INTRODUCTION

The aim of this article is to promote, among primary care physicians, the knowledge and application of good clinical practice in the diagnosis, treatment and prevention of uncomplicated urinary tract infections (UTI) in both children and adults.

SUBJECTS AND METHODS

This review was developed by physicians working in second- and third-level care public hospitals and private fa-
cilities in Mexico. Physicians were selected on the basis of their experience in the field of UTI. A multidisciplinary approach included experts in infectious diseases (pediatric and adult), urology (pediatric and adult) and gynecology.

The methodology for this study consisted of review of articles published in the medical literature on UTI up to January 2011. We excluded those articles published before 1999 unless they were articles that described the pathophysiology of the disease. As part of a systematic review, controlled clinical studies were included (with placebo or active drug) and descriptive studies related to the etiology, epidemiology, diagnosis and treatment of UTI. Also included were in vitro studies to determine the profiles of sensitivity/resistance to antimicrobials. We performed the literature search using PubMed and Cochrane Library databases. We reviewed other consensus, guidelines and recommendations published by governmental and nongovernmental agencies from different countries. We excluded abstracts, unpublished studies, studies with small sample sizes and studies with poor internal and external validity. The authors’ final meeting was held on February 18 and 19, 2011. The final document was subsequently reviewed by the members for final correction.

EPIDEMIOLOGY

In Mexico, the National Epidemiological Surveillance System reported that in 2010 UTIs occupied third place among the leading causes of morbidity.2

Adults
UTI is the leading cause of medical consultation in women of reproductive age. During pregnancy, it is the most common cause of serious perinatal complications1-5 and is the third leading cause of neonatal sepsis.6 In 2010 there were 1,204,032 cases reported in adults 25-44 years of age, with an incidence rate of 3000/100,000 inhabitants.2 In subjects >60 years of age, the incidence rate was 6000/100,000 inhabitants, with predominance in males.2

Children
In this age group, UTI is a common cause of consultation and hospitalization. The frequency varies depending on age and gender. Symptomatic infection occurs in 1/1000 newborns and children <1 month of age and is more common in males.2 After this age, it is more common in girls, with a prevalence of 1-2%. In general, the risk of UTI during the first decade of life is 1% to 3% for males and females. After the second decade of life, UTI continues with a female predominance with a ratio of 4:1.7,8

Definitions
Definitions of each type of disease that were addressed in the present study are listed in Table 1.

ETIOLOGY

Bacteria that generally cause UTIs are gram negative of intestinal origin. Of these, Escherichia coli represents 75-95%, with the remainder being caused by Klebsiella sp., Proteus sp. and Enterobacter sp.9 Among the gram positive bacteria, Staphylococcus saprophyticus and Streptococcus agalactiae are the most frequent.9,10
In the neonatal group, the frequency of gram positive bacteria increases, although gram negative species predominate.11-15

PATHOPHYSIOLOGY

Children
The urinary tract is sterile. The retrograde ascent of bacteria is the most common mechanism of infection. In girls, bacteria can more easily access and ascend the urinary tract due to the relative proximity of the urethral opening to the anus and the shorter length of the urethra. Another proposed route as a uropathogenic bacterial reservoir has been the presence of the intact foreskin in infants, in whom the frequency of UTI is ten times that of circumcised males.11-15

High pressure in the bladder, incomplete or infrequent emptying of the bladder and lack of pelvic floor relaxation during voiding, and constipation or encopresis are other factors that predispose to UTI.12,13 Congenital abnormalities of the urinary tract (obstructive uropathy and reflux) and neurogenic bladder including the group of patients with intermittent bladder catheterization are risk factors particularly important to consider in infancy.14

Patients with a susceptible urothelium facilitate increased bacterial colonization. The predisposition to colonization in children with recurrent UTI in the ab-
Diagnosis and treatment of urinary tract infections: a multidisciplinary approach for uncomplicated cases

sence of anatomic or functional alterations is related to an increased adhesion capacity of bacteria like *E. coli* to the inner foreskin, perineum, opening to the vagina and urethra. Often, these microorganisms have type P fimbriae, a mechanism for bacterial adherence, yielding them more virulent and with affinity to the urethelium. In these patients, some type of immunodeficiency associated with low levels of IgA and IgG may be present.

**Adults**

In adults, UTIs predominate in females. UTI is frequently associated with two important life events: 1) during pregnancy, with an increase in perinatal morbidity and mortality, and 2) from the initiation of sexual activity.

Certain characteristics of the female anatomy predispose to infection: first, the vicinity of three natural orifices (vagina, urethra and anus, the latter usually colonized by gram negative microorganisms) and second, the length of the urethra. Other factors include increased residual urine secondary to problems of static pelvis and sexual activity because intercourse promotes colonization of the urinary tract by vulvo-perineal microorganisms.

In addition, during pregnancy there are some factors that increase susceptibility to the development of UTI: 1) progesterone induces decreased smooth muscle tone, which decreases ureteral peristalsis and makes bladder emptying difficult. It can also alter the expression of decay accelerating factor (DAF/CD55), which is a regulator of the complement and serves as a receptor of many pathogens, including *E. coli*; 2) anatomic changes favoring anterior superior elevation of the bladder, compression of ureters (more on the right side) and thus an increase in urinary stasis; 3) a renal hypertonic state inhibiting leukocyte migration, phagocytosis and complement activity as well as a decreased T cell activity, thereby favoring the infectious processes.

Moreover, UTI is the most common medical complication in pregnant women. Treatment is mandatory, in addition to being the only state in which an asymptomatic bacteriuria should be treated because of the implications of perinatal morbidity and mortality (preterm birth, which is responsible for 75% of neonatal deaths and 50% of long-term neurological disorders).

In addition, pregnancy makes women particularly susceptible due to the factors already discussed, complicating the initial infection and converting it into an acute pyelonephritis, whose incidence increases by 7%.

There is a growing group of patients in which UTI is associated with sexual activity. The spectrum of this phenomenon ranges from the so-called “honeymoon cystitis” to multiple recurrences of infection. In these cases, application of various hygiene/dietary modifications and the use of single-dose postcoital antimicrobials is justified.

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**Table 1. Different types of UTI**

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic bacteriuria</strong></td>
<td>In the normal population defined as the presence of &gt;100,000 CFUs of the same microorganism/mL (10^5 CFU/mL) of urine and absence of symptoms. During pregnancy and in children, defined as the presence &gt;100,000 CFU/mL of the same species in two subsequent cultures in the absence of symptoms.</td>
</tr>
<tr>
<td><strong>Uncomplicated UTIs</strong></td>
<td>Symptoms characteristic of dysuria, difficult urination, pollakiuria/increase in urinary frequency, vesicular tenesmus and occasionally urgency, suprapubic pain, nocturia and hematuria. These symptoms usually correspond with lower urinary tract infection. It occurs in patients with a normal urinary tract (anatomic and physiological) without data of systemic involvement (fever, toxicity, persistent vomiting, dehydration) and no history of renal disease or comorbidities (diabetes, immunocompromise). There are no conditions that predispose to UTI or treatment failure.</td>
</tr>
<tr>
<td><strong>Complicated UTIs</strong></td>
<td>Involves recurrent infection or involvement of the upper urinary tract with fever, nausea, vomiting, back pain and malaise. Also includes all cases that present persons with anatomic alterations.</td>
</tr>
<tr>
<td><strong>Acute pyelonephritis</strong></td>
<td>Infection of the renal parenchyma, secondary to lower UTI. The patient presents malaise, frequency, dysuria, hematuria, pain in lower back and flank, fever &gt;39°C lasting &gt;48 h and positive Giordano sign.</td>
</tr>
<tr>
<td><strong>Reinfection</strong></td>
<td>Two episodes of UTI caused by different microorganisms within &lt;6 months.</td>
</tr>
<tr>
<td><strong>Recurrent infection</strong></td>
<td>&gt;3 episodes of UTI during a 12-month period or 2 episodes en &lt;6 months.</td>
</tr>
<tr>
<td><strong>Persistence of bacteria</strong></td>
<td>Microbiological evidence of bacterial growth despite appropriate treatment.</td>
</tr>
</tbody>
</table>

UTI, urinary tract infection; CFU, colony-forming units.
DIAGNOSIS

Children
Suspicion of UTI should be confirmed by urinalysis and urine culture. In newborns and infants it is advisable to take a urine sample through a urethral catheter. In children with bowel control, a urine sample should be obtained from the second half of the stream, either after retracting the foreskin and disinfecting the glans in boys or opening the lips and cleaning the periurethral area in girls. A sample obtained with a collection bag only has value if the result is negative.12,13,23

The urine dipstick test can reveal the presence of leukocyte esterase and nitrites. In the microscopic analysis, a count of five or more leukocytes per field and bacteriuria are suggestive of a UTI.12,13,23-25 The urine culture is considered positive if there are >100,000 colony forming units (CFU)/mL in a properly collected sample. Specimens for urine culture should be refrigerated if there is no possibility of sending them to the laboratory within 30 min after collection.12,13,24-26 A urine culture with up to 1,000 CFU/mL in certain clinical situations may be considered as an actual UTI; however, it is necessary to consider that when the CFUs are low, the chances of contamination increase. There will be situations in which urine culture results must be taken in the context of the clinical picture and the symptoms.27

Current recommendations are that all newborns and infants (children <2 years of age) with their first documented UTI with fever >38.5°C should undergo an ultrasound of the urinary tract to detect anatomic anomalies and, optionally, a renal scan with dimercaptosuccinic acid (DMSA) to confirm evidence of pyelonephritis and evidence of scarring.29 Voiding cystourethrogram (CUG) is not routinely recommended after the first febrile UTI and is only indicated if the ultrasound reveals hydrourephrosis, scarring, or ureteral dilation or if there is recurrence of febrile UTI. Given that the data of the most recent studies do not support the use of antimicrobial prophylaxis to prevent recurrent febrile UTI in infants without vesicoureteral reflux (VUR) and primary grade I-IV reflux, both the American Academy of Pediatrics and the European Association of Urology recommend doing a CUG only if the ultrasound of the urinary tract reveals an abnormality or if febrile UTI recurs in infants 2-24 months of age.27,28 Renal DMSA scan should be repeated at any time after 3 months following the acute infectious event to look for extension of the scarring.29

Adults
Diagnosis of uncomplicated UTI is made based on the clinical picture. In cases where the symptoms are mild or incipient, it is recommended to perform if possible during the consult, “a bedside” urine dipstick examination to detect nitrite and leukocyte esterase. Expanded general urine test with the microscopic analysis of the sediment does not provide additional evidence for UTI diagnosis. No urine culture or imaging studies are warranted in case of an isolated uncomplicated UTI. These should be performed only in patients with fever that persists even 72 h after beginning treatment.7 Urine culture is recommended in cases of suspected pyelonephritis, persistent symptoms or those that recur within the first 2-4 weeks after completion of treatment and in the case of atypical symptoms.7,31

The most important differential diagnosis is made with vulvovaginal infections, where it is common for the patient to confuse dysuria with terminal vulvar burning, which produces irritation with the urine on the inflamed vulva. The hyperactive bladder is another differential diagnosis. It is generally an idiopathic disease whose cardinal symptoms are urgency, frequency and urinary incontinence.32

TREATMENT

Currently, the pattern of susceptibility of the bacteria has changed due to the progressively increasing resistance as a result of indiscriminate use of antibiotics as described for E. coli (Figure 1).33 To be able to consider an antibiotic as empirical therapy in the Mexican population, the recommended threshold must be ≤20%, according to treatment guidelines for this condition proposed by the IDSA (Infectious Diseases Society of America (Figure 1)).9

Children
Initial empirical treatment should include broad spectrum antibiotic coverage and its adaptation, based on the culture results. In children, short-term treatment is not recommended. Treatment should continue for 7-10 days.7,28 Given the documented high resistance of E. coli to certain antibiotics such as ampicillin and trimethoprim, ceftibuten is recommended (at doses of 9 mg/kg/day) or cefixime (at a dose of 10 mg/kg/day) for 7 days in patients <2 years
of age with UTI.\textsuperscript{12,13,23,24,34,35} This therapy is also recommended for children >2 years of age or high UTI (kidney infection or pyelonephritis). In cases of documented UTI and without fever, nitrofurantoin (7 mg/kg/day in 3 to 4 doses for 1 week) provides good results. The single dose with fosfomycin (2 to 3 g) is an option where there is controlled patient follow-up (Table 2).\textsuperscript{12,13,23,24}

**Adults**

In pregnant women the use of nitrofurantoin, fosfomycin and cephalosporins (except first generation) is recommended.\textsuperscript{7,36} Due to the high resistance shown by \textit{E. coli} in our environment (79%), its use as an empiric first option is not recommended.\textsuperscript{3}

In the Mexican population, during pregnancy, it is recommended to provide antimicrobial management of asymptomatic bacteriuria and uncomplicated UTI without laboratory tests (urine culture) on the basis of the high incidence of \textit{E. coli} as the causative organism.\textsuperscript{1} It is recommended that laboratory and imaging studies be carried out only in cases of persistent symptoms (mainly fever) or in complicated UTIs.\textsuperscript{7,37} Due to the impact of treatment on the embryo and fetus, as well as the resistance shown to certain antibiotics, the therapeutic options are limited. Trimethoprim should not be used during the first trimester due to its action on folic acid metabolism.\textsuperscript{38} Quinolones are contraindicated for the possible effects on fetal cartilage.\textsuperscript{38} Sulfur drugs should not be used in the third trimester due to its binding to albumin and its competition with bilirubin, which increases the risk of fetal hyperbilirubinemia.\textsuperscript{39}

In the remainder of the adult population, choice of empirical antibiotic is based mainly on resistance rates of community isolates. In recent years there has been a significant increase in the resistance of \textit{E. coli} to ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, and quinolones (which include nalidixic acid).\textsuperscript{33-35} Therefore, management with nitrofurantoin or second- or third-generation cephalosporins is suggested because they are safe and well tolerated. Another option is fosfomycin, especially in cases of suspected or proven infection with \textit{E. coli} producer of extended spectrum b-lactamase (ESBL), although this has been little studied in our environment.\textsuperscript{40}

**PROPHYLAXIS**

The recommended measures are the usual for the prevention of UTI\textsuperscript{4,7} and include adequate hydration (forced hydration is not recommended because the theoretical advantage of a rapid decline in bacterial count is canceled with the disadvantage of diluting the antimicrobial agents (level of evidence IIIC),\textsuperscript{5} cleaning of the vulvo-perineal area and bladder emptying before and after intercourse when this has been identified as the triggering factor. Regarding the use of lyophilized extracts (immmuno-active fractions) of \textit{E. coli} administered for 3 months on a daily basis in patients with recurrent urinary tract infections, in 2002 a meta-analysis was carried out of five controlled studies with a random-

![Figure 1. Rates of resistance of \textit{E. coli} in community isolates reported in México.\textsuperscript{3,9,11,33-35}](image-url)
ized, placebo, double-blind study with a similar design. In these studies it was shown that the extracts act as immuno-
stimulants, with an effective prophylactic approximation of the recurrent urinary tract infection (level of evidence IB) \( (p < 0.01; 95\% \text{ CI } 0.64-0.72) \).41

The use of nitrofurantoin in doses of 100 mg/day for a period of 1-6 months is another useful preventive mea-
sure (level of evidence IA).7 In recurrent UTIs, we sug-
gest the use of cranberry juice (at doses of 250-300 mL capsules daily or 300 mg/8 h)42 because cranberry juice contains fructose and proanthocyanidins that apparently have an affinity to the fimbrae of E. coli, covering them and preventing them from binding to the glycoside recep-
tors of the urothelial cells, thereby decreasing urinary tract colonization by this organism (level of evidence IIC).5

Although acidification of the urine through ascorbic acid has shown some encouraging results,43 new research is re-
quired with placebo-controlled double-blind studies. Currently, it is impractical, difficult and unnecessary to achieve and maintain acidification of the urine because most antibiotics have appropriate action with the usual pH values of urine (level of evidence IID).5

**HYGIENE EDUCATION**

In adults, conventional personal hygiene of the urogeni-
tal area and frequent bladder emptying is recommended, which reduces bacterial adherence to the urothelium. In young girls and women, normal hygiene at voiding is rec-
ommended,44 proper intake of fluids (especially water), urinating when the urge is felt and complete emptying of the bladder, and wiping the area from front to back when using toilet paper. In women, urinating after intercourse is recommended, wearing loose-fitting cotton underwear and washing the underwear with mild soap, cleaning the urogenital area with soap and water at least once daily, bathing in the shower instead of a tub, and avoiding oil baths, powder, spray, shower or douches. As a general rule, it is advisable to avoid products that contain perfume or other allergens near the genitourinary area.

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**Table 2. Recommended dosage of antimicrobials for uncomplicated UTIs**

<table>
<thead>
<tr>
<th>Antibiotic*</th>
<th>Children</th>
<th>Adults</th>
<th>Level of evidence**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Males and females</td>
<td>Pregnant subjects</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>10 mg/kg/day in 2 doses</td>
<td>160/800 mg/12 h</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>7 mg/kg/day in 3 or 4 doses</td>
<td>100 mg/6-8 h</td>
<td>100 mg/6-8 h</td>
</tr>
<tr>
<td>Fosfomycin tromethamol</td>
<td>2 g single dose orally</td>
<td>3 g single dose orally</td>
<td>3 g single dose orally</td>
</tr>
<tr>
<td>Naldixic acid</td>
<td>NA</td>
<td>1 g orally/6 h</td>
<td>Under strict medical supervision</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>NA</td>
<td>500 mg/12 h</td>
<td></td>
</tr>
<tr>
<td>or 1 g/24 h</td>
<td>Contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>NA</td>
<td>400 mg/12 h</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>NA</td>
<td>400 mg/24 h</td>
<td></td>
</tr>
<tr>
<td>or 200 mg/12h</td>
<td>Contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rufloxacin</td>
<td>NA</td>
<td>200 mg/12 h</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>10 mg/kg/day in 2 or 3 doses</td>
<td>NA</td>
<td>500 mg/12 h</td>
</tr>
<tr>
<td>Cefibuten</td>
<td>9 mg/kg/day in one dose</td>
<td>400 mg/24 h</td>
<td>400 mg/24 h</td>
</tr>
<tr>
<td>Cefixime</td>
<td>8 mg/kg/day in one dose</td>
<td>400 mg/24 h</td>
<td>400 mg/24 h</td>
</tr>
</tbody>
</table>

* Treatment can be prolonged 3-5 days. TMP, trimethoprim; SMX, sulfamethoxazole. Adapted from References 3, 4, 7-9, 40. ** I. Evidence from ≥1 randomized controlled trial. II. Evidence from ≥1 well-designed clinical trial without randomization, from cohort analytic studies or case control (preferably to include more than one center), from multiple case series or significant results from uncontrolled experiments. III. Evidence from opinions of respected authorities, based on clinical evidence, descriptive studies or communications from expert committees. Strength of the recommendation: A. Good evidence for recommending its use. B. Moderate evidence for recommending its use. C. Poor evidence for recommending its use. D. Moderate evidence for not recommending its use. E. Good evidence for not recommending its use.
REFERENCES

34. Arredondo-García JL, Amábile-Cuevas CF. High resistance prevalence towards ampicillin, co-trimoxazole and cipro-