INVESTIGATIONAL LIMITS AND MULTI-DRUG RESISTANCE AMONG CHILDREN'S URINARY TRACT INFECTIONS – OUR RECOMMENDATIONS

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Abstract

Introduction: It has been estimated that approximately 1% of boys and 3% of girls will experience a symptomatic urinary tract infections (UTI) before their 11th year of life. Infants and young children with UTI are of particular concern because the risk for renal damage is greatest in this age group and because the diagnosis is frequently challenging: the clinical presentation tends to be non-specific and valid urine specimens cannot be obtained without invasive methods - suprapubic aspiration (SPA) and transurethral catheterisation. Renal scarring, hypertension, and even renal failure can develop after recurrent pyelonephritis which is the most-common preventable cause of end-stage renal disease.

Objective: Our aim is to identify proper investigation methods and antibiotic regimens for UTI in children from the Timis County, by comparing two studies on UTI, recurrent and non-recurrent, with the results available in the international literature.

Material: We compared the result of two studies on patients admitted in the IIIrd Pediatric Clinic Timisoara with UTI between 2004-2005 and 2006-2007 (the first six months) and the data available in the international literature. The first group included 36 patients admitted in the IIIrd Pediatric Clinic UMF Timisoara in 2004 and 2005. The second study included a number of 81 patients admitted in the IIIrd Pediatric Clinic UMF Timisoara in 2006 and the first six months of 2007.

Results of our studies: Our patients continued to present recurrence under treatment in comparison with literature data. Only 15,12% of the E. Coli strains were sensible to ampicillin and trimethoprim-sulfomethoxazole. Male patients were most frequently affected (65,85%) in the age group of 0- 3 years; female patients were most frequently affected (75%) in patients above 6 years.

The strains responsible for the community acquired infections were initially sensible to ciprofloxacin, ampicillin, gentamicin, and colistin, but most of the strains developed resistance to these antibiotics; thus the % of successful empiric treatment with these antibiotics is reduced (<30%).

Conclusions: In case of infections due to more than one micro organism, it is essential to use multi-drug therapy, because the organisms are usually high-resistant and they have a selective sensibility.

Long term therapy must have high sensibility to pathogens and interfere as little as possible with non pathogenic flora, and reconsideration of fluoroquinolones group interdiction is mandatory. The study proved that organisms developed resistance, even to the late generation antibiotics, probably due to the irrational use of antibiotics. The antibiotics should be used in Romania according to our guidelines, on the basis of the sensibility/resistance and frequency of the organisms in our territory.

Key words: urinary tract infections, investigation methods, antibiotics

Introduction

The urinary tract is a relatively common site of infection in infants and young children. UTI are important because they cause acute morbidity and may result in long-term medical problems, including secondary hypertension and reduced renal function. Management of children with UTI involves repeated medical check-ups, use of antimicrobial drugs, exposure to radiation, and cost. Accurate diagnosis is extremely important for two reasons:

- it allows identification, treatment, and evaluation of the children who are at risk for kidney damage

- it avoids unnecessary treatment and evaluation of children who are not at risk, for whom interventions are costly, potentially harmful and provide no benefit.

It has been estimated that approximately 1% of boys and 3% of girls will experience a symptomatic UTI before their 11th year of life (6). The prevalence of UTI in boys is higher in the first 3 months of life (7). Another study showed that both febrile UTI and APN were more prevalent in males under 1 year and females over 1 year (8).

Infants and young children with UTI are of particular concern because the risk for renal damage is greatest in this age group and because the diagnosis is frequently challenging: the clinical presentation tends to be non-specific and valid urine specimens cannot be obtained without invasive methods - suprapubic aspiration and transurethral catheterization. Considerable variation in the methods of diagnosis, treatment, and evaluation of children with UTI was documented 3 decades ago (21). Since then, various changes have been proposed to aid the diagnosis, treatment, and evaluation, but no data is available to suggest that such innovations have resulted in reduced variation in practice.

The aim of the clinical guidelines on management of acute UTI in childhood is to improve diagnosis and treatment of pyelonephritis and the conditions predisposing to UTI, such as congenital malformations of the urinary tract (1).

Renal scarring, hypertension, and even renal failure can develop after recurrent pyelonephritis (2,3) which is the most-common preventable cause of end-stage renal disease (ESRD). Guidelines from England and Wales (1991) (4) and Finland (1992) (5) recommend that all children, regardless of age and gender, should have renal tract imaging after the first episode of confirmed acute UTI. Failure to diagnose UTI could be reflected in subsequent increased occurrence of ESRD and a large number of kidney transplants due to recurrent pyelonephritis. Overdiagnosis of UTI, on the other hand, causes considerable extra cost for the healthcare system, mainly due to unnecessary imaging examinations and follow-up. Knowledge of the variable occurrence of acute UTI in children will help us to increase awareness and to improve the treatment of acute UTI as well ad giving valuable clues to possible etiological factors.

This article is intended for use by clinicians who treat infants and young children in a variety of clinical settings (e.g., private practices, emergency departments, other departments of hospitals).

Objectives

Our aim is identifying proper investigation methods and antibiotic regimens for UTI in children from the Timis County by comparing two studies about UTI, recurrent and non-recurrent, with the results available in the international literature. In the first study we included children aged 3 months to 2 years, which presented more than one UTI and which didn't had any renal tract malformations. We discussed the regimens for relapsed UTI in children using the antibiogram data and then finding the suitable treatment. In the second study we included a number of 81 patients, presented UTI, associated or not with renal tract malformations.

Material and method

We compared the results of two studies on patients admitted in the IIIrd Pediatric Clinic Timisoara with UTI between 2004-2005 and 2006-2007 (the first six months) and the data available in the international literature.

The first group included 36 patients admitted in the IIIrd Pediatric Clinic Timisoara in 2004 and 2005, selected according to the following criteria:
- age from 3 months to 2 years
- all the patients presented recurrent UTI, but none of the patients had any renal tract malformations
- 6 children were admitted for more than 2 episodes of UTI during this study.
- all patients were required to provide urine samples for uroculture.
- positive urocultures were investigated for in vitro response to antibiotics
- in specific cases, other investigations such as ultrasound-echo, urography, scintigraphy and voiding cystography were performed.

Exclusion criteria:
- patients with obvious neurological or anatomic abnormalities known to be associated with recurrent UTI
- children older than 2 years who experience their first UTI, because they are more likely than younger children to have symptoms referable to the urinary tract, are less likely to have predisposing factors for renal damage, and are at lower risk of developing renal damage.

The second study included a number of 81 patients admitted in the IIIrd Pediatric Clinic Timisoara in 2006 and the first six months of 2007, selected by the following criteria:
- age from 3 months to 18 years
- all the patients presented UTI, associated or not with renal tract malformations
- all patients were required to provide urine samples for uroculture, no invasive methods (SPA) were performed
- positive urocultures were investigated for in vitro response to antibiotics.
- in specific cases other investigations such as ultrasound-echo, urography, scintigraphy and voiding cystography were performed.

Results

Of the first study:
1. The recurrence rate of UTI had a low correlation with the reflux grade in all the cases.
2. Our patients continued to present recurrence under treatment in comparison with literature data (Greenfield 2001, Brumariu 2005).
3. Urocultures during re-admissions revealed:
    - Girls 0-6 y: 7 cases (5 - E. Coli, 2 – Proteus)
    - Girls over 6y: 13 cases (11 - E. Coli, 2 – Proteus)
    - Boys 0-6 y: 12 cases (7 - Proteus, 4 - E.Coli, 1 – Klebsiella)
    - Boys over 6y: 4 cases (E. Coli)
4. Best responses were obtained with cephalosporin group antibiotics (Ceftazidime, Ceftriaxone) and with Ciprofloxacin.
5. Less than 50% of the E. Coli and Proteus strains were resistant to Nitrofurantoin.

Regarding the second study:
1. The most frequent organism responsible for UTIs was Escherichia Coli (40,74%), followed by Proteus spp. (12,31%), Klebsiella spp. (2,46), Pseudomonas Aeruginosa (2,46%), Citrobacter Koseri
2. (1,23%), Enterobacter spp. (1,23%) and fungus (1,23%). Infections with more than one organism were found in 4,93% of the cases (Fig 2).
3. Intermediary resistant E. Coli strains:
    - 54,54% of the UTIs with E. Coli
    - Resistant to Ampicillin and Trimethoprim-sulfomethoxazole

4. High resistant E.Coli strains:
   • 30,33% of the UTIs with E. Coli
   • Resistant to: Ampicillin, Gentamicin, Trimethoprim-sulfomethoxazole, Colistin and Ciprofloxacin.
5. Only 15,12 of the E. Coli strains were sensible to Ampicillin and Trimethoprim-sulfomethoxazole.
6. Proteus spp. was resistant to: Ampicillin, aminoglycozides (Gentamicin, Amikacin, and Netilmicin), Kanamicin, Trimethoprim-sulfomethoxazole, Colistin, and Ciprofloxacin/Nalidixic acid.
7. Klebsiella spp. was proven to be resistant to Ampicillin, Gentamicin, Amikacin, Trimethoprim-sulphomethoxazole, Kanamicin and Nalidixic acid.
8. Pseudomonas Aeruginosa was resistant to: Ampicillin, Gentamicin, Trimethoprim-sulphomethoxazole, Kanamicin, Nalidixic acid.
9. Acute pyelonephritis (APN) only presented an incidence of 23,45%.
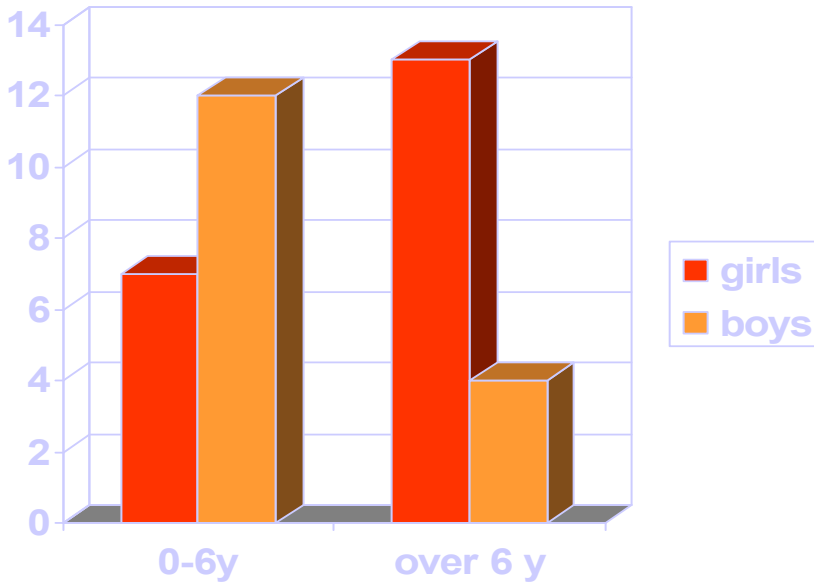

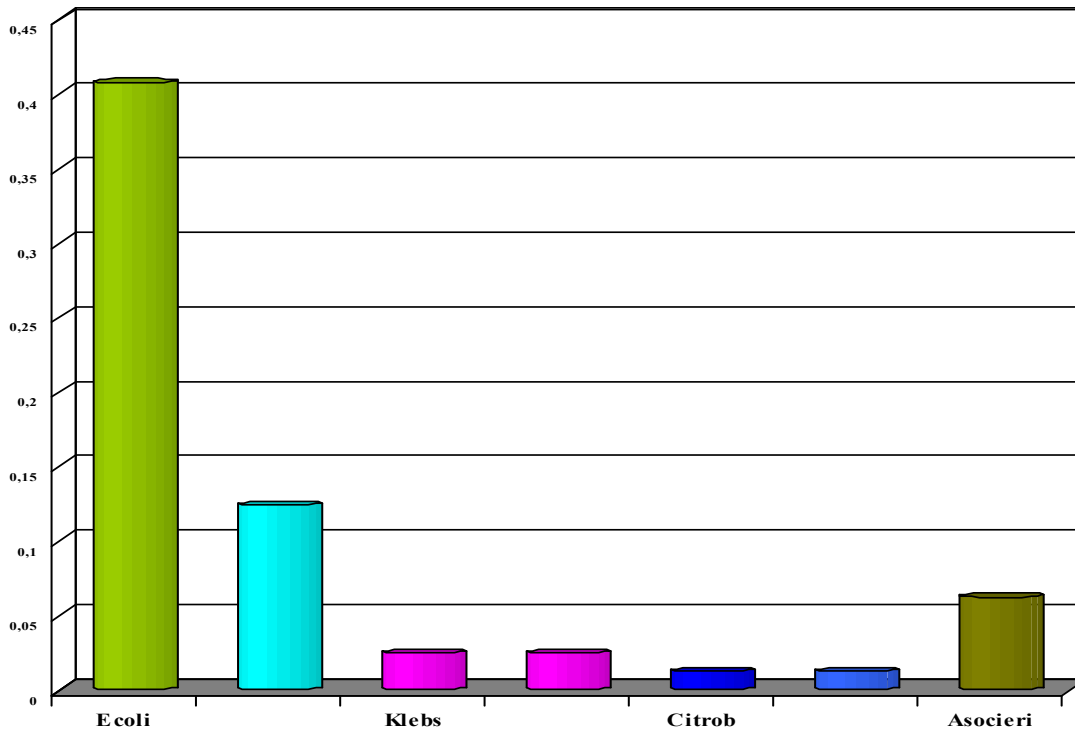Fig 1: The distribution of recurrent of UTI according to age and sex.

Fig. 2: The frequency of microorganisms causing UTI.

Our study conclusions

1. The study on recurrent UTI:
- Long term therapy must have high sensibility to pathogens and interfere as little as possible with non pathogenic flora, and reconsideration of fluoroquinolones group interdiction is mandatory.
- The understanding and awareness of the resistance pattern of pathogens in our region is essential in order to provide the best antibiotic regimen to our patients.
- Up-to-date antibacterial treatment must take into account the modification of pathogenic and non pathogenic colon flora as a result of past antibiotic administrations.

2. The second study:
- The study confirmed the previous statistics according to which the congenital malformations predispose to UTI.
- Male patients were most frequently affected (65,85%) in the age group of 0- 3 years; female patients were most frequently affected (75%) in the group above 6 years.
- The strains responsible for the community acquired infections were initially sensible to ciprofloxacin, ampicillin, gentamicin, and colistin, but most of the strains developed resistance to these antibiotics; thus the percentage of successful empiric treatment with these antibiotics is reduced (<30%).
- The study proved that organisms developed resistance, even to the late generation antibiotics, probably due to the irrational use of antibiotics. The antibiotics should be used according to the guidelines, on the basis of the sensibility/resistance and frequency of the organisms.
- In case of infections due to more than one microorganism, it is essential to use multi-drug therapy, because the organisms are usually high-resistant and they have a selective sensibility.
- The antibiotics should be used in Romania according to our guidelines, on the basis of the sensibility/resistance and frequency of the organisms in our territory.

Discussions

The prevalence of UTI, from international literature, in infants and young children 2 months to 2 years of age who have no obvious source of fever from history or physical examination is high - 5% (22,23,24). The genders are not affected equally - the prevalence of UTI in febrile girls aged 2 months to 2 years is more than double than that in boys (in girls younger than 1 year it is 6.5%; in boys, it is 3.3%; in girls between 1 and 2 years of age is 8.1%; in boys it is 1.9%). The rate in circumcised boys is low, 0.2% to 0.4% (25,26,27).

UTI may be limited to the bladder (cystitis) or may involve the renal parenchyma (pyelonephritis). APN can result in irreversible renal damage and in the well-recognized sequelae of scarring, including hypertension, proteinuria, and chronic renal failure (13,14). Infants and young children are at higher risk than are older children for developing acute renal injury with UTI. The incidence of vesico-ureteral reflux (VUR) is higher in this age group than in older children, and the severity of VUR is greater, with the most severe form (with intrarenal reflux or pyelotubular backflow) limited to infants. Infants and young children with UTI need special attention because of the possibility to prevent kidney damage. Firstly, the UTI may indicate a child with an obstructive anomaly or severe VUR, and secondly, because infants and young children with UTI may have a febrile illness and no localizing findings, there may be a delay in diagnosis and treatment.

The presence of fever has long been considered a finding of special importance in infants and young children with UTI, because it has been accepted as a clinical marker of renal parenchyma involvement (pyelonephritis). The concept that fever in a child with UTI indicates renal parenchyma involvement is based on the comparison of children with high fever (>39°C) and the clinical diagnosis of APN with those with low fever (<38°C) and a clinical diagnosis of cystitis (28). Indirect tests for localization of the site of UTI, such as the presence of a reversible defect in renal concentrating ability, and non-specific tests of inflammation, such as elevated white blood cell (WBC) count, C-reactive protein, or erythrocyte sedimentation rate, are encountered more frequently in children with clinical pyelonephritis than in those with clinical cystitis. However, the indirect tests for localization of the site of infection and the non-specific indicators of inflammation do not provide confirmatory evidence that the febrile infant or young child with UTI has pyelonephritis. Cortical imaging studies using technetium 99 m Tc-dimercaptosuccinic acid (DMSA) may prove useful in determining whether the presence of high fever does identify children with pyelonephritis and distinguishes them from those with cystitis. The likelihood that UTI is the cause of the fever may be increased if there is a history of crying on urination or of foul-smelling urine. An altered voiding pattern may be recognized as a symptom of UTI as early as the second year after birth in some children. Dysuria, urgency, frequency, or hesitancy may be present but are difficult to discern in this age group. Non-specific signs and symptoms, such as irritability, vomiting, diarrhoea, and failure to thrive, also may reflect the presence of UTI, but data are not available to assess the sensitivity, specificity, and predictive value of these clinical manifestations.

Current studies that assess fever as a marker of pyelonephritis, defined by a positive scan, provide a wide range of sensitivity (53% to 84%) and specificity (44% to 92%) (29,30,31).

The incidence of APN in infants - around 60% - is similar in the studies (9). Several studies (10,11) have reported that the susceptibility of the renal parenchyma to infection varies with age, with those under 1 year at greatest risk. Both the host's immunological defence and microbiological virulence factors are critical co-factors for renal scarring (12).

Although high-grade VUR allows migration of bacteria into the parenchyma, APN and renal scarring can

still occur in the absence of reflux. The relationship between the extent of kidney inflammation in the acute phase and the late outcome in the presence or absence of VUR is still insufficiently explored. We hypothesize that VUR is one of the multiple risk factors for APN and renal scar formation, along with host susceptibility, urinary tract obstruction, inflammatory response and therapeutic delay.

Experimental studies in animals have validated dimercaptosuccinic acid (DMSA) scintigraphy as an accurate technique for the detection of acute infection (15,16).

Clinical, biological, and ultrasound parameters do not accurately identify children with acute renal infections documented by DMSA scan. Thus, the distinction between cystitis and pyelonephritis in children with acute UTI is not accurate and some (17) recommend that the DMSA scan should be added to the initial work-up of children with UTI. In our country we cannot performed this scan in the last two years!

Cortical scintigraphy with DMSA in the acute phase of a UTI allows detection of kidney involvement, thus presenting two advantages. The first advantage is the possibility of estimating the severity of the disease in each kidney and the presence of bilateral disease. The second advantage is represented by the possibility of evaluating the patient's risk for developing renal sequelae from the very onset of the acute disease. The available data support the hypothesis that the risk of developing renal sequelae is low when the early scintigraphy is normal and high in the presence of abnormalities during the acute phase of infection (18,19,20).

In the Kuang study the DMSA scan in most children with renal scarring (the incidence of APN in children with first febrile UTI was of 70%, and nearly half developed a renal scar) showed a small unifocal area. The long-term clinical significance of these unifocal areas of renal scarring is unknown. The incidence of febrile UTI or APN was higher in males than females under the age of 1 year, and the reverse was true thereafter. Since VUR was present in a third of our patients with APN, half of whom showed scar formation; other risk factors should be evaluated in infants with APN and renal scar formation (8).

Micturating cysto-urethrography (MCUG) gives information about the presence and degree of VUR, the bladder and the urethra. VUR may also be detected using mercapto-acetyl-triglycine renography (MAG3) renography (34).

Establishing the diagnosis of UTI requires a strategy that minimizes false-negative and false-positive results. Urine obtained by SPA is the least likely to be contaminated; urine obtained by transurethral bladder catheterization is next best (Table 1). Either SPA or transurethral bladder catheterization should be used to establish the diagnosis of UTI, definitive option in all the North-America guidelines. Cultures of urine specimens collected in a bag applied to the perineum have an unacceptably high false-positive rate; the combination of a 5% prevalence of UTI and a high rate of false-positive results (specificity: 70%) results in a positive culture of urine collected in a bag to be a false-positive result 85% of the time.

The probability of infection according to various methods of collection of urine is illustrated in Table 1.

Method of Collection	Colony Count (Pure Culture)	Probability of Infection (%)
Suprapubic aspiration	Gram-negative bacilli: any number Gram-positive cocci: more than a few thousand	>99%
Transurethral catheterization	$>10^5$	95%
	$10^4 - 10^5$	Infection likely
	$10^3 - 10^4$	Suspicious; repeat
	$<10^3$	Infection likely
Clean void		
Boy	$>10^4$	Infection likely
Girl	3 specimens $\geq 10^5$	95%
	2 specimens $\geq 10^5$	90%
	1 specimen $\geq 10^5$	80%
	$5 \times 10^4 - 10^5$	Suspicious; repeat
	$10^4 - 5 \times 10^4$	Symptomatic: suspicious; repeat Asymptomatic: infection unlikely
	$<10^4$	Infection unlikely

Table 1: The probability of infection according to various methods of collection of urine.

If antimicrobial therapy is initiated before obtaining a specimen of urine for culture that is unlikely to be contaminated, the opportunity may be lost to confirm the presence or establish the absence of UTI. Therefore, in the situation in which antimicrobial therapy will be initiated, SPA or catheterization is required to establish the diagnosis of UTI. SPA has been considered the "gold standard" for obtaining urine for detecting bacteria in bladder urine accurately and the technique has limited risks. Using other methods, variable success rates for obtaining urine have been reported (23% to 90%) (6,32).

Technical expertise and experience are required, and many parents and physicians perceive the procedure as unacceptably invasive compared with catheterization.

A recent randomized controlled trial of 218 children with acute pyelonephritis (age 3 months to 18 years) demonstrated no benefit of antibiotic prophylaxis for preventing recurrent UTI, pyelonephritis, or scarring in children with or without reflux (grades I – III only) after one year of follow up. The overall incidence of UTI recurrence after pyelonephritis was 20.1% with no statistically significant differences between those with or without VUR or those with or without prophylaxis. Most cases of recurrence were cystitis. Twelve patients had recurrence of pyelonephritis. Thirteen of the 218 patients developed renal scars, including 7 with VUR and 6 without. Most of the patients with scarring and VUR had grade III reflux (35).

The follow-up of patients is only necessary in the group of high-risk children (34), which are those with:

- Recurrent infections;
- Clinical signs such as poor urinary stream or palpable kidney;
- Unusual organisms (those which are not E. Coli);
- Bacteraemia or septicaemia;
- Prolonged clinical course with failure to respond fully to antibiotic treatment within 2-3 days;
- Unusual clinical presentation such as an older boy;
- Known dilatation or abnormality on antenatal screening of the urinary tract.

The first randomized controlled study that shows the role of probiotic L. acidophillus for preventing recurrent UTI in children with persistent primary VUR was finished last year. However, this study has the limitation of lacking a treatment arm and a low calculated power (78%). Further clinical trials are necessary, to compare antibiotic prophylaxis with probiotics and no prophylaxis in children with or without VUR (33).

Recommendations:

1. The presence of UTI should be considered in infants and young children 2 months to 2 years of age with unexplained fever. If an infant or young child 2 months to 2 years of age with unexplained fever is assessed as being sufficiently ill to warrant immediate antimicrobial therapy, a urine specimen should be obtained by SPA or transurethral bladder catheterisation; the antimicrobials commonly prescribed in such situations will be effective against the usual urinary pathogens. Some clinicians may choose to obtain a specimen by non-invasive means (e.g., in a collection bag attached to the perineum). The false-positive rate with such specimens dictates that before diagnosing UTI, all positive results must be confirmed with culture of a urine specimen unlikely to be contaminated.

2. If the diagnosis of UTI is established, the general practitioner and the paediatrician should NOT prescribe empirical therapy without an accurate knowledge of the local resistance, susceptibility and frequency of the infecting organisms.

3. Once the diagnosis of UTI is confirmed (by culture), the next step should be an effort to investigate renal involvement (by renal ultrasound, scan, MRI or, if not possible, by urography or a micturating one - MGUG).

4. If renal involvement is present, appropriate therapeutical measures should be taken. The possibility of renal function reduction should be always taken into account when starting the antimicrobial treatment.

5. After the first UTI the decision regarding the usefulness of prophylactic antibiotics should be taken after an evaluation of:
   • individual risk of recurrence of UTI, especially of pyelonephritis
   • individual risk of scarring or other renal damage
   • presence of voiding dysfunction
   • adverse effects of long-term use of antibiotics
   • individual patient/family adherence/compliance behavior (35).

6. The follow-up of patients is essential, since recurrence of pyelonephritis can lead to severe kidney damage. The clinician should decide weather or not the patient is a high-risk child. If so, the investigations required are:
   - Renal tract ultrasound during acute infection
   - All children under 3 years of age with normal renal ultrasound findings (or abnormal ultrasound findings without dilatation) require a 99mTc- DMSA scan (if this result is abnormal they will also require a MCUG).
   - All children 3 years of age or older, who have normal renal ultrasound findings (or abnormal ultrasound findings without dilatation) require MAG3 renography and an indirect radioisotope cystogram. This is because normal renal ultrasound findings in a high-risk child do not exclude the presence of focal renal damage nor do they exclude bladder dysfunction in high-risk children. For children over 3 years of age and toilet-trained, MAG-3 and indirect radioisotope cystograms will provide information on renal function, drainage in the supine position and the

effect of a change of posture. Observing the entire urinary tract before, during and after normal micturition gives valuable information on bladder dynamics and avoids the catheterisation required for MCUG. The early MAG3 images give valuable information on renal parenchymal function and have

an 80% sensitivity in the detection of focal renal damage (34).

7. The antibiotics should be used in Romania according to our guidelines, on the basis of the sensibility/resistance and frequency of the organisms in our territory.

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