**Urinary tract infection: a search for evidence**

Vera H. Koch¹, Sandra M.C. Zuccolotto²

**Abstract**

**Objective:** to review urinary tract infection in children taking into consideration evidence-based medicine.

**Sources:** search of Medline and Cochrane databases, comprising the period between 1996 and 2002, with the following key words: urinary infection, vesicoureteral reflux, children, adolescents, diagnosis and treatment. Cohort studies, quality assurance studies, consensus, meta-analysis studies, randomized controlled trials and audits were selected.

**Summary of the findings:** the studies were selected according to their methodology, relevance and clinical applicability. Some studies were selected based on the parameters proposed by the American Academy of Pediatrics in 1999 for the diagnosis and treatment of urinary tract infection in children between two months and two years of age.

**Conclusions:** consensus statements on diagnosis and treatment of urinary infection in children and adolescents are still mostly opinion-based. Randomized multicentric controlled trials, with double-blind allocation are necessary to improve quality of diagnosis and management of pediatric urinary tract infection.


**Introduction**

The healthy urinary tract is sterile. Except for the neonatal period, the ascending contamination of the urinary tract by microbial agents found in the intestinal flora is the most frequent pathogenic mechanism of urinary tract infection.

Male children are more susceptible to urinary tract infection (UTI) in the first two or three months of life. Later on, female children are proportionally more affected. At least 8% of girls and 2% of boys are estimated to have at least one episode of UTI during childhood.¹ The incidence of childhood UTI is unknown. Jakobsson et al.,² by way of a prospective multicenter study carried out in Sweden, analyzed all diagnoses of first urinary tract infection in children younger than two years (cases of meningomyelocele and genital malformations were not included) and found an average incidence of 1% for both sexes.

*Escherichia coli* is involved as etiologic agent in 75% of UTI cases. In male children, *Proteus sp* is isolated in approximately 30% of the cases. Imaging exams after the first urinary tract infection show obstruction in up to 4%

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¹ PhD, Head, Pediatric Nephrology Unit, Children’s Institute, Hospital das Clínicas, School of Medicine, Universidade de São Paulo
² Assistant physician, Children’s Institute, Hospital das Clínicas, School of Medicine, Universidade de São Paulo.
of the cases and vesicoureteral reflux (VUR) in 8% to 40% of the patients.3

Recurrence of UTI after the first infection occurs in 50% of girls in the first year of follow-up and in 75% of the cases in a two-year period; no comparative data for males are available.4

Special attention has been given to early diagnosis and treatment of the acute infectious episode in children with UTI, in addition to the reduction of chronic renal damage and its clinical consequences. The presence of renal scarring has been documented in 5% to 15% of the children assessed after the first febrile urinary tract infection.5-8

Children with VUR may present with new renal scars or expansion of the site affected by old scars in sequential imaging exams. This often occurs in the presence of recurrent urinary tract infection.9-13

The risk of development of chronic renal damage in children with few episodes of UTI (one or two), properly diagnosed and treated, has not been determined yet and may be negligible. Some studies investigated the long-term risk of development of arterial hypertension and chronic renal insufficiency in children diagnosed with UTI.9,14-19 The analysis of these studies shows that although the figures that could define the risk of development of these morbid events in children with UTI are imprecise, the combination of severe VUR, recurrent urinary tract infection and renal scarring at the diagnosis of the first infection seems to be associated with poorer prognosis.

The American Academy of Pediatrics published, in 1999, a set of guidelines for the diagnosis, treatment and investigation of first urinary tract infection in febrile children aged between two months and two years.20 Such document clearly states that most recommended guidelines are based on a consensus rather than on well-established clinical evidence. The selection of the age range (two months to two years) is justified by the frequency of urinary tract infection in this age group, potential development of long-term clinical problems, such as arterial hypertension and impaired renal function and by the diagnostic difficulty regarding the clinical presentation of the disease and collection of urine samples for the diagnosis. For older children and adolescents, the clinical and laboratory-based diagnoses of urinary tract infection are believed to be simpler, since the complaints made by patients this age are more accurate and urine samples can be obtained through midstream collection (sphincter control is already present) and, even though there is no common agreement, the diagnostic, treatment and initial follow-up measures are admittedly similar to those accepted for infants, after febrile urinary tract infections in which acute pyelonephritis is considered.

The aim of the present study is to discuss urinary tract infection in light of clinical evidence. For this purpose, Medline and Cochrane databases were searched between 1996 and 2002, using the following key words: urinary tract infection, vesicoureteral reflux, child, adolescent, diagnosis and treatment related to the words quality, consensus, meta-analysis, cohort studies, randomized and controlled trials, auditing. The articles we found were selected according to methodological aspects, clinical relevance and application, with special emphasis on controversial aspects of diagnosis and treatment.

What is the best method for collecting urine samples for urine culture?

The American Academy of Pediatrics recommends that the urine of febrile patients aged between two months and two years be collected by invasive methods (suprapubic aspiration, urethral catheterization), in female children and in uncircumcised boys, since in these cases, bag specimens have a high level of contamination.20 After the child has sphincter control, the collection of a midstream urine specimen is possible and produces reliable results.

Hansson et al.21 developed a two-year, prospective, multicenter project in Sweden for the assessment of the quality of diagnosis and follow-up of first urinary tract infection in patients aged less than two years. They assessed 2,309 children. Suprapubic aspiration was used for 39% of urine samples, and was predominantly performed in the first year of life (63% from 0 to 3 months; 46% from 3 to 6 months; 36% from 6 to 12 months; 12% from 1 to 2 years.) Bagged specimens, used in 50% of urine sample collections, were the method of choice for older children (30% from 0 to 3 months; 43% from 3 to 6 months; 53% from 6 to 12 months and 73% from 1 to 2 years), whereas midstream urine samples were obtained in 11% of the cases.

Greaves and Buckmaster22 audited the database of a microbiology laboratory and assessed collection methods and urine culture results of febrile children for three months. Afterwards, they analyzed the obtained data, compared them with those recommended in the literature, and implemented an educational program for the rationalization of urine sample collection and optimization of UTI diagnosis. After the qualification phase, the number of collected samples drops from 60% to 14% per bag of urine, with remarkable reduction of false-positive and inconclusive UTI diagnoses.

Among the methods for urine collection, suprapubic aspiration has the best sensitivity, and urethral catheterization is the second best. The wide use of bag specimens in the Swedish study shows the difficulty in implementing an invasive method for urine collection, even in industrialized countries with a high alert level for the diagnosis of UTI in children. On the other hand, the study conducted by Greaves & Buckmaster22 indicates the possibility of success of local consciousness-raising programs.

Bag specimens are of great value when they yield negative results, because they rule out the diagnosis of
UTI, but they have a large frequency of false-positive results. Therefore, they should not be used in situations that require immediate implementation of antibiotic therapy.

**What parameter of urinalysis should be valued when urinary tract infection is suspected in children?**

Urinalysis for leukocyturia and bacteriuria may be carried out by conventional methods, with spun urine, or by using a hemocytometer - a graduated chamber to which 1 ml of unspun urine is added. Kass' defined pyuria as the presence of at least 5 leukocytes/field in spun urine. The sensitivity, specificity and positive predictive value of this type of urinalysis were unacceptably low, correctly identifying only 30-50% of UTI cases. This finding encouraged the investigation of new methods. Dukes' introduced the counting of urinary elements, in unspun urine placed in a hemocytometer, and Stamm' defined pyuria, using the same technique, as the presence of at least 10 leukocytes/mm$^3$, with a sensitivity of 96% in symptomatic adults with UTI. Similar findings were obtained by Hoberman et al. in febrile children, from whom the urine was collected through urethral catheterization, with a sensitivity of 91.2% and specificity of 96.5% for the diagnosis of UTI confirmed via urine culture.

Lin et al. analyzed urine samples of 230 febrile children, submitted to suprapubic aspiration, using conventional urinalysis, hemocytometer and quantitative urine culture. For conventional analysis, a urine sample was centrifuged at 2,000 rpm for 10 minutes and later submitted to microscopy; in the analysis using a hemocytometer, 1 ml of unspun urine was used. The authors found a sensitivity of 83.8%, positive predictive value of 60.8% and specificity of 89.6% with the hemocytometer, where conventional urinalysis showed a sensitivity of 64.9%, positive predictive value of 51.1% and specificity of 88.1%.

Conventional urinalysis, in addition to showing poorer results than the hemocytometer, is performed with little methodological homogeneity for standardization of the volume to be analyzed, duration and intensity of centrifugation, volume for resuspension of the spun material and number of fields analyzed on microscopy. The hemocytometer technique eliminates the heterogeneity caused by the centrifugation and resuspension of the sample, since it uses a fixed urine volume and counting of elements in a graduated field.

Gorelick & Shaw assessed the usefulness of rapid tests with diagnostic strip (leukocyte-esterase and nitrite tests) by performing a systematic review and meta-analysis of the literature, a microscopic analysis and Gram stain of spun and unspun urine for the diagnosis of UTI in patients younger than 12 years. For this purpose, 1,489 titles of articles were surveyed, 26 of which showed criteria for analysis. The presence of any bacterial count on unspun urine on Gram stain obtained the best combination of sensitivity (93%) and specificity (95%). Quick tests had a sensitivity of 88% for leukocyte-esterase or nitrite and specificity of 96% for concomitant positivity of both. The presence of pyuria showed the worst sensitivity and specificity, which varied according to the type of analyzed sample, that is, sensitivity and specificity of 67% and 79% for leukocytes > 5 /field in spun urine and of 77% and 89% for leukocytes > 10 mm$^3$ in unspun urine.

The initial and final portions of the urine sample obtained through urethral catheterization were also investigated. The initial portion is more appropriate for the detection of leukocyturia (p < 0.01) and bacteriuria (p < 0.05), that is, detection of contamination, than the final portion. Therefore, it is important to discard the first 2-3 ml of samples collected by way of urethral catheterization in order to avoid false-positive results.

The enhanced assessment of urine samples, which includes leukocyte-esterase and nitrite tests and microscopy for the detection of leukocyturia and bacteriuria, has a sensitivity of 99.8% and specificity of 70% for the diagnosis of UTI, when any of these exams, in isolation or combined, yields abnormal results. It is recommended that urine specimens be obtained through collection bags from febrile children without sphincter control, if there is no need for immediate implementation of antibiotic therapy. If any of the items of the enhanced assessment of the urine sample is altered, urine should be collected by invasive methods. On the other hand, if the enhanced assessment of the urine sample is normal, the child can be observed without the need of urine culture. In our setting, this recommendation may be implemented by performing a qualitative urinalysis, in a urine sample collected under aseptic conditions, by using a nitrite and leukocyte-esterase test strip and urinary microscopy for quantification of leukocyturia and bacteriuria.

**Should the foreskin be regarded as a risk factor for urinary tract infection?**

Schoen et al. retrospectively assessed the presence of UTI in a cohort of newborn infants, treated at an American prepaid medical service. Among UTI episodes diagnosed in the first year of life, 86% occurred in uncircumcised boys. The incidence of UTI in the first year of life was of 2.15% in uncircumcised boys, 2.05% in girls and 0.22% in circumcised boys, leading us to conclude that neonatal circumcision results in a 9.1-fold reduction of UTI incidence in the first year of life, especially during the first three months. In a meta-analysis published in 1999 and in other studies, results similar to those reported by Schoen et al. were obtained, showing that the presence of foreskin elevates the risk for UTI by 3.7 to 11 times.
What other risk factors should be considered in children with urinary tract infection?

Risk of recurrence

Panarett et al.37 assessed the risk of UTI recurrence in a population of 261 children, aged less than five years, with a one-year follow-up after the diagnosis of their first infection. Forty-six recurrent episodes were reported in 34 children and multiple recurrence occurred in 14/34 children. The recurrence of UTI was more frequent in infants with first infection aged less than six months, presence of VUR ≥ grade III and confirmation of renal scarring at the diagnosis of first urinary tract infection.

Risk of urological malformation and renal damage

Honkien et al.,38 carried out a 14-year retrospective cohort study and assessed the association between the bacterial strain isolated from the first urinary tract infection in children, in urine samples collected by suprapubic aspiration or urethral catheterization, and the presence of abnormalities in subsequent imaging studies. E.coli accounted for 80% (982/1,237) of infections, VUR was diagnosed in 30% of infections caused by E.coli. In patients with first urinary tract infection caused by Klebsiella sp or Enterococcus sp, the frequency of VUR diagnosis nearly doubled and the necessity for surgical intervention was four times higher than in the group with infections caused by E.coli. The identification of E.coli with absence of pyelonephritogenic factors (galactose-alpha and galactose-beta (Gal-Gal)-specific adhesins and pap homologous DNA39) was frequent in patients with VUR-associated acute pyelonephritis. The development of renal scarring was more frequent in patients with urinary tract infection caused by non-E.coli organisms or by less virulent E.coli strains. In conclusion, bacteria do not require special virulence factors when the host shows predisposing factors for pyelonephritis, such as VUR.

How to program imaging exams in children after their first urinary tract infection?

Deshpande and Jones40 retrospectively assessed children aged from 0 to 12 years with diagnosis of UTI for one year and found that the prevalence of alterations observed in imaging exams complied with the local protocol.41 One hundred sixty four children were observed in imaging exams complied with the local protocol. One hundred sixty four children were observed in imaging exams complied with the local protocol. One hundred sixty four children were observed in imaging exams complied with the local protocol.

Should 99mTc DMSA scintigraphy be performed in the acute phase of urinary tract infection or only for detection of renal scarring?

A recent consensus of Nuclear Medicine experts45 established that renal scintigraphy with 99mTc DMSA should be used for detection of renal scarring, even though its indication for the assessment of the acute phase of UTI is controversial.

Yet, there is no common agreement about the time interval necessary for 99mTc DMSA renal scintigraphy, for detection of renal scarring, to be performed. Jakobsson and Svensson46 prospectively studied 185 children aged between 0.1 and 9.8 years, with acute UTI, by using 99mTc DMSA renal scintigraphy, repeated on average 9.2, 120 weeks and 1.5-3.9 years after initial examination, with the aim of evaluating the development of renal scarring based on acute alterations. Positivity of alterations in this exam was of 85% in the acute phase, 58% on the second examination and 36% after 20 weeks. The assessment made 1.5-3.9 years after the acute phase still evidenced the disappearance of 10% of alterations observed 20 weeks after the acute infectious process. The authors concluded that 99mTc DMSA renal scintigraphy for detection of chronic renal damage should be carried out at an interval greater than five months after the acute infectious process.
Is micturating cystourethrography mandatory in the investigation of children with urinary tract infection when urinary and renal ultrasonography and 99mTc DMSA renal scintigraphy yield normal results?

Kass et al. evaluated four hundred fifty three 99mTc DMSA renal scintigraphies obtained as part of the assessment of children with UTI, of which 157 were normal, and 101 showed normal urinary and renal ultrasonography. Of 101 patients with normal renal scintigraphy and urinary ultrasonography, 23 (23%) revealed VUR, of which 14 had bilateral VUR and 13 showed VUR ≥ grade III. We can conclude that micturating cystourethrography is mandatory in the assessment of febrile childhood UTI.

Should the treatment of acute urinary tract infection be made with short-course (< 5 days) or conventional antimicrobial therapy (7 to 14 days)?

In women, the treatment of lower urinary tract infection (uncomplicated cystitis) with short-course antimicrobial therapy, whose duration ranges from one single dose to three days, proved to be efficient and is standardized in the literature. The advantages of the short-course over conventional therapy are: (1) cost containment; (2) improvement of treatment adherence; (3) minimization of side effects. In addition, the hypothesis that short-course antimicrobial therapy reduces the development of bacterial resistance in the intestinal and periurethral flora, compared to conventional treatment, is still under analysis. With all these advantages, studies on whether the efficiency shown in the treatment of lower UTI in women also occurs in infants have been under way, since it is commonly known that age groups behave differently in relation to UTI: up to now, it has not been possible to accurately identify the site of urinary tract infection (upper or lower) in children, - either by the symptoms or routine lab exams; when compared to adults, children are more likely to have anatomic/functional malformations and vesicoureteral reflux, which could favor the development of pyelonephritis and, consequently, of renal scarring and their possible lifelong repercussions - arterial hypertension and/or chronic renal damage.

We found three meta-analyses in the literature on the treatment of lower UTI (uncomplicated cystitis), which compare short-course and long-course therapies in children and adolescents up to the age of 18.

In the first meta-analysis, published in 2001, Tran et al. selected 22 randomized and controlled studies, with a total of 1,279 children from 0 to 18 years, in order to assess the cure rate provided by the following antimicrobial therapy regimens against uncomplicated cystitis: single dose, short course (< 4 days) and conventional regimen (≥ 5 days). Based on the duration of the short course and on the type of antimicrobial used in short-course and conventional therapies, the authors found five subgroups: (1) 17 clinical trials, in which the same antimicrobial agent was used for short-course and conventional treatments; (2) nine studies, in which the single dose of antibiotic was compared with the conventional course; (3) 13 clinical trials, in which the short course with more than one dose of antimicrobial was compared to the conventional therapy; (4) five studies in which amoxicillin was used in short-course and conventional therapies; (5) six studies in which sulfamethoxazole-trimethoprim was used in short-course and conventional regimens. When 22 studies were submitted to statistical heterogeneity tests, the results were significant, suggesting that the different definitions of short course and the use of different antimicrobial agents could interfere with the results. The cure rate was defined as [1- (number of treatment failures/number of patients that completed the treatment)] and treatment failure was defined as the presence of bacteriuria with the same bacterial strain observed in the initial infection, after cessation of the treatment. The authors reached the following conclusions: (1) a short-course antimicrobial therapy has a lower cure rate than conventional treatment; (2) single dose of amoxicillin is inadequate for the treatment of childhood cystitis; (3) a three-day treatment with sulfamethoxazole-trimethoprim seems to be as effective as conventional treatment as far as uncomplicated cystitis is concerned.

In the second meta-analysis, published in 2002, Michael et al. selected 10 randomized and controlled studies, including 652 children aged from three months to 18 years, with lower UTI (children with fever, vomiting, flank pain, toxemia or with known urinary tract infection) and who received antibiotic therapy for two to four days or for seven to 14 days. The parameters for assessment the efficacy of therapeutic regimens after cessation of treatment were persistence of bacteriuria and recurrence of UTI. As to the quality of the 10 selected studies, only two were adequately randomized (the other ones did not clarify how the cases were allocated) and only one was double-blind. In this meta-analysis, no significant difference was observed between short-course and conventional regimens in terms of persistence of bacteriuria and recurrence of UTI within 10 days to 15 months after cessation of treatment. However, in the discussion of the results, the authors state that it is not possible to give irrefutable evidence that the short-course regimen is better or worse than the long-course one at eradicating childhood UTI, due to residual statistical inaccuracy, especially in children with recurrent UTI.

In the third meta-analysis, published in 2002, Keren et al. selected 17 randomized and controlled studies of children with lower UTI, aged from 0 to 18 years, which compared short-course (≥ 3 days) and conventional (7 to 14 days) antimicrobial regimens. The parameters for assessment of the efficacy of the regimens after cessation
of treatment were treatment failure, defined as persistence of bacteriuria or relapse (UTI caused by the same agent after bacteriologic cure), and reinfection (by a different agent). In this meta-analysis, conventional regimen proved to be more efficient in treating UTI since there was less treatment failure and lower rate of reinfection than in the short-course regimen. The authors, in an attempt to explain the difference between these results and those observed in adults, put forward two hypotheses: (1) great difficulty in distinguishing upper from lower UTI in children; (2) in children, cystitis requires longer antimicrobial therapy than in adults. They question about the quality of the analyzed studies and suggest a series of methodological parameters that should be followed in case of new research is conducted into this topic.

Therefore, as far as the treatment of children and adolescents with lower UTI is concerned, whether the short-course regimen could be as efficient as the conventional one it is still a matter for discussion, since the results produced by the three meta-analyses disagree with each other. In two of them, the conventional regimen showed to be more efficient and in one of them no significant difference was noted between the short-course and the conventional regimens. These results indicate the necessity to invest in research in order to clarify this issue once and for all, emphasizing the stratification of results according to age, sex, and site of infection in the urinary tract. In our daily practice, we use the conventional regimen (7 to 10 days).

In cases with clinical suspicion of pyelonephritis and in those with urinary tract disorders, the treatment should be maintained for at least 10 days.

The American Academy of Pediatrics,19 in 1999, recommended that children with UTI aged between two months and two years, including those whose initial treatment consisted of parenteral drug administration, should complement the conventional antimicrobial regimen (7 to 14 days) with oral antibiotic therapy. Most uncomplicated UTI cases are resolved by means of antimicrobial therapy for 7-10 days. Several authors prefer to maintain the treatment for 14 days, when the child has clinical suspicion of pyelonephritis and poor general health status. However, no studies exist comparing the results with 10 and 14 days of treatment.

Can pyelonephritis be treated at home?

The management of children with UTI requires early diagnosis and treatment of acute pyelonephritis for minimizing the possibility of renal scarring52,53 - Some textbooks recommend that children with pyelonephritis be initially treated with parenteral antibiotic therapy. Hoberman et al.54 carried out a randomized, multicenter study with 306 children with fever and UTI aged from one to 24 months, with the aim of assessing the efficiency of oral antibiotic therapy (for 14 days) versus initial intravenous therapy (for three days or until the child is feverless for 24 hours, followed by oral therapy up to the fourteenth day.) Clinical outcome during treatment, complications and presence of renal scarring after six months of treatment were evaluated. Children whose general health status was compromised (three cases) and those with vomiting (one case) were not included in the randomization process. No significant difference was found between the two routes of administration of the antimicrobial drug. The authors defended the length of treatment for 14 days, as when this study was implemented in 1992, this was the local standardized treatment against pyelonephritis. Nevertheless, they believe that the administration of the medication for 10 days may be enough.

The American Academy of Pediatrics,19 in the 1999 publication about quality parameters for the diagnosis and treatment of children with febrile UTI aged between two months and two years, recommends that initial therapy in children whose general health status is not compromised and in those who do not have vomiting consist of oral or parenteral antibiotics.

It is advisable that the first oral dose of antimicrobial be given at the health service in order to check acceptance and tolerance of the drug. In addition, in our setting, due to the poor living conditions of most individuals and to the high price of medications, we recommend that, in cases of children whose lower or upper UTI can be clinically treated at home, the family leave the health service with enough medication to continue and complete the treatment or that they be referred to an easily accessible health unit where they can readily get the medication. The family should be instructed to return to the health service if the fever persists after 72 hours of treatment, or before that, if the child’s general health status deteriorates or if vomiting occurs.

Are low doses of antimicrobials efficient in the long term in preventing recurrent childhood urinary tract infection?

As previously mentioned, the recurrence rate of UTI is of approximately 50% in girls, in the first year after infection; there are no comparative data for boys.4 Renal scarring is estimated to occur in 5% to 15% of children after a febrile episode of UTI.5-8 Since renal scarring is a risk factor for subsequent arterial hypertension, methods to prevent febrile childhood UTI are being constantly researched. One of the main ways to reduce recurrence is to treat intestinal constipation or voiding dysfunction, whenever the case. The aim of chemoprophylaxis is to maintain the dose of antimicrobial drug in the bladder so as to prevent the multiplication of bacteria in the urinary tract and to avoid the development of pyelonephritis.
The risk of side effects with the prolonged use of antimicrobials ranges from 8% to 10%. Most of these side effects are not serious, such as nausea, vomiting, and skin reactions; however, the possible development of antimicrobial resistance of the intestinal and nasopharyngeal flora is enhanced.

We found two systematic reviews whose aim was to determine whether the prophylaxis with antimicrobials significantly reduces the frequency of UTI episodes. In the first review, published in 2000, Saux et al. reported that, although several textbooks of pediatrics and nephrology regard chemoprophylaxis as efficient in the prevention of UTI, they could only include six studies that reasonably met some methodological criteria for this type of research, after extensive review of the 1966-1999 literature. The inclusion criteria were as follows: (1) intervention: comparison between treatment with antimicrobials with placebo or with control (no treatment); (2) target population: up to the age of 18 years; (3) UTI episode: clear and standardized definition; (4). Type of study: randomized and controlled clinical trial.

For the six studies selected, we applied the research quality scale developed by Jadat et al., which ranges from 0 to 5. Five studies obtained score 5 and one study scored zero.

Of the five studies that scored 2 points, three dealt with prophylaxis in children with normal urinary tract and two were concerned with children with neurogenic bladder. The three studies with children with anatomically normal urinary tracts showed that chemoprophylaxis was somewhat efficient in preventing UTI. One study about chemoprophylaxis in children with neurogenic bladder showed that this type of therapy was efficient, but the other study yielded contrary results.

In the second systematic review, published in 2002, Williams et al. defined the following inclusion criteria: randomized trials of two or more antibiotics and placebo and of two or more antibiotics used to prevent UTI. Three studies were selected, totaling 151 cases, comparing antibiotic therapy with placebo/no treatment. The length of antimicrobial prophylaxis ranged from 10 weeks to 12 months. The method of allocation was adequate in only one clinical trial, inadequate in another one and unclear in the other one. Based on these three studies, the authors found out that the recurrence risk of UTI in the group that used antimicrobials was lower than in the group that received placebo/no treatment.

In both systematic reviews, the authors concluded that the results obtained may overestimate the effect of chemoprophylaxis of UTI, due to the inappropriate design of most trials already published, as when the quality of the trial is poor, the studied strategy tends to be overestimated. Based on these results, the authors stated that clinical trials with appropriate methodological design, with emphasis on groups stratified according to risk of recurrent UTI, are necessary so that an accurate conclusion about the efficiency of this method can be reached.

Therefore, since the benefits of antimicrobial prophylaxis seem to be negligible and as bacterial resistance may arise from its use, the possibility of using it in children with recurrent UTI and with anatomically normal urinary tract is remote. Chemoprophylaxis may be used in cases of recurrent UTI associated with conditions that predispose to urinary stasis, for instance, intestinal constipation and voiding dysfunction, while an endeavor is made to treat these conditions. The use of chemoprophylaxis in patients with VUR will be discussed next.

**In what cases should chemoprophylaxis be used in children with vesicoureteral reflux diagnosed after an episode of urinary tract infection and for how long should it be maintained?**

In prospective, randomized and controlled studies, no difference was observed as to the prognosis of children with primary VUR, after a follow-up of five to 10 years, submitted to conservative treatment (prophylaxis with low doses of antimicrobials in the long term) and to surgery for correction of VUR, in terms of development of chronic renal damage and new renal scars.

In 1997, the American Urological Association continued to recommended antimicrobial prophylaxis for any VUR grade reported after a UTI episode. However, in the Swedish guideline published in 1999, Jodal et al. do not recommend prophylaxis for VUR with grades I and II and recommend it during one year for high-grade VUR.

Until further studies clarify the management of VUR cases, we opt for the conservative proposition of implementing and maintaining chemoprophylaxis for every child with primary VUR (regardless of its grade), as long as it is present.

**In what situation should endoscopic correction of vesicoureteral reflux be indicated?**

As previously mentioned, the coexistence of VUR and UTI increases the risk of chronic renal damage in children.

In children with primary VUR, most authors prefer the conservative treatment, with prolonged use of antimicrobials. The indication of surgery is restricted to some cases and depends on age, sex, and severity of VUR or presence of recurrent pyelonephritis due to the poor adherence of the child or family to the prophylactic treatment.

In 1981, Matouschek first described the endoscopic correction of VUR by way of injection of
polytetrafluoroethylene (Teflon) into the bladder, below the ureteral orifice, so as to prevent urine from flowing back to the ureter.

In 2002, Leonard64 published the analysis of a 20-year (1981 through 2001) literature review, in which 42 articles about endoscopic injection for treatment of VUR were studied, with the following results: (1) this procedure was successful in resolving VUR in 60% to 80% of the cases; (2) the cure rate was higher with some particulate materials (Teflon and Macroplastique) than with bovine collagen or autologous condrocytes; (3) studies about the prognosis of the cure for VUR in the long term are scant. (4) although there is some concern with the side effects of these materials on the body, such as migration of particles to several regions of the body and development of autoimmune disease, these effects have not been described in clinical experience; (5) endoscopic injection may be given at an outpatient clinic, with lesser morbidity than ureteroneocystostomy.

As to the persistence of the cure of VUR in the long term, Chertin et al.65 published, in 2002, their experience in Denmark with the follow-up of 11 to 17 years (mean of 13.5 ±3.4 years) of 258 patients with primary VUR endoscopically treated with subureteral injection of polytetrafluoroethylene (Teflon) and found a recurrence of nearly 5%.

Leonard64 concluded that endoscopic therapy may be a therapeutic option for patients with surgical indication. The ideal material for subureteral injection is yet to be developed and, in this sense, research into the engineering of autologous tissues is of paramount importance.

References