

## ***Brief Report***

# **Resistance of Uropathogenic Bacteria to First-Line Antibiotics in Mexico City: A Multicenter Susceptibility Analysis**

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## **ABSTRACT**

**Background:** Growing antibiotic resistance demands the constant re-assessment of antimicrobial efficacy, particularly in countries with wide antibiotic abuse, where higher resistance prevalence is often found. Knowledge of resistance trends is particularly important when prescribing antibiotics empirically, as is usually the case for urinary tract infections (UTIs). Currently, in Mexico City, ampicillin, cotrimoxazole (trimethoprim/sulfamethoxazole), and ciprofloxacin are used as "first-line" antibiotic treatment for UTI.

**Objective:** The aim of this study was to analyze the resistance of bacterial isolates to antibiotics, with a focus on first-line antibiotics, in Mexican pediatric patients and sexually active or pregnant female outpatients.

**Methods:** In this multicenter susceptibility analysis, bacterial isolates from urine samples collected from pediatric patients and sexually-active or pregnant female outpatients presenting with acute, uncomplicated UTIs in Mexico City from January 2006 through June 2006, were included in the study. Samples were tested for susceptibility to 10 antibiotics by the disk-diffusion method.

**Results:** Four-hundred and seventeen bacterial isolates were derived from sexually active or pregnant female outpatients (324 *Escherichia coli*) and pediatric patients (93 *Klebsiella pneumoniae*). We found a high prevalence of resistance towards the drugs used as "first-line" when treating UTIs: ampicillin, cotrimoxazole, and ciprofloxacin (79%, 60%, and 24% resistance, respectively). Ninety-eight percent of *K pneumoniae* isolates were resistant to ampicillin, whereas 66% of the *E coli* isolates were resistant to cotrimoxazole. Resistance towards third-generation cephalosporins was also high (6%–8% of *E coli* and 10%–28% of

*K pneumoniae*). This was possibly caused by chromosomal  $\beta$ -lactamases, as 30% of all isolates were also resistant to amoxicillin/clavulanate. In contrast, 98% of the *E coli* isolates and 84% of the *K pneumoniae* strains (96% of all isolates) were found to be susceptible to nitrofurantoin, which has been in clinical use for much longer than most other drugs in this study.

**Conclusion:** In these urine samples from laboratories in Mexico City, resistance of *K pneumoniae* and *E coli* isolates to first-line treatment (ampicillin, cotrimoxazole, or ciprofloxacin) of UTI was high, whereas most *E coli* and *K pneumoniae* isolates were susceptible to nitrofurantoin and the fourth-generation cephalosporin cefepime. (*Curr Ther Res Clin Exp.* 2007;68:120–126) Copyright © 2007 Excerpta Medica, Inc.

**Key words:** urinary tract infection, uropathogenic bacteria.

## INTRODUCTION

The clinical efficacy of antibiotics declines with time.<sup>1</sup> This decline, which is specific to antimicrobial drugs, is caused by the emergence of bacterial varieties that withstand or even thrive in the presence of formerly inhibitory concentrations of such chemical agents. Resistance surveillance is the main strategy to provide clues to guide the empirical use of antibiotics.<sup>2</sup> Such surveillance should be localized and updated as often as possible because resistance trends can vary even between hospitals in the same city.<sup>2</sup> Antibiotic resistance has been recognized as the consequence of antibiotic use and abuse.<sup>3</sup> As such, it is likely to be more prevalent in countries where antibiotic usage is not strictly regulated. For instance, in Mexico antibiotics are available as “over-the-counter” drugs and self-prescription might account for up to one-third of antibiotic sales at drugstores.<sup>4</sup> Similar situations are common in Latin American, Asian, and African countries.<sup>5</sup> Therefore, resistance prevalence figures published from developed countries are not useful to guide empirical therapy in developing countries. Currently, in Mexico City, ampicillin, cotrimoxazole (trimethoprim/sulfamethoxazole), and ciprofloxacin are used as “first-line” antibiotic treatment for urinary tract infections (UTIs).

The aim of this study was to analyze the susceptibility of bacterial isolates to antibiotics, with a focus on first-line antibiotics, in Mexican pediatric patients and sexually active or pregnant female outpatients.

## MATERIAL AND METHODS

### Bacterial Strains

In this multicenter susceptibility analysis, *Klebsiella pneumoniae* isolates from positive routine urine cultures in male and female pediatric outpatients and *Escherichia coli* isolates from sexually active or pregnant female outpatients, all presenting with acute, uncomplicated UTIs, were included in this study (these 2 populations were chosen because most uncomplicated UTIs in Mexico

City are observed in them). Isolates were identified using standard biochemical techniques,<sup>6</sup> and stored after isolation at  $-70^{\circ}\text{C}$  in a glycerol-containing medium until antibiotic susceptibility testing was performed. Only *E coli* and *K pneumoniae* isolates were included, as those species were the only ones occurring frequently enough to draw representative data.

### Susceptibility Testing

Susceptibility was tested by the disk-diffusion method, using commercially-available disks (Becton, Dickinson and Company, Franklin Lakes, New Jersey), following standard guidelines.<sup>7</sup> The antibiotics tested included the following:  $\beta$ -lactams, ampicillin, amoxicillin/clavulanate, aztreonam, ceftazidime, ceftizoxime, and cefepime; the aminoglycoside, netilmicin; the fluoroquinolone, ciprofloxacin; cotrimoxazole (trimethoprim/sulfamethoxazole); and nitrofurantoin. Inhibitory halo diameter was interpreted for each isolate to determine susceptibility. The prevalence of “intermediate” strains was not reported because most of the drug concentrations obtained in urine were high enough to inhibit these organisms,<sup>8</sup> deeming them fully susceptible.

### RESULTS

Three hundred twenty-four *E coli* isolates from sexually active or pregnant female outpatients and 93 *K pneumoniae* isolates from positive routine urine cultures in pediatric outpatients, all presenting with acute, uncomplicated UTIs in Mexico City from January 2006 through June 2006, were included in this study. Resistance prevalence for each species is shown in the **table**.

We found a high prevalence of resistance towards the drugs used as “first-line” against UTIs: ampicillin (78%), cotrimoxazole (60%), and ciprofloxacin (24%). Almost all (98%) *K pneumoniae* isolates were resistant to ampicillin, whereas 66% of the *E coli* isolates were resistant to cotrimoxazole. Resistance towards third-generation cephalosporins was also high (6%–13% of all isolates). This was possibly caused by chromosomal  $\beta$ -lactamases, as 30% of all isolates were also resistant to amoxicillin/clavulanate. In contrast, 98% of *E coli* isolates and 84% of *K pneumoniae* strains (96% of all isolates) were found to be susceptible to nitrofurantoin, which has been in clinical use for much longer than most other drugs.

### DISCUSSION

Susceptibility of uropathogenic bacteria in developed countries, although certainly growing, is low enough to still consider the use of cotrimoxazole, aminopenicillins, or fluoroquinolones as drugs of first choice. A 2003 study<sup>9</sup> of antimicrobial susceptibility of pathogens from uncomplicated UTIs that included 252 health centers from 16 European countries and Canada, found that among 2478 *E coli* isolates, 30% were resistant to ampicillin, 14% to cotrimoxazole, and

**Table.** Resistance prevalence in isolates of *Escherichia coli* collected from sexually-active or pregnant female outpatients and *Klebsiella pneumoniae* collected from pediatric patients in Mexico City suffering acute, uncomplicated, urinary tract infections. Values are no. (%).

Antibiotic	Resistant Strains		
	<i>E coli</i> (n = 324)	<i>K pneumoniae</i> (n = 93)	Total (N = 417)
Ampicillin	236 (73)	91 (98)	327 (78)
Cotrimoxazole*	213 (66)	36 (39)	249 (60)
AMC	74 (23)	52 (56)	126 (30)
Ciprofloxacin	92 (28)	7 (8)	99 (24)
Aztreonam	34 (10)	23 (25)	57 (14)
Ceftazidime	27 (8)	26 (28)	53 (13)
Netilmicin	17 (5)	24 (26)	41 (10)
Ceftizoxime	18 (6)	9 (10)	27 (6)
Nitrofurantoin	8 (2)	15 (16)	23 (6)
Cefepime	14 (4)	0	14 (3)

AMC = amoxicillin/clavulanate.

\*Trimethoprim/sulfamethoxazole.

2% to ciprofloxacin. Studies in the United States have found that the resistance prevalence was roughly the same.<sup>10,11</sup>

Our results include resistance prevalences that are 2- to 10-fold higher for these antibiotics: 73% of the *E coli* isolates in our study were resistant to ampicillin, 66% to cotrimoxazole, and 29% to ciprofloxacin. This increase in resistance has been observed for some time in Mexico and other Latin American countries. In a Mexican survey from 1997,<sup>12</sup> 60% of uropathogenic *E coli* were found to be resistant to ampicillin, 55% to cotrimoxazole, and 32% to norfloxacin. In Argentina, between 1996 and 1998,<sup>12</sup> 44% to 76% of uropathogenic *E coli* were found to be resistant to ampicillin, 27% to 46% to cotrimoxazole, and 2% to 26% to ciprofloxacin.

These differences might be attributed to a number of reasons: (1) medical abuse of antibiotics, as several studies have shown that higher rates of antibiotic prescription are linked to higher resistance prevalence<sup>3</sup>; (2) self-prescription, which may account for up to 30% of antibiotics sold at drugstores in Mexico City<sup>4</sup>; drugs more often used by self-prescription include aminopenicillins and sulfonamides (the 2 drug classes with higher resistance prevalence in this study); and self-prescribed treatments are often shorter than the clinically-accepted length,<sup>13</sup> which is more likely to select resistant organisms; and (3) abundance of generic drugs without adequate quality control, which might result in suboptimal plasma and/or tissue concentrations of drugs because of deficient pharmaceutical formulations. However, the lack of accurate data on antibiotic usage prevents the aforementioned from being more than educated guesses.

Some further information can be inferred from the results. The high prevalence of resistance towards amoxicillin/clavulanate in this study (23% of *E coli* strains, 56% of *K pneumoniae* strains) suggests that the over-expression of chromosomal  $\beta$ -lactamase AmpC is an important component of overall resistance to  $\beta$ -lactams. The high prevalence of fluoroquinolone resistance (represented in this study by ciprofloxacin), is considered to be caused primarily by mutations on chromosomal genes.<sup>14</sup> Combined, these data suggest that the uropathogenic bacteria observed are not acquiring resistance through horizontal gene transfer, but by isolated selective events. Because the urinary tract is mainly sterile and infections located there are mostly caused by a single type of pathogenic organism, perhaps this tract is an isolated environment where gene exchange cannot occur often. However, it is also possible that conditions in the urinary tract convey invading bacteria towards a hyper-mutable state, as reported for other kinds of infectious processes.<sup>15</sup>

One of the most effective antimicrobial agents amongst the ones tested here was nitrofurantoin; only less effective than the fourth-generation cephalosporin cefepime in overall results and the best agent observed versus *E coli*. This was particularly interesting as the drug has been available in crystalline form since 1953,<sup>16</sup> well before all of the other drugs tested in this study. Because of its pleiotropic mechanism of action, resistance to nitrofurantoin has been slow to occur.<sup>16</sup> And, despite resistance being seldom found in developed countries (1.2% in Europe,<sup>9</sup> 0.5% in the United States<sup>10</sup>), this drug is not usually considered as a first choice. Among neonates, where UTIs are regarded as a potential sign of bacteremia, drugs other than nitrofurantoin are preferred; but, when the infection is presumably localized, this drug may be a valid option. Nitrofurantoin is a well tolerated drug even for pediatric and extended use<sup>16</sup>; the in vitro results shown here indicate that nitrofurantoin might be an alternative in countries where other antibiotics face a high prevalence of resistance.

Based on the results of this study, we suggest there is a need for local surveillance to guide the empirical prescription of antibiotics against UTIs, and how drugs such as nitrofurantoin, that have been used clinically for a long time, might be considered as important options in the handling of infectious diseases caused by bacteria resistant to newer drugs.

## CONCLUSION

In these urine samples from laboratories in Mexico City, resistance of *K pneumoniae* and *E coli* isolates to first-line treatment (ampicillin, cotrimoxazole, or ciprofloxacin) of UTI was high, whereas most *E coli* and *K pneumoniae* isolates were susceptible to nitrofurantoin and the fourth-generation cephalosporin cefepime.

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