Renal Scintigraphy", "CAKUT", "Imaging Investigation", "Renal Ultrasonography", "Pediatric Guidelines"
Timeframe	There were no temporal limits after the search started until the submission date on August 5th, 2021
Inclusion and exclusion criteria	We emphasized peer-reviewed articles, guidelines (AAP, NICE, EAU/ESPU), systematic reviews, meta-analyses, prospective cohort and observational studies. Limiting us to publications in English, Spanish, and Portuguese critically reviewed and carefully selected
Selection process	The articles were selected independently by two authors (LGPPJ and BCCV). All authors collectively reviewed and analysed the articles

CAKUT, congenital anomalies of the kidney and urinary tract; AAP, American Association of Pediatrics; NICE, National Institute for Health and Care Excellence; EAU, European Association of Urology; ESPU, European Society for Pediatric Urology.

methods and guidelines of imaging investigation after UTIs in pediatric patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-86/rc).

Methods

The information utilized to write this article was obtained independently by the authors, who performed a non-systematic search in the following databases: PubMed, Cochrane, Scopus, and SciELO, and in renowned books from the subjects of pediatric nephrology and pediatric urology (*Table 1*). To attain adequate information, search strategies included terms from the Medical Subject Headings as: "Urinary tract infection", "Renal and Bladder Ultrasound", "Voiding Cystourethrography", "Renal Scintigraphy", "CAKUT", "Imaging Investigation", "Renal Ultrasonography", "Pediatric Guidelines". We emphasized peer-reviewed articles published recently, written in English or Portuguese, guidelines, systematic reviews, meta-analyses, prospective cohort, and observational studies, which were critically reviewed and carefully selected by the authors. The search was performed on July 2021 without temporal limits and included the guidelines from AAP, NICE and EAU/ESPU.

Imaging methods

Ultrasonography

General principles

Ultrasonography is the primary exam employed for the initial assessment of the kidneys and urinary tract (6). It consists of a non-invasive, versatile, and relatively economical procedure that utilizes high-frequency sound waves to produce real-time images of the inspected region, allowing the detection of urinary tract dilations and anomalies (15). An alternating electric current in the crystals of a transducer emits the waves. A technician performs the exam in direct contact with the patient, who is normally in the supine position (16).

The most widely used modality of RBUS is the "two-dimensional gray-scale imaging", which uses information regarding the amplitude and time of detection of the sound waves reflected by tissues to generate images in different gray levels. In this modality, the amplitude of the reflected waves provides data about the tissue echogenicity, what corresponds to different levels of brightness shown on the screen. A computer determines, with high precision, the spatial distribution of the evaluated structures and analyzes the time necessary for the wave to get back to the font. This process allows the quick generation of trustworthy images of the kidney and urinary tract anatomy (17).

Different from "gray-scale" imaging, Doppler

ultrasonography relies upon the homonymous effect to permit the evaluation of fluid flows in the patient's body, especially blood. The reflection of the sound waves on moving bodies, like red blood cells, generates changes in their frequencies and phases, which, once detected by the ultrasonography device, can be used to describe the movement precisely. Even though urine does not have abundant components like erythrocytes, it is possible to use this modality of US to detect bubbles created by the flow of gases dissolved in it, which represents potential in the analysis of urodynamics (18).

Another ultrasound modality is the contrast-enhanced voiding urosonography (CeVUS), which utilizes contrasts based on microscopic bubbles coated by phospholipids to enhance and amplify the results and applicability of the exam (19). It will be discussed in more detail later.

Applications

Ultrasonography is the primary exam for the evaluation of patients after UTIs as a result of its capacity of detecting CAKUT and other disorders (calculi, abscesses, tumors), which indicate the necessity of further interventions or subsequent evaluations for the patient (20). The renal and bladder ultrasound (RBUS) permits a precise evaluation of kidney size, parenchymal thickness, and the lower urinary tract structures (21). RBUS is the first-line exam for the detection of upper urinary tract abnormalities, such as dilations (hydronephrosis) (22), multicystic dysplastic kidney, renal hypoplasia, and agenesis. The exam is also crucial for the monitoring of kidney growth and of renal pelvis and calyces dilations in cases of hydronephrosis (17). Ultrasound also detects calculi, abscesses, and obstructions of the urinary tract, which may require investigations with other imaging methods or changes in the clinical approach to the patient (16).

Advantages

The ultrasonography presents several advantages, which are responsible for making it the main instrument for the assessment of the urinary tract. It is hardly invasive, versatile, and relatively inexpensive, factors that contribute to its applicability in a wide range of clinical situations. With the technological advancements, devices are becoming progressively smaller, with affordable laptop-based portable units that further enhance their usability (17).

There are other important advantages of RBUS, namely the rapid and noninvasive generation of quality images, the absence of exposure to ionizing radiation, and the absence of sedation and patient immobilization. In addition, it allows the dynamic and sequential monitoring of upper and lower urinary tract structures (6,23).

Limitations

As mentioned earlier, ultrasonography depends on the generation of images from the rapid processing and interpretation of information collected by a transducer and, as such, is susceptible to the occurrence of artifacts. These artifacts are mostly related to anomalous interactions between the sound waves and tissues or air-filled cavities, producing unreliable representations of their anatomy. Certain patterns of distortion, however, can be useful for the differential diagnosis on some occasions (16,24). Other limitations from the RBUS are due to the patient's characteristics, especially morbid obesity, presence of gas in the intestine, lesions and deformities, which can impair the capture of high-quality images. This capture can also be affected in children with an empty bladder (25).

However, the main limitation associated with the exam is its dependence on the operator and the examiner expertise, which are responsible, respectively, for the production and analysis of the images. Ideally, the operator and examiner should be the same person, although the operator can complete the exam before it is necessary, as he found results wrongly classified as satisfactory, resulting in the generation of insufficient amount of images for an accurate assessment. There are also difficulties associated with the proper handling of the transducer under the patient's conditions (26). In view of these complications, the examiner must have vast anatomical knowledge, experience in the assessment of kidney and urinary tract anomalies, and mastery of the ultrasonography technique to draw adequate conclusions about the patient's clinical condition.

Furthermore, it is important to emphasize that RBUS is not able to provide exact information about all clinically relevant changes that may be present in a child with febrile UTI. This is the case, for example, for the identification of VUR or the detection of acute lesions and/or renal scars, situations in which other imaging tests have greater reliability and sensitivity (27,28).

VCUG

General principles

The VCUG is a fluoroscopic exam that allows the assessment of the anatomy and function of the lower urogenital tract—mainly the urethra, bladder neck,

and bladder—by means of the production of images of structures filled with radioactive contrast medium. It is the main exam for the diagnosis and grading of VUR.

Before starting a VCUG, the recommendations are to collect clinical data and perform simple abdomen radiography to reveal potential abnormalities or complications that may be crucial for the diagnosis or that may show the need for a different evaluation process (29).

The contrast medium consists of a solution containing iodine at concentrations between 15% and 20% (mass/volume). Ideally, it should be heated, close to body temperature, as it ensures more comfort for the patient without increasing the volume needed or the time of radiation exposure (30).

To reach the bladder and to initiate filling, aseptic catheterization is applied with catheters of size 8F or smaller, according to the child's age. It is inserted into the urethra after application of an antiseptic solution and a sterile lubricant to the skin. This process can be aided by the use of short-acting sedative agents, such as midazolam, as a way to reduce the anxiety of the patient and their parents (17). Some radiologists prefer that the child does not urinate before VCUG, as it allows the use of urine flow through the catheter as an indicator of its correct positioning. On the other hand, when voiding occurs before the procedure, the presence of urine in the tubercle can be used as a measure of the residual volume in the bladder. The catheter is then fixed with adhesive tape on the inner thigh in girls or in the dorsal region of the penis and lower abdomen in boys (29).

The contrast, after catheter insertion, is more conveniently applied by continuous gravity drip, but it can also be infused manually with a syringe, provided care is taken not to apply excessive pressure during the procedure. To detect VUR properly, the bladder must be filled and hyperextension must be strongly avoided. Bladder capacity can be estimated by the formula [(age + 2) × 60] (31), but the variability of this measure leads to the conclusion that the capacity is actually the volume at which voiding begins spontaneously (17).

During bladder filling and emptying, the remaining fluoroscopy procedures must take place to produce images that capture important steps in the process. The number of images has a direct impact on the radiation doses to which children are exposed and the time spent during VCUG. Therefore, it is recommended that well-defined protocols be followed for practical and efficient image acquisition (32). The images normally take place in the following steps:

(I) Initial bladder filling;
(II) When the bladder is filled;
(III) During voiding;
(IV) Post-voiding.

A cyclic modality of VCUG can be utilized to ensure effective detection of VUR and consists of repeating bladder filling and imaging during voiding. This practice has been shown to be effective in detecting VUR with a small increase in radiation exposure time (33). The grade of VUR varies from I to V, according to the International Reflux System (34).

Applications

VCUG is the gold standard for the diagnosis of VUR (35), one of the most common CAKUT and the one most associated with recurrent febrile UTIs, which have high morbidity and can lead to renal scarring (6,36). The exam is utilized for the detection and grading of reflux, as well as for the anatomical and functional evaluation of the urethra and bladder, allowing the measurement of the position of the ureterovesical junction considering the bladder neck, identification of the presence of bladder diverticula, in a complete way—or incomplete—voiding and the detection of a possible lack of coordination between the bladder and the sphincters (37). It allows the diagnosis of posterior urethral valves, urethral strictures, and other anomalies by evaluating the structure during voiding. It also permits the identification of bone malformations in the vertebral column and the lumbosacral region. In addition, it is possible, with VCUG, to check for contrast drainage and to differentiate obstructive megaureter from reflux (38-40).

Advantages

VCUG, despite being considered a stressful and invasive procedure, remains one of the most requested urological imaging modalities due to its advantages over other imaging exams. Compared with ultrasonography, it is the gold standard for the diagnosis of VUR, since traditional RBUS does not have the necessary accuracy for the identification or grading of VUR in children after the first UTI (28). However, the development of new RBUS modalities shows promise for the diagnosis of VUR. Contrast-enhanced ultrasonography, for instance, maintains the accuracy of VCUG with the advantage of eliminating radiation exposure, but it is still highly dependent on the operator's expertise and on the availability of necessary contrast media, which are not unavoidably available for pediatric use in all countries (41). Moreover, the fact that VCUG produces

detailed images with excellent anatomical resolution and has the ability to provide a reliable way of evaluating the urethra increases its applicability, making it more used than radionuclide cystography, an exam with the same ability to diagnose VUR, but without providing a detailed view of the urethra and bladder (42).

Limitations

Despite being widely performed, the VCUG still presents important limitations. Among them appears the impossibility of executing the exam in children during a febrile UTI (32), since, to avoid complications and worsening of the infection, the patient's urine must be sterile (43). In addition, perhaps one of its greatest limitations is the anxiety faced by patients, parents, and healthcare staff during the procedure, due to its invasive nature. This discomfort occurs at various stages of the exam, which can lead to severe distress that affects 61% to 71% of non-sedated patients (44). The critical moments of the procedure are urethral catheterization—with the possibility of injury due to catheter displacement (45)—and public voiding, which can be problematic depending on the age of the child. It is common for the patient to report "full bladder" despite the infusion not reaching the full bladder volume. Besides that, if the child is crying or squirming, increased intra-abdominal pressure can impair contrast flow. In neonates and very young children, voiding happens spontaneously as a reflex to bladder distension, but from 2 years of age, children may be aware of bladder fullness and be able to contract the external sphincter, in a movement contrary to stimuli voiding (17). The resistance exhibited by toilet-trained children can also diminish micturition. Cases of non-voiding can represent up to 20% losses in the diagnosis of VUR (29,46). To get around these difficulties, some strategies can be adopted, namely the use of running water or dripping on the subject's perineum. However, the restlessness associated with other factors makes it important to seek less invasive methods for the diagnosis of VUR.

The radiation to which infants are exposed also constitutes a limitation of the exam. Even if the as low as reasonably achievable (ALARA) principle is employed when making decisions regarding factors influencing exposure time—notably time, distance to source, and protection (use of blockers like lead shielding)—developing infants are especially more sensitive to ionizing particles (40,47). In addition, gonadal exposure significantly increases the relative risk of genetic anomalies and carcinogenesis (48). The exposure time depends on following a well-defined protocol for the exam, which makes it more efficient. On the other side, the voiding difficulties presented by the patient can increase the time of procedure and the period of vulnerability to ionizing particles. Furthermore, even with the use of effective methods to limit radiation, VCUG still has ten times less exposure than radionuclide cystography (49).

In addition to the aforementioned limitations, there are still some complications rarely associated with VCUG, namely discomfort during voiding, UTI, bacteremia, reactions to contrast media, catheter knots, and urinary bladder rupture. Cohen *et al.* also reported cases of hypothyroidism in children exposed to contrast medium iodine. Dysuria, hematuria, and urinary retention may also occur, but the exam is usually of low risk (50-54).

Renal scintigraphy—DMSA, diethylenetriamine-pentaacetic acid (DTPA)

General principles

The exam evaluates tubular function and the renal cortex, detecting cortical dysfunction resulting from an acute lesion, caused by UTI, or from renal scarring. DMSA is a compound that mainly adheres to the cells of the proximal convoluted tubule and the upper segments of the loop of Henle, which occurs due to the peritubular blood flow or reabsorption of glomerular filtrate. After a maximum of 2 hours following drug administration, 45% to 60% of it is detectable in the renal cortex, while a variable percentage is excreted in the urine, allowing the assessment of the renal parenchyma (55).

It is important to highlight the drug's affinity for plasma proteins, which reduces its glomerular filtration. DMSA is usually administered in doses of 2 mBq/kg (0.05 mCi/kg), with a minimal dose of 20 mBq (0.5 mCi) (56).

The scintigraphy procedure requires parental consent and patient sedation, although not mandatory, may be necessary given requirement that the child remain immobile during the exam. Technetium-99m-labeled DMSA is then administered by intravenous injection (57) and, after 2 to 3 hours, tracking and imaging of the radioactive tracers take place (58). The radioactive material remains in the body for more than 24 hours, which gives certain flexibility between administration and imaging. Delayed imaging (until 24 hours after drug injection) may be necessary for quantitative measurement of renal function when a severe obstruction of the tubular system is present.

Images are obtained using a high field of view

scintillation counter, equipped with a pinhole-type collimator. Static images of the anterior and posterior projections of the abdomen are captured.

Urethral catheterization is recommended for children under 4 years of age and for older children who do not cooperate or remain immobile during the exam.

A normal exam shows kidneys with similar dimensions and homogenous cortical reabsorption, with 3 areas of reduced reabsorption due to the pyelocaliceal system. DMSA traces should not be observed above the bladder or in other organs.

In addition to static scintigraphy, it is also possible to perform dynamic scintigraphy, whose most utilized compound is DTPA, also associated with 99m-technetium. Ethylenedicysteine (Ec) and mercaptuacetyltriglycine (MAG3) can be used as substitutes for DTPA (59). In this procedure, the patient is injected with the radiotracer and, soon after that, imaging takes place, capturing sequential images of bladder and kidneys. The exam lasts about 40 minutes. While DTPA is excreted by glomerular filtration, Ec and DMSA are mainly excreted by the proximal convoluted tubules (60).

Applications

Static scintigraphy is most commonly used for the detection of cortical injuries that occur as a consequence of acute lesions caused by recent UTIs, as well as for the detection of renal scars related to chronic pyelonephritis and reflux nephropathy. It is also valid for the assessment of renal uptake as an indicator of renal function, detection of horseshoe kidney and ectopic renal tissue. Scintigraphy procedures can be performed in patients allergic to iodinated contrast media.

Dynamic scintigraphy aims to evaluate renal glomerular function, tubular secretion, and permeability. In addition, it is used for the assessment of ureteropelvic junction obstruction, megaureter, horseshoe kidney, polycystic kidney, ectopic ureterocele, and post-surgery evaluation of pyeloplasty and ureteral reimplantation (61).

Advantages

The DMSA exam does not require much preparation by the patient before it is performed and it is not affected by the presence of intestinal gas. This technique allows the capture of renal images at different angles, including anterior, posterior, and oblique views. Regarding radiation, patient exposure is minimal.

The test is able to identify twice as many cortical lesions as ultrasonography and four times more than intravenous urography. It is considered the gold standard for detecting renal scarring.

In children, acute pyelonephritis, a high-risk disease for this age group, is not always followed by high fever or leukocytosis. Renal scintigraphy is the most reliable exam for detecting acute parenchymal lesions.

Limitations

For dynamic scintigraphy, its main obstacle is the influence of the bladder, which, when full, exerts pressure to the upper urinary tract, which significantly reduces the excretion of administered radiotracer (60).

The use of non-steroidal anti-inflammatory drugs, as diclofenac for example, blocks the production of prostaglandins and inhibits the spontaneous contraction of the ureter, which leads to a delay on the ^{99m}Tc-MAG3 renogram curve apex in healthy individuals (62). This effect can contribute to the production of false positives.

In patients with impaired renal function, dynamic scintigraphy with ^{99m}Tc-DTPA may result in misunderstandings or false positives in comparison with ^{99m}Tc-MAG3, given the different ways in which these radiotracers are excreted.

Additionally, when compared to other methods, the long time required to perform static scintigraphy, associated with its high cost, restricts its performance in patients with suspected acute pyelonephritis in emergency services.

Other imaging methods

CeVUS

CeVUS is an exam recently implemented in clinical practice, whose first report in literature occurred in 1998 (63). The procedure starts with conventional ultrasound of the kidneys and urinary tract, followed by the injection of contrast medium and saline solution via bladder catheterization. Currently, the most used contrast is the second-generation SonoVue, made with a stabilized aqueous suspension of microbubbles and sulfur hexafluoride, coated with phospholipids. After its administration, an ultrasound is performed during bladder filling and emptying. CeVUS has been commonly compared with VCUG since both exams aim to identify the presence of VUR.

Performing CeVUS, rather than VCUG, has been recommended as the next test for patients diagnosed with VUR and as a diagnostic exam for girls and high-risk patients. Among the advantages of CeVUS, some that

deserve to be highlighted are the low radiation exposure and less discomfort for the child. Also, the number of side effects from taking SonoVue is low.

A study performed by Papadopoulou *et al.* (64) compared VCUG and CeVUS. The authors reported that CeVUS, when executed with second-generation contrast media and harmonic imaging, shows a higher sensitivity for detecting VUR (64). However, SonoVue is not available in some countries, and the first-generation contrast media, Levovist, does not provide similar image quality.

Excretory urography

Excretory urography qualitatively evaluates kidney function and the structure of the upper urinary tract. It can be used to assess the size, shape, position, and density of the kidney, using a water-soluble contrast medium. Structural aspects of the ureters can also be evaluated. The main advantage of this imaging method is the ability to determine anatomical aspects of a large part of the excretory apparatus.

The performance of the exam requires the patient to refrain from eating or drinking for 8 to 12 hours, and begins with an intravenous injection of iodinated and water-soluble contrast, followed by the capture of ventrodorsal and right lateral radiographic images after 5, 20, and 40 minutes.

Among the side effects of the exam, there is the possibility of severe allergic reactions to the contrast, making this investigation impossible in individuals with a known allergy to iodine. Intravenous administration of contrast may interfere with the results of urine tests and RBUS performed a short time after the urography. Diuresis caused by the contrast medium can lead to temporary pyeloureteral dilation, which can be confused with mild hydronephrosis. It is recommended to respect a minimum interval of one day between the performance of the excretory urography and the RBUS.

Currently, excretory urography has been less frequently used for investigation after UTI episodes. This is because less invasive exams, especially RBUS and scintigraphy, show a greater ability to assess the kidneys and urinary tract (65).

Protocols of UTI imaging investigation

AAP

The AAP guidelines, updated in 2011 and reaffirmed in 2016, address protocols for the diagnosis and assessment of UTIs in children aged 2 to 24 months (66,67). These guidelines recommend, based on observational studies, the performance of RBUS in all febrile infant with UTI (evidence level C; recommendation). The RBUS is considered a screening test to identify patients who need more specific approaches or new evaluations. The adequate time to perform the exam, according to the AAP, will be determined by the patient's clinical situation, as RBUS is recommended in the first 2 days of treatment for those who do not show significant clinical improvement or who have systemic complications. However, in patients who respond well to treatment, there is no recommendation for RBUS during the acute phase of the infection because, according to the guidelines, the exam is subject to errors and can be misleading in these situations.

About renal scintigraphy with DMSA, the 2011 guidelines emphasize that the exam result rarely changes the clinical management of the patient. Therefore, the recommendation is that a DMSA scan should not be routinely performed (evidence quality C; recommendation).

Regarding VCUG, the guidelines suggest that the exam should not be routinely performed in infants with a febrile UTI. This recommendation is based on the low prevalence of high-grade reflux and on the conclusions reached by AAP committee, which analyzed data provided by researchers who had recently published RCTs on antibiotic use and questioned the role of antibiotic prophylaxis on the reduction of renal scarring and recurrent UTI (66). It is worth noting that, in 2011, the RIVUR trial, which followed a large cohort of patients to determine the effects of antibiotic use (9), was still in production, but despite the study showing that the use of antibiotics can be relevant, the reaffirmation of the AAP guidelines, which occurred after the release of RIVUR results, kept the recommendations unchanged. This approach is based on the observation that the dose of antibiotics required to prevent UTI recurrence would be excessive and impractical. VCUG is, therefore, restricted to situations in which anomalies are detected in RBUS or atypical occurrences, such as febrile UTI recurrence or obstructive uropathies (evidence quality B; recommendation). The 2016 reaffirmation also raises the question of the relevance of VUR for the prognosis of patients with UTI, and the trend to reduce the number of VCUGs performed is further reinforced by radiation exposure, financial costs, and suffering generated by the exam.

NICE

NICE compiles guidelines for the clinical management of children under 16 years of age with UTI. These guidelines were originally published in August 2007 and were updated

in 2018. However, 2018 update did not substantially change the recommended protocols for the imaging approach to patients with UTI, but it still maintains significant distinctions compared to AAP guidelines (68).

According to NICE, ultrasonography should be performed during the acute phase of UTIs in children with atypical infections, which are characterized by the existence of pathogens other than *E. coli*, deficient urine flow, failure to respond to treatment within 48 hours, high levels of creatinine, septicemia, and presence of masses in the abdomen or bladder (evidence quality B/C; recommendation). For infants less than 6 months of age and who respond well to treatment, RBUS is recommended for up to 6 weeks after the infection. On the other hand, the exam is not routinely recommended for children older than 6 months who respond well to treatment. It is recommended to perform the RBUS in every patient who has recurrent infections or who is younger than 6 months of age and has a confirmed UTI (evidence quality C; recommendation).

DMSA scan is recommended 4 to 6 months after recurrent infection in all patients and in cases of acute infection in those under 3 years of age (evidence quality B/C; recommendation). However, the time before the exam can be shortened if the child has another UTI during the waiting time.

VCUG is not recommended in most age groups and clinical situations described by the NICE guidelines. VCUG should only be performed for infants under 6 months of age who have atypical or recurrent UTIs. In these situations, 3 days of antibiotic prophylaxis is recommended, with VCUG being performed on the second day of medication. In children between 6 months and 3 years of age, although VCUG is not routinely endorsed, it can be performed in special clinical situations, including the presence of dilation in RBUS, family history of VUR, urine flow dysfunction, or bacteria other than *E. coli* (evidence quality B/C; recommendation).

EAU/ESPU

The EAU guidelines, updated in 2019, encompass children of all ages and recommend RBUS for every patient with febrile UTI in the first 24 hours after starting treatment, especially for those who do not respond to medication. EAU guidelines indicate that measurements of residual volume after voiding should be performed to detect voiding abnormalities or to exclude the possibility of the increased in residual urine as a cause of UTI (69) (evidence quality B/C; recommendation).

DMSA scan and VCUG are recommended in different orders according to the followed approach (70). In the "top-bottom" approach, a DMSA scan is performed close to the period of infection to identify the presence of acute lesions in the renal parenchyma. If a lesion is detected, the patient undergoes VCUG. This strategy can avoid cystourethrography in numerous cases. In the "bottom-up" approach, VCUG is performed, and, if the patient is diagnosed with VUR, DMSA is recommended. The EAU/ESPU recommendations differ from those made by AAP and NICE, indicating investigation for VUR in all patients (evidence quality C; recommendation). This approach, according to EAU guidelines, is justified by the increased risk of renal scarring in patients with VUR. Another aspect highlighted by this protocol is the search for bladder and bowel dysfunction, which is a known risk factor for UTI and should always be evaluated in children with the infection (evidence quality B; recommendation).

Table 2 summarize some of the possible strengthens and limitations of the commented guidelines.

Discussion

Among many protocols, it is consensual to perform RBUS in pediatric patients after confirmation of the first episode of UTI, although NICE guidelines do not recommend the exam for children other than 6 months or with good response to clinical treatment. NICE guidelines contradict the common to use RBUS as a first-line investigation for all cases of febrile UTI, and this approach has raised questions about the risks associated with it. Ristola and Hurme, in a retrospective study with a cohort of 672 patients, indicate that NICE guidelines can cause problems such as failure to detect high degree VUR in 31% of patients with this anomaly (71). Coulthard *et al.* (72) support these findings, suggesting that the application of NICE guidelines can cause the loss of more than half of the diagnosis of renal scarring in patients from Newcastle Primary Care Trust. However, there are also studies suggesting that the decrease of ultrasonography exams would not imply significant disadvantages for patients, as reported by the retrospective analysis of Deader *et al.* (73). The authors indicated a possible reduction of 65% in the number of exams performed (73). RBUS, as mentioned before, is a

Table 2 Critical summary of the guidelines for pediatric UTI diagnosis and imaging investigation

Guidelines	Strengths	Limitations
AAP	• Strict definition for UTI diagnosis	• Target only 2–24-month-old infants
	• Stringent requirements for urine collection and preservation	• Last update in 2016
		• Recommendations for long-term management and prophylaxis have not been updated according to recent trials
	• Least radiation exposure	• Recommendation of only invasive techniques may be used to confirm diagnosis of a UTI
NICE	• Give additional recommendations for long-term management	• Strict recommendations for imaging investigation of the urinary tract
	• Stress that dysfunctional elimination syndromes should be addressed in children who have had a UTI	• Recommendations for long-term management and prophylaxis have not been updated according to recent trials
	• Recommendation for predictingthe risk of chronic kidney damage	
	• Least costly	
	• Updated in 2018	
EAU/ESPU	• Highlight the importance of investigation of bladder and bowel dysfunction	• No recommendations for long-term management
	• Updated in 2021	

UTI, urinary tract infection; AAP, American Association of Pediatrics; NICE, National Institute for Health and Care Excellence; EAU, European Association of Urology; ESPU, European Society for Pediatric Urology.

widely used exam for many reasons, such as its versatility and affordability and the fact that it is minimally invasive. On the other hand, the traditional exam, which usually is sufficient, does not allow evaluation of all relevant conditions for the clinical management of children under observation, including VUR or renal function, and it relies on the experience of the radiologist (25,74). In addition, it is common to assume that major complications regarding the structure and function of the urinary tract are detected in prenatal screening, an approach that is not available or performed in some settings (75).

The techniques and strategies related to ultrasonography are constantly evolving, with the exam as a first-line investigation method in UTI and as a possible alternative to more invasive procedures. Contrast-enhanced voiding urosonography, not mentioned in the AAP, NICE and EUA guidelines, is an alternative to VCUG that has been used more often due to the emergence of second-generation contrast agents that seem to be safer for the general pediatric population. A prospective study with 1,010 children carried out by Papadopoulou *et al.* (76) reported that only 3.66% of patients manifested complications after the exam, which are similar to those observed in VCUG and other well-established procedures. This imaging method, in addition to having a low rate of adverse effects, also has a similar sensibility to VCUG, without exposing the patient to ionizing radiation (64,77). However, the application of contrast via a catheter is necessary, leading to technical problems such as the loss of contrast agent in case of high intra-abdominal pressure, in crying children or patients resistant to the exam (77). Although not included in many guidelines, this recent modality of ultrasonography is indicated for male infants and already offers a reliable alternative to VCUG, a criticized exam in the management of febrile UTI in children.

Due to the limitations of RBUS, we seek to combine it with other imaging methods to obtain a more accurate and comprehensive diagnosis in the least invasive way. Therefore, VUR is an anomaly with questionable impact for the patient and with an invasive and stressful exam as a reference and an important topic in the scientific community. The guidelines presented above allow the

identification of important recommendations that aimed at reducing the amount of VCUGs performed. Especially after the publication of AAP guidelines in 2011, there was a substantial decrease in the amount of VCUGs recommended for children from days of life to 2 years of age (78). Following AAP, one of the main reasons for this change in imaging protocols revolves around questioning of the effectiveness of antibiotic prophylaxis as a result of the diagnosis of VUR. Regarding the use of antibiotic prophylaxis, the RIVUR trial, a double-blind study with 607 children published in 2014 and cited by AAP, showed a statistically significant difference in recurrent UTI between children with VUR that received antibiotics compared to those who did not take antibiotics. Children without antibiotic prophylaxis had more UTIs after 2 years of observation. This study pointed out that the difference is only detectable for cases of low-grade VUR (I–II), even though it is probably due to the low number of patients with high-grade VUR (9). In the Swedish Reflux Trial, whose groups had an unusual number of girls with recurrent UTI, antibiotic prophylaxis reduced the recurrence rates of UTI, but only in female children less than 2 years old with VUR and dilatation (79). On the other hand, Hewitt *et al.* (12), in a systematic revision published in 2017, concluded that, based on studies published between 1946 and 2016, the antibiotic prophylaxis in not effective in preventing renal scarring. Pennesi *et al.* (80), in a randomized controlled trial that evaluated the effectiveness of the use of antibiotic prophylaxis in preventing pyelonephritis in patients with VUR, showed the absence of significant differences to justify the use of antibiotics for this purpose.

The use of antibiotic prophylaxis is still a matter of debate. An approach proposed by Wang *et al.* (11), after a post hoc analysis of the RIVUR trial, suggests that the antibiotic prophylaxis is more beneficial to children who fall into high-risk categories, which include those with high-grade VUR. In light of the low prevalence of high-grade VUR, the recommendations of AAP and NICE guidelines make sense, since these guidelines support the idea to avoid VCUG as an exam only to detect VUR. VCUG should be considered in case of other abnormalities that increase the risk of complications for the patient.

Even though more studies are needed to obtain a consensus about antibiotic prophylaxis use in patients with VUR, this is not the only point that motivates the general tendency to reduce the performance of VCUG. In addition to the invasive characteristics and previously cited limitations of the exam, the impact of a VUR for the clinical evolution of the patient has been questioned and debated (80-82). However, some physicians still considered relevant the presence of VUR in the context of UTI. The contribution of VUR as a risk factor for the recurrence of UTIs and the appearance of renal scarring is based on the concept that the inability to eliminate contaminated urine allows the proliferation of bacteria in the urinary tract that can result in infection of the renal parenchyma (14). However, there is a lack of studies that directly support this statement. In a review of the most recent RCTs, Garin *et al.* (82) concluded that the data currently available do not support the hypothesis that VUR contributes to the development of UTIs. Regarding the impact of VUR on the development of renal scarring, Snodgrass *et al.* (81) evaluated 565 patients and found that all degrees of VUR had an impact on the risk of renal scarring, which was identified by changes in the DMSA. However, the risk of renal scarring was significantly higher for VUR grades IV and V (81). On the other hand, Garin *et al.* (82) evaluated 218 patients with acute pyelonephritis and aged 3 to 18 months and verified the absence of association between mild or moderate VUR with the increased risk of renal scarring, pyelonephritis, and UTI. The presence of high-grade VUR (IV and V) was an exclusion criterion for this study, thus preventing conclusions about this condition (82). A more recent study published by Shaikh *et al.* (83) suggests that the risk of renal scarring increases substantially with the recurrence of febrile UTIs, being 11.8 times higher for patients who had a second febrile UTI (83). Therefore, the search for factors that predispose the recurrence of UTI is of great relevance. It is also noteworthy that, although the literature has questions about its importance, VUR, especially high-grade (IV–V), continues to be considered a risk factor for recurrent UTI. The method of choice for diagnosing VUR remains VCUG.

The literature suggests that the detection of high-grade VUR may have negative consequences for the prognosis of a patient with a UTI, but, as pointed out by the AAP guidelines, its frequency is of about one in 100 children with a febrile UTI (66). The prevalence of VUR in neonates with a UTI is between 50% and 70% and decreases with age, but the higher proportion of low-grade VUR supports the decision to avoid routine performance of VCUG (14). VUR grades I to III have high-resolution rate over time, without needing surgical interventions. In sharp contrast, this is not true for grades IV and V of VUR. The age of VUR resolution is about 9.5 years for grade IV, but ranges from 2.7 to 4.5 years, respectively for grade I and III (13).

There are also new technologies that emerge in an attempt to detect individuals who would most benefit from performing VCUG. A recent study showed promising results (AUC of 0.761) with the use of machine learning to predict the presence of VUR in patients with recurrent febrile UTI. New predictive models may be an alternative to better discern the situations in which VCUG should be performed, reducing criticisms regarding the frequent use of the exam (84).

A study carried out in Italy and published by La Scola *et al.* (85) compared, under the light of several criteria, NICE guidelines, AAP guidelines, top-down approach (TDA), and the "all tests protocol" (ATP) control, which involved performing US, VCUG, and late DMSA. At first, the amount of radiation from VCUG and DMSA was compared. Although the results of VCUG are more variable, being in the spectrum of 0.5 to 3.2 mSv, it was concluded that the most accepted value for the standard quantity of the two exams is 1.0 mSv. A general analysis defined the TDA strategy as the one with the highest radioactive exposure (624 mSv), due to the performance of a DMSA exam in the acute and late phase, in contrast to the AAP that presented the lowest one (42 mSv). Meanwhile, ATP was the most expensive protocol and NICE was the less expensive.

Regarding the ability to identify VUR, TDA was the most successful, with high sensitivity (76% for VUR I–V and 85% for VUR III–V), despite the relatively low specificity, which was close to 50%. The other two guidelines, NICE and AAP, because they depend on the findings of RBUS to recommend the DMSA, were not sufficiently able to identify VUR, since the RBUS does not reliably detected this condition.

Referring to renal scarring, a late DMSA, after a positive DMSA in the acute phase, guarantees 100% sensitivity. As the TDA recommends DMSA in the acute and late phases, this approach allows the diagnosis of most children with renal scarring. On the other hand, even though NICE guidelines impose restrictions for exams in the acute phase, the guidelines recommend a late performance, resulting in less than half of the children with diagnosed scarring. The AAP guidelines do not recommend delays in DMSA, or failure to diagnose children with renal scarring.

It is worth mentioning, however, that the aforementioned study does not include children with recurrent UTI. The authors only considered those with the first episode of UTI. In addition, Bush *et al.* (86), reported that only 66% of children with reduced kidney function or with cortical defects evidenced by the DMSA had changes in the RBUS. The authors conclude that using RBUS as the only imaging method is risky and not recommended.

Conclusions

To sum up, the ideal imaging protocol for investigation after UTI is not yet established. Several guidelines with diverse recommendations have been published so far. However, doubts remain about defining an approach not so invasive, but able to detect with accuracy CAKUT patients that need follow-up.

However, some points are more consensual. The use of RBUS as an initial screening imaging test is generally accepted considering the safety of the exam, the morphological data provided, and the potential to define patients who need further evaluation. On the other hand, the quality of the equipment and the expertise of the examiner must be taken into account when interpreting the findings of RBUS. The second point is to limit the use of VCUG to selected cases in which morphological details of bladder and urethra are necessary as well as the search for high-grade VUR. The third point is the importance to detect patients with obstructive uropathies who may benefit from surgical treatment. In general, additional imaging exams depend on findings provided by RBUS. Prospective studies with large samples are necessary to compare different imaging protocols and to propose more personalized approaches based on clinical data and findings provided by the first RBUS.

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Footnote

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