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Updated Italian recommendations for the diagnosis, treatment and follow up of the first febrile urinary tract infection in young children

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ABSTRACT

Aim: Our aim was to update the recommendations for the diagnosis, treatment and follow up of the first febrile urinary tract infection in young children, which were endorsed in 2012 by the

Italian Society of Pediatric Nephrology.

Methods: The Italian recommendations were revised on the basis of a review of the literature published from 2012 to October 2018. We also carried out an *ad hoc* evaluation of the risk factors to identify children with high-grade vesicoureteral reflux or renal scarring, which were published in the previous recommendations. When evidence was not available, the working group held extensive discussions, during various meetings and through email exchanges.

Results: Four major modifications have been introduced. The method for collecting urine for culture and its interpretation has been re-evaluated. We have reformulated the algorithm that guides clinical decisions to proceed with voiding cystourethrography. The suggested antibiotics have been revised and we have recommended further restrictions of the use of antibiotic prophylaxis.

Conclusion: These updated recommendations have now been endorsed by the Italian Society of Pediatric Nephrology and the Italian Society for Pediatric Infectivology. They can also be used to compare other recommendations that are available, as a worldwide consensus in this area is still lacking.

Keywords:

Antibiotic treatment, Children, Febrile urinary tract infection, Prophylaxis, Vesicoureteral reflux

Key Notes

- We updated the 2012 Italian recommendations for the first febrile urinary tract infection in young children and introduced four major modifications.
- The method for collecting urine for culture and its interpretation has been re-evaluated and we have reformulated the algorithm that guides clinical decisions to proceed with voiding cystourethrography.
- The suggested antibiotics have been revised and we have recommended further restrictions of the use of antibiotic prophylaxis.

INTRODUCTION

In this paper we present the updated recommendations for the diagnosis, treatment and follow up of the first febrile urinary tract infection (UTI) in young children, endorsed by the Italian Society of Pediatric Nephrology and the Italian Society for Pediatric Infectivology. Our previous document (1)
has been revised six years after its publication, on the basis of recently published literature and the results of an ad hoc evaluation of the risk factors previously proposed to guide clinicians in the identification of children with high-grade vesicoureteral reflux (VUR) (2). As regards risk factors, only the presence of a pathogen other than *Escherichia coli* significantly predicted high-grade reflux both in the univariate (Odd Ratio 2.52, 95% Confidence Interval 1.32–4.81, $p < 0.005$) and multivariate analyses (Odd Ratio 2.74, 95% CI: 1.39–5.41, $p= 0.003$). The other three most frequent risk factors, abnormal renal and bladder ultrasound (RBUS), abnormal prenatal ultrasound, male younger than six months at UTI occurrence, were neither significantly nor independently associated with the presence of high-grade reflux (2).
As in the previous version, these recommendations apply to infants and young children, 2 months to 3 years of age, with a first febrile UTI, based on a temperature of at least 38°C. We excluded infants younger than two months of age, because of their specific features and specific treatment needs and children older than 3 years of age because of the lower risk of nephro-urologic abnormalities and different clinical presentation. Children with immunodeficiency, a previous workup for congenital malformation of the kidney or urinary tract, or those requiring admission to an intensive care unit were also excluded. The updated recommendations follow the same structure as previously, considering 4 major topics: diagnosis, treatment, imaging and antibiotic prophylaxis and grading the evidence on the basis of the SORT criteria: strong (grade A), moderate (grade B) or weak (grade C) in support of a particular intervention (3).
The recommendations are intended for use by all physicians dealing with febrile infants and children inside and outside the hospital and by specialists in paediatric and adult nephrology and urology.

DIAGNOSIS

When to suspect a UTI

A diagnosis of UTI should be considered in children presenting with fever of 38°C or higher (4),

with no apparent source (grade A) (5). In children aged 2 to 3 months, fever may be absent and clinical manifestations may include lethargy, irritability, and vomiting (6). The absence of fever in the first 3 months of life does not correlate with a less severe condition (6), and the risk of complications, such as sepsis and meningitis, at this age is greater (7). In older children, frequency, dysuria, and changes in continence habits may be early symptoms, while abdominal pain and loin tenderness can be associated with fever. The presence of malodorous urine is neither specific nor sensitive enough to help in the diagnosis of febrile UTI (grade B) (8). Poor growth has also been reported as a possible sign of UTI, but in our opinion poor growth is mainly related to recurrent infections or to associated conditions such as chronic kidney disease.

What to do when a UTI is suspected

Urine should be collected and analyzed by dipstick or microscopy to identify children in whom UTI is very likely (9), and, if urinalysis is abnormal, by urine culture (UC) to obtain a definitive diagnosis (5)(grade A). The presence of leukocyturia and bacteriuria in a fresh urine specimen and/or positivity for leukocyte esterase (LE) at dipstick suggest a diagnosis of UTI in symptomatic children. Urine culture can confirm the diagnosis based on the growth of a single bacterial strain (5,10). The interpretation of urine dipstick which is positive for nitrites and negative for leukocytes is not simple, as infection stimulates an inflammatory response in the host, represented in UTI by the presence of urinary leukocytes. Therefore, the positivity of urine culture in the absence of leukocyturia has to be evaluated with caution, as it could represent bacteriuria and not UTI. If fever persists we recommend to repeat dipstick to check for the appearance of leukocyturia.

How to collect urine

Collecting urine in small children represents a hard practical task. Four methods of urine collection are utilised, with no agreeement in the literature: urinary bag, clean voided urine (CVU), transurethral bladder catheterization (BC) and suprapubic aspiration (SPA). Each method has to be performed following standardized procedures (11-18). As regards dipstick and urinalysis implementation, any method for urine collection is feasible (grade A) (5,11,12,19-22).

How to collect urine for UC has been extensively analyzed by the NICE Working Group (4) and by Whiting et al (23), and is summarized in Table 1. Suprapubic aspiration and transurethral BC are the least likely to yield a contaminated growth (grade A). These methods are cumbersome to implement in primary care as a routine procedure, but feasible in hospital settings (5,11,19). In

particular, SPA should be recommended in some circumstances, such as severe phimosis, vulvar synechia , infections or malformations of the external genitalia (20). The use of CVU as an alternative to invasive methods is controversial (20,21); it is recommended by the Australian and English guidelines (4,11,23), while the American Academy of Pediatrics does not consider it a valid method for UC (5). When CVU is used in infants, a simple, quick, and effective method to stimulate micturition has been reported, though contamination has not been evaluated (14-18). The use of a bag to collect a UC sample is only recommended by our previous guidelines (1) and the 2018 NICE guidelines (4); in the recent literature, most authors recommend its use only in order to perform dipstick analysis (5,11,12,19-22).

On the basis of these data from the literature and following extensive discussions within our working group, we recommend obtaining urine for culture according to the child's clinical condition. In a febrile child in poor general clinical condition or a severely ill appearing child, urine must be collected by transurethral BC or SPA (4) (grade A). In a febrile child in good clinical condition a "two steps" approach is feasible (5,22 24); urine can be collected by CVU or bag for dipstick (5,11,12,19,21,22,25). If dipstick shows the presence of LE with or without nitrites, urine for UC should be collected by CVU or transurethral BC (4,11,19,21,25,26) (grade A). If dipstick does not show the presence of LE and nitrites we do not recommend UC but a clinical follow-up and a new dipstick if fever persists after 24-48 hours (grade B).

What is the clinical significance of urine dipstick, microscopy, and culture?

The sensitivity and specificity of dipstick and microscopy have been well summarized in a metanalysis (9) and are reported in Table 2.

Results of the LE test are comparable to those of white blood cells by microscopy. Microscopy with Gram staining for bacterial differentiation is the rapid test with the highest sensitivity and, specificity, however this test is almost never performed in routine settings in Italy. While in our previous recommendations the use of dipstick in children <2 yrs of age was discouraged due to its unreliability (1,27), more recent data in the literature agree on the use of the dipstick test also in children <2yrs (4,28,29- 31). A practical approach, based on the results of LE and nitrite dipstick analysis, is suggested in Table 3.

When urine microscopy is employed, it should be performed on a fresh specimen by an expert operator (grade B). Urine culture is required to confirm the diagnosis (grade A): it is considered positive if the culture demonstrates the growth of a single organism with a colony count threshold which depends on the method used for collection, as indicated in Table 4 (grade C). However, it is

difficult to establish a precise cut-off for interpreting the results of UC, because of the heterogeneity and variability of the available literature, as well summarized by some authors (10,21). Of course, each result has to be evaluated against anamnestic, clinical and laboratory data (fever, leukocyturia, bacteremia) (10). We give some recommendations on cut-offs, keeping in mind that the UC result must be evaluated in the context of the clinical situation.
In our settings, where we mainly use CVU samples, we believe that both urinary leukocytes and a significant colony count in UC (Table 4) are needed for the diagnosis of UTI (grade B).

Are blood tests necessary when a UTI is suspected?

Routine blood tests are not necessary to identify the site of infection. If the child is hospitalized, a complete blood count, C-reactive protein, procalcitonin and renal function tests are indicated (grade B), and always recommended in infants <3 months (4,11,32).

When should a child be hospitalized?

We recommend to hospitalize any critically ill child (sepsis, dehydration and vomiting) (grade A), when serious concern of noncompliance (grade B) is present and when fever persists after 3 days of appropriate antibiotic treatment, as shown by sensitivity testing (grade A) (33,34).

TREATMENT

In a febrile child with suggestive clinical signs and/or positive urine dipstick or microscopy, antibiotic treatment has to be initiated soon after a urine specimen for UC has been obtained. Prompt antibiotic treatment is necessary to eradicate the infection, to prevent bacteremia (in particular, during the first months of life) and to improve clinical condition (grade A) (20,35,36). As regards the risk of UTI-related renal scarring, it is now an established fact the time to initiation of antibiotic treatment makes no difference in the frequency and severity of scarring, as long as it is initiated within 3-4 days from the onset of fever (35,37-40). Many studies have demonstrated that starting treatment either orally or parenterally is of equal effectiveness, and the clinician should base their choice of the route of administration on practical considerations (5,33,34,41-49): if the UTI is complicated, i.e. when the child appears septic or severely dehydrated or is vomiting, or if concerns regarding compliance are present, treatment should be started parenterally and continued with an oral antibiotic as soon as the clinical conditions of the child allow it (grade A); if the UTI is not complicated, i.e. when the febrile child is in good clinical condition and able to retain oral fluids and medications and compliance is expected, treatment should be administered

via the oral route (grade A) (5,33,34,35,46-49) (Figure 1). The results of oral versus parenteral route do not differ in terms of duration of fever, recurrence of UTI or incidence of UTI-related renal scarring (5,11,33,34,42,43).

Clinicians should also base their choice of the antibiotic on local antimicrobial sensitivity patterns (if available) and adjust it according to sensitivity testing of the isolated uropathogen (grade A) (5,11,33,34,49). *E. coli* remains the predominant uropathogen isolated in acute community-acquired uncomplicated infections (80%), followed by *Klebsiella*, *Enterobacter*, *Proteus* species and *Enterococci*. Many of the characteristics of these pathogens are changing, particularly due to antimicrobial resistance (50-56). According to our national pattern of resistance (57-62), we recommend amoxicillin-clavulanic acid as the first-line oral antibiotic and ampicillin-sulbactam or amoxicillin-clavulanic acid if the intravenous route is indicated (grade B). The increasing resistance of *E. coli* to third generation cephalosporins (about 30% in Italy) is mainly due to the widespread and not always appropriate use of this class of antibiotics (62-64). Therefore, we suggest considering cephalosporins (cefixime or ceftibuten for the oral route and cefotaxime or ceftriaxone for i.v. administration) in children with severe infections (5,11,33,34,45-49,62,65,66). In effect cephalosporins have a superior efficacy and rapidity of action, making the possible onset of resistance a less important issue (grade C). Because ceftriaxone is known to cause cholestasis (67), it should be used with caution in infants with jaundice or those younger than 3 months; cefotaxime should be preferred, also due to pharmacokinetic/pharmacodynamic considerations and especially because of its renal excretion (grade C).

If UC results show resistance to the prescribed antibiotic but the patient's condition is improving, treatment should be continued without change (grade C) (68,69). In children who are allergic to beta-lactams, an aminoglycoside, such as amikacin or gentamicin, is the best choice (grade A), bearing in mind that *Pseudomonas Aeruginosa* quickly develops antibiotic resistance when aminoglycosides are used as a monotherapy (70,71).

Because of the high rate of resistance, the empirical use of trimethoprim must be avoided; it should be used only on the basis of antibiogram sensitivity (72).

The use of ciprofloxacin in pediatric patients is controversial. The use of quinolones should be limited to patients whose clinical condition is severe or who are unresponsive to other antibiotics, only on the basis of sensitivity patterns, as indicated in recent recommendations (73,74). The worrying increase in resistance due to the widespread use of quinolones in adults should also be taken into consideration (75).

Agents that are excreted in the urine but do not achieve therapeutic blood concentrations, such as nitrofurantoin, should not be used to treat febrile UTIs, because parenchymal and serum antimicrobial concentrations may be insufficient to treat pyelonephritis or urosepsis (grade A) (47).

The suggested dosages of the aforementioned antibiotics are outlined in Table 5.

There is no consensus in the literature on the optimal duration of antimicrobial therapy (5,11,33,34,45-49,76-78); we suggest a 10-day course for pyelonephritis. For urosepsis we recommend a 14-day course to be started parenterally; however parenteral therapy can be limited to 3 days in most cases (grade B).

There is insufficient evidence and no recommendations on the use of methylprednisolone in the management of acute pyelonephritis, with one small study showing a significant reduction in scarring in the treatment arm that warrants a larger series (48,79).

IMAGING

When and how should ultrasound be performed?

We recommend performing RBUS in all children, 2-4 weeks after the first febrile UTI, in order to detect renal and urinary tract anomalies (grade B). We do not recommend a RBUS during the febrile UTI, unless it is complicated, atypical or severe (presence of any of the following: septic state, fever persisting after 3 days of appropriate antibiotic treatment, elevated plasma creatinine, oliguria)(grade B)(49).

The RBUS report should always describe the characteristics of the kidneys, and in particular renal length, echogenicity and thickness of the parenchyma. Other important characteristics are the features of the calices, the antero-posterior diameter of the renal pelvis at the exit from the renal parenchyma, the maximum diameter of the ureter, the wall thickness of the bladder and, if possible, pre and post-void bladder volume. We also recommend that the presence or absence of renal pelvic uroepithelial thickening is reported.

It is, however, important to point out that a great deal of evidence exists on the low predictive value of renal ultrasound as regards the presence of VUR. This examination is frequently normal in children with low-grade, and even in some with high-grade, VUR, and while mild and transient renal pelvic or ureteral distension is common, it is often not associated with VUR. On the other hand, abnormal RBUS findings represent a risk factor for UTI-related renal scarring and are present in up to 86 % of patients with high-grade VUR .(80). Among the abnormal findings, of

particular relevance are: mono- or bilateral renal hypoplasia, major pelvi-calyceal dilatation, ureteral dilatation, uroepithelial thickening of the renal pelvis (81).

When and how should imaging to detect VUR be performed?

We recommend imaging in order to detect VUR after the first febrile UTI when RBUS reveals mono- or bilateral renal hypoplasia, anomalies of parenchymal echogenicity, ureteral dilatation, uroepithelial thickening of the renal pelvis, pelvi-calyceal dilatation, particularly if associated with uroepithelial thickening, bladder abnormalities (grade B). An isolated dilatation of the renal pelvis generally does not represent an indication for further imaging (grade B). In addition, imaging for the detection of VUR should be performed when the UTI is caused by a pathogen other than *E. coli* (grade A) (2,82) and in children with recurrent febrile UTIs (Figure 2).

Imaging options

Currently, there are four imaging modalities available for the detection of VUR.

Fluoroscopic contrast voiding cysto-urethrography (VCUG) is the standard method for the diagnosis of VUR and assessment of the degree of reflux and the anatomy of the male urethra (grade A). A standardized protocol for VCUG performance has recently been issued: in boys, lidocaine gel is instilled in the urethra before catheterization; a small age-appropriate (3.5–8 French) non-balloon catheter is inserted by means of a sterile procedure; the bladder should be filled until voiding occurs and if VUR is not identified on the first void, a second filling with the same catheter should be performed to increase the chance for detection of VUR (83).

Vesico-ureteric reflux is detected with equal or superior sensitivity by direct radionuclide cystography, which delivers much less radiation than VCUG, but is less readily available and does not provide anatomic details of the male urethra; it could represent the first choice in females (grade B).

Contrast enhanced voiding ultrasonography is a sensitive modality used to detect VUR (84,85); in addition, a second-generation contrast agent and a transperineal approach enables a precise evaluation of the bladder and male urethra (86). It is less commonly performed because it is time consuming, expensive and not available on a large scale.

The last option is indirect radioisotopic cystography, which can be obtained during the last phases of a MAG 3 scintigraphy, however it has a low sensitivity and specificity.

Is antibiotic treatment necessary at the time of catheter insertion for imaging?

Even though it is widely prescribed in clinical practice, prescription of antibiotic therapy is debated: some guidelines recommend its use (11), but recent data show that the risk of UTI after

VCUG is very low (87). We suggest administering antibiotic treatment at full dosage for three days in infants, especially within the first 12 months of life, or when major urinary tract abnormalities are present at RBUS (grade C).

Scintigraphy

Scintigraphy is not routinely recommended after the first UTI. The implementation of a renal cortical scintigraphy (with DMSA) is recommended in all children with VUR grades IV and V, which have been recognized as major risk factors for permanent renal damage (grade B) (88,89). In order to evaluate the presence of UTI-related renal scarring, a renal scan has to be performed at least 6 months after the febrile UTI, the time required to avoid misinterpretation of transient changes related to the acute infection.

WHAT TO DO AFTER THE FIRST FEBRILE UTI?

Most febrile UTIs in children are uneventful infections, occurring in otherwise normal children who have an excellent prognosis. A relatively small number of children (6-10%) will develop recurrences, generally during the following year (46). Recurrence risk factors are high-grade reflux, age below one year in males, female sex, and bladder bowel dysfunction.

Generally speaking, it is important to instruct parents to recognize UTI symptoms and to prevent modifiable risk factors for recurrent UTIs and in particular constipation and bladder bowel dysfunction (90,91). We believe that also a low fluid intake has to be taken into consideration (grade C).

Circumcision is a conceivable option in selected cases of males with high grade VUR, and with recurrent febrile UTIs despite other efforts to prevent infections.

As regards antibiotic prophylaxis**,** it has been used for decades in children with VUR, with the assumption that renal damage and its progression would be prevented if recurrent UTIs were avoided. Currently, its effectiveness is under debate. A number of recent randomized controlled trials have shown no or a minimal effect of antibiotic prophylaxis in reducing the recurrence of UTIs (92-96). Various meta-analyses have been published (97-99); among those, the one published by De Bessa et al appears of particular interest, as the authors separated dilating (grades III-IV-V) and non-dilating (grades I-II) VUR as far as breakthrough infections are concerned (99). Analyzing the first published studies, the authors found that antibiotic prophylaxis would be beneficial only in children with high grade VUR. With the addition of the data from the RIVUR study (100), these results changed, supporting antibiotic prophylaxis in all children with VUR. It has to be underlined that the RIVUR trial evaluated 607 children (92% female) with an age range

of 2-71 months, 126 were toilet trained, 71 of them had bladder bowel dysfunction, and 92% had grade I to III reflux. We believe that the treatment showed statistical, but not clinical significance: 22 patient-years of antibiotics were required to prevent one febrile UTI. Therefore, the analysis of the data regarding recurrent infections does not stand in favor of the use of antibiotic prophylaxis, at least in children with low-grade reflux.

An additional concern is the propensity of antibiotics to induce bacterial resistance. A recent meta-analysis by Selekman et al (101) showed that prophylaxis increases the risk of multidrug resistance (children receiving prophylaxis had 6.4 times the odds), with important implications in the risk-benefit assessment of prophylaxis.

Concurrently, it has become clear that prophylaxis does not reduce the appearance and progression of permanent renal damage, as shown by multiple recent meta-analyses (97-99,102). Furthermore, the treatment group from the RIVUR trial received together over 600 years of prophylaxis, without a demonstrable effect on scar formation.

In conclusion, antibiotic prophylaxis is not routinely recommended in infants and children after the first febrile UTI (grade A). It may be considered in infants and children after treatment of the acute episode until VCUG is performed (grade C), with reflux grades IV and V (grade C), and with recurrent febrile UTIs, defined as > 3 febrile UTIs within 12 months (grade C).

These recommendations are in line with the main international guidelines (4,5,11).

As a first choice prophylactic agent, we suggest amoxicillin–clavulanic acid, while ceftibuten or nitrofurantoin should be regarded as secondary options, keeping in mind that nitrofurantoin may cause gastrointestinal intolerance and is inactive against most strains of *Proteus* (103). There is insufficient evidence to recommend a specific dose; however, traditionally, the dose used for prophylaxis has been one-quarter to one-third of the treatment dose, given once per day. There are no data on the efficacy of the practice of alternating prophylactic antibiotics.

Similarly, the optimal duration of prophylaxis has not been established. According to the longer susceptibility to UTI in girls than in boys, we suggest 12 to 24 months in girls and 6 to 12 months in boys (grade C).

Other interventions for preventing UTI

Several interventions, other than antibiotic prophylaxis, have been used for the prevention of recurrent UTIs, but evidence for their effectiveness in infants and children is lacking (104).

The efficacy of cranberry juice remains questionable. In a study on children aged 1 to 6 years, with recurrent UTIs, but no or minor urologic malformations, the intervention (cranberry for 6 months) did not significantly reduce the number of children who experienced a recurrence of UTI, but it was effective in reducing the actual number of recurrences and related antimicrobial use (105).

Few studies are available on probiotics and, at present, no significant benefit has been demonstrated for UTI prevention (106).

HEALTH BENEFITS, POTENTIAL RISKS AND LIMITATIONS OF OUR RECOMMENDATIONS

Our recommendations are useful in helping the practicing clinician to determine the diagnostic and therapeutic approach to a child with a febrile UTI. Furthermore, the clinical use of the recommendations will lead to a reduction in the number of performed VCUG, and therefore to a reduction of radiation and financial costs. On the other hand, reducing the number of VCUG could produce the risk of missing a small number of high grade VUR after the first febrile UTI; anyhow, a second febrile UTI represents in our recommendation an indication to further imaging. Another health benefit may be represented by a more restricted use of antibiotic prophylaxis, also addressing the problem of growing antibiotic resistance; of course, the risk of increasing UTI recurrences has to be kept in mind.

FUTURE RESEARCH

The authors of these recommendations have found some gaps in the knowledge on UTI in infants and children, needing further studies. In particular we suggest the need to study the number of colony count needed to make a diagnosis of UTI and the scientific rationale to recommended different numbers of colony counts for different urine collection modalities. Other points are the meaning of nitrites in the absence of leukocyturia, the role of steroids in preventing the appearance of scarring, the role of a high fluid intake in preventing recurrent infections and the need of antibiotic prophylaxis in children with high grade reflux.

Further research should also establish if a shorter duration of antibiotic treatment is warranted. Most importantly, needed to establish the potential morbidity of UTIs in the long-term (107), are prospective studies following a first febrile UTI of children with normal kidneys as well as in children with prenatally diagnosed hypodysplasia.

LIST OF ABBREVIATIONS

UTI urinary tract infection

VUR vesicoureteral reflux

RBUS renal and bladder ultrasound

UC urine culture

LE leukocyte esterase

CVU clean voided urine

BC bladder catheterization

SPA suprapubic aspiration

VCUG voiding cysto-urethrography

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The authors have no conflicts of interest to declare.

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Table 1 **Urine culture collection methods**

Method	Recommendation	References
Bag	Not recommended	5,11,19, 21
CVU	Recommended in primary care Second choice in hospital settings (consider micturition stimulating methods in infants <6 mo, < 10 kg)	11,14-19, 21,23,
Transurethral BC	First choice in hospital settings and mandatory in critically ill children	5,11,19,21,26
SPA	Gold standard, but not feasible as a routine procedure in primary care.	5,11,12,19-21

CVU = clean voided urine; BC = bladder catheterization; SPA = suprapubic aspiration

Table 2

Sensitivity and specificity of urinary dipstick (leukocyte esterase and nitrite) and microscopy (white blood cells and bacteria) for diagnosis of urinary tract infection (adapted with permission from Williams GJ)(9)		
Test	Sensitivity % (range)	Specificity % (range)
Leukocyte esterase	79 (73-84)	87 (80-92)
Nitrite	49 (41-57)	98 (96-99)
Leukocyte esterase or nitrite positive	88 (82-91)	79 (69-87)
Both leukocyte esterase and nitrite positive	45 (30-61)	98 (96-99)
Microscopy: white blood cells	74 (67-80)	86 (82-90)
Microscopy: unstained bacteria	88 (75-94)	92 (83-96)
Microscopy: Gram stain	91 (80-96)	96 (92-98)

Table 3

Interpretation and suggested practical approach following the result of nitrite and leukocyte esterase urine dipstick		
Nitrite positive Leukocyte esterase positive	UTI very likely	Perform urine culture and start antibiotics empirically
Nitrite negative Leukocyte esterase positive	UTI likely	Perform urine culture and start antibiotics empirically
Nitrite negative Leukocyte esterase negative	UTI quite unlikely	Search for alternative diagnosis

Legend: UTI: urinary tract infection

Table 4 **Cut-off for a significant colony count in urine culture according to urine collection method**

Method	Cut-off values indicated in the literature (Reference number)	Our Recommendation (Grade C)*
SPA	Any growth (11,19,20) or > 50.000 CFU/ml (or less if fever and leukocyturia) (5)	> 10.000 CFU/ml
Transurethral BC	> 50.000 CFU/ml (5,10) Or > 10.000 CFU/ml (11,19) if fever and leukocyturia (5,10)	> 10.000 CFU/ml
CVU	> 100.000 CFU/ml (4,11,19,20,21)	> 50.000 CFU/ml
Bag**	> 100.000 CFU/ml (20,21)	> 100.000 CFU/ml

* *It refers to children with fever ≥38°C* and leukocyturia

** Not recommended

Legend: SPA= suprapubic aspiration; BC= Bladder catheterization; CVU= clean voided urine

Table 5 **Suggested dosage for antibiotic treatment of febrile urinary tract infections**

Treatment	Dose
Intravenous	
Penicillins	
Ampicillin-Sulbactam	100 mg/kg/day of ampicillin in 3-4 doses
Amoxicillin-clavulanic acid	100 mg/kg/day of amoxicillin in 3-4 doses
Cephalosporins	
Cefotaxime	150-200 mg/kg/day in 3-4 doses *
Ceftriaxone	75-100 mg/kg/day in 1 dose *
Aminoglycosides	
Amikacin	15 mg/kg/day in 1 dose **
Gentamicin	6-7.5 mg/kg/day in 1 dose **
Oral route	
Amoxicillin-clavulanic acid	50-90 mg/kg/day of amoxicillin in 3 doses
Cephalosporins	
Cefixime	8 mg/kg twice/day 1st day, once daily thereafter
Ceftibuten	9 mg/kg twice/day 1st day, once daily thereafter
Ciprofloxacin	20-40 mg/kg/day in 2 doses
Trimethoprim-sulfamethoxazole	8–12 mg/kg/day of trimethoprim in 2 doses ***

* The highest dose in children with urosepsis

** Serum levels must be monitored and dosage adjusted accordingly

*** To be used only on the basis of antibiogram sensitivity, because of the high resistance rate

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Dosages, in accordance with those cited in References 1 and 35 and with the Sanford Guide to Antimicrobial Therapy, may vary from those used in some Institutions or trials. Always compare with current product monographs.

Table 6

UTI recommendations at a glance
Diagnosis. The diagnosis of UTI should be considered in children presenting with fever (38°C or higher) and no apparent source. Urine should be collected and analyzed by microscopy or dipstick to identify children in whom UTI is very likely (leukocyturia with or without nitrites) and by urine culture to make a definitive diagnosis. **Urine culture**. To collect urine, a two-step approach is feasible in febrile children in good clinical condition. Urine can be collected by clean voided method or bag for dipstick. If the dipstick shows the presence of leukocytes with or without nitrites, a sample for urine culture should be collected by clean voided urine or transurethral bladder catheterization. If the dipstick is normal, there is no need to perform a urine culture and a new dipstick is recommended after 24-48 hours, if the fever persists. In a severely ill febrile child urine must be collected by transurethral bladder catheterisation or suprapubic aspiration. **Treatment**. In a febrile child with positive urine dipstick or microscopy, antibiotic treatment must be initiated soon after urine culture is obtained. Suggested antibiotics are: amoxicillin-clavulanic acid as first line if the oral route is possible in children who appear well and ampicillin-sulbactam or amoxicillin-clavulanic acid if the intravenous route is indicated in severely ill children. **Imaging**. A renal and bladder ultrasound is suggested in all children, 2-4 weeks after the febrile UTI, while voiding cystourethrography is indicated when ultrasound reveals major anomalies of the kidney and/or urinary tract and/or when the UTI is caused by a pathogen other than Escherichia. coli. **Antibiotic prophylaxis.** This is not routinely recommended after the first febrile UTI. It may be considered in children with reflux grade IV and V, or with recurrent febrile UTIs, defined as more than three febrile UTIs within 12 months.

Figure 1 **Treatment of urinary tract infection**

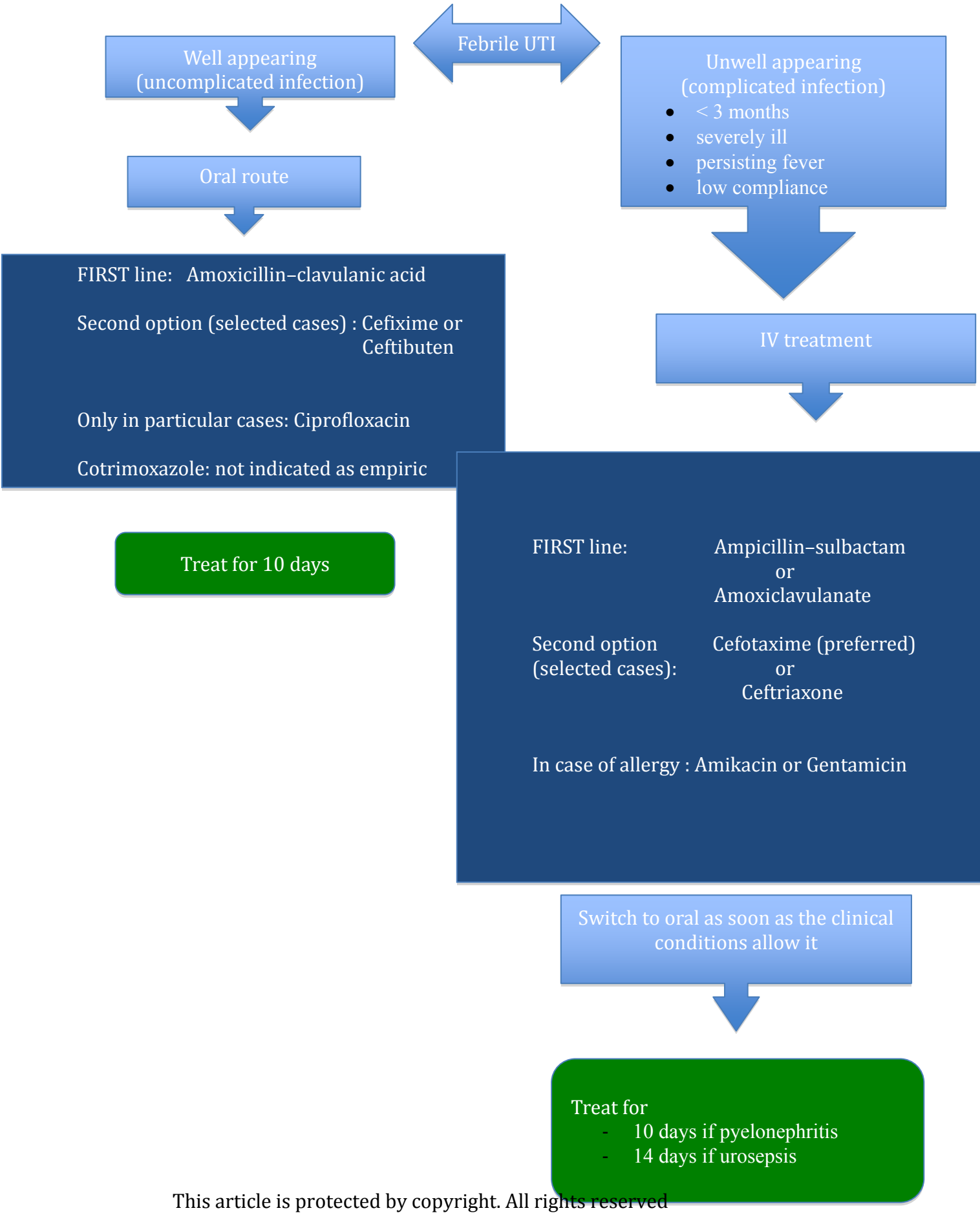
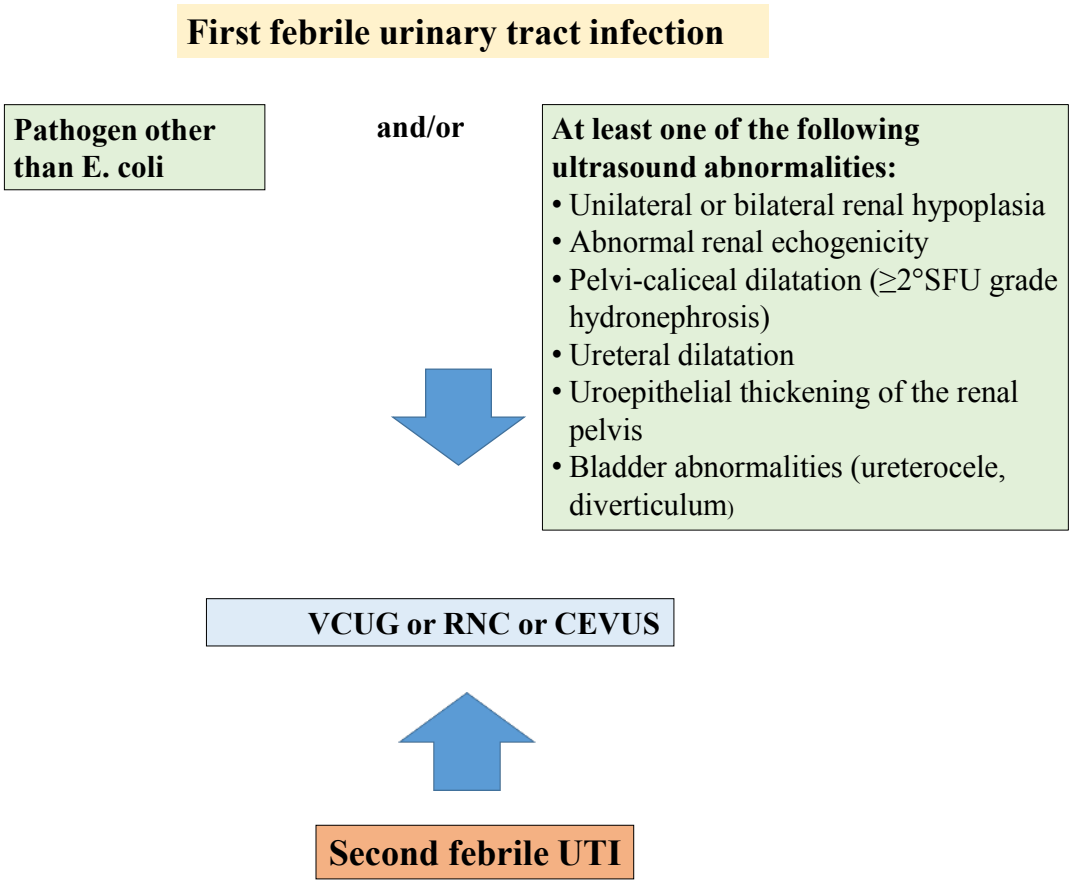


Figure 2 **When should imaging to detect vesicoureteral reflux be performed**?



Legend:
SFU: Society for fetal Urology; VCUG: fluoroscopic contrast voiding cysto-urethrography; RNC: direct radionuclide cystography; CEVUS: contrast enhanced voiding ultrasonography