Susceptibilities of Urinary Tract Isolates of Extended-Spectrum (ESBL) and AmpC-Type (AmpC) -Lactamase-Producing *Escherichia coli (E. coli)* against Six First-line Oral Antibiotics Commonly Used for Community-Acquired Urinary Tract Infections (UTIs)

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ABSTRACT

Background: Serious infections due to organisms harbouring broad-spectrum -lactamases, such as ESBL and/or AmpC -lactamases, have been reported worldwide with significant morbidity and mortality. We conducted a retrospective study to assess susceptibility profiles of ESBL- and/or AmpC-producing *E. coli* urinary strains among nonhospitalized patients. **Methods:** Over a 2 year period, all isolates of *E. coli, Klebsiella pneumoniae, and K. oxytoca* isolated from nonhospitalized patients were screened for ESBL production, followed by confirmatory testing if warranted, in accordance with NCCLS guidelines.The *in vitro* antimicrobial susceptibility profiles of ESBL- or AmpC-producing organisms were analyzed for six oral antimicrobials commonly used for UTIs, including ampicillin (AMP), cephalothin (CF), ciprofloxacin (CIP), norfloxacin (NOR), trimethoprim-sulfamethoxazole (TMP/SMX), and nitrofurantoin (F/M). **Results:** A total of 81 urinary isolates were confirmed as ESBL- or AmpC-producing organisms, all *E. coli*. Of these 81 isolates, 81 (100%) were resistant to AMP and CF; 31 (38%) were resistant to CIP and NOR; 25 (31%) were resistant to TMP/SMX; and 2 (2.5%) were resistant to F/M. F/M was significantly more active *in vitro* than the other antimicrobials tested (P = 0.04). **Conclusion:** Due to its high *in vitro* activity, nitrofurantoin may be a good option for the empiric treatment of uncomplicated lower UTIs caused by ESBL- or AmpC-producing *E. coli*.

INTRODUCTION

Serious infections due to organisms harbouring broad-spectrum -lactamases, such as extended-spectrum (ESBL) and/or AmpC type -lactamases, have been reported worldwide with significant morbidity and mortality.

Although ESBLs typically do not hydrolyze 7- -methoxy-cephalosporins and are inactivated by -lactamase inhibitors (e.g., clavulanate), recent reports suggest that treatment of infections due to ESBL producing organisms with cephamycins or -lactam/ -lactamase inhibitor combinations may result in clinical failure. As a result, both ESBL and AmpC producing organisms should be considered resistant *in vivo* to all -lactams and -lactam/ -lactamase inhibitor combinations, except for carbapenems. Many of these strains are also resistant to other antimicrobial classes, such as the aminoglycosides and fluoroquinolones.

A significant number of these strains had been often isolated from urine cultures of hospitalized patients. We conducted a retrospective study to assess susceptibility profiles of these strains in urine cultures among nonhospitalized patients against six first-line oral antibiotics commonly used in the treatment of community-acquired urinary tract infections (UTIs).

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Figure 1. Number of urinary isolates of confirmed ESBL/ AmpC-producing *E. coli* over the 24 month study period

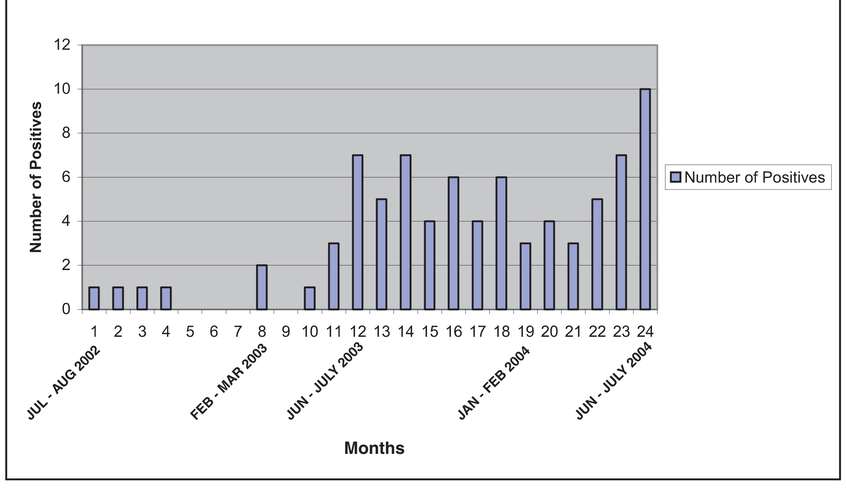

Table 1: Susceptibilities of study strains of ESBL- or AmpC-producing *E. coli* (*n* = 81) against six first-line oral antimicrobial agents

Antimicrobial agent	Susceptible *n* (%)[1]	Intermediate *n* (%)	Resistant *n* (%)	Total *n*
Ampicillin	0 (0)	0 (0)	81 (100)	81
Cephalothin	0 (0)	0 (0)	81 (100)	81
Ciprofloxacin	50 (62)	0 (0)	31 (38)	81
Nitrofurantoin	73 (90)	6 (7)	2 (2.5)	81
Norfloxacin	50 (62)	0 (0)	31 (38)	81
Trimethoprim/ sulfamethoxazole	53 (65)	3 (4)	25 (31)	81

[1] Percentages may not add up to 100, due to rounding of fractions.

METHODS

Bacterial Strains:

Over a 2 year period, from July 17, 2002 to July 17, 2004, all isolates of *E. coli, Klebsiella pneumoniae*, and *K. oxytoca* isolated from urine specimens collected from nonhospitalized patients were evaluated.

Antimicrobial Susceptibility Testing:

Antimicrobial disks (Becton Dickinson and Company, Sparks, MD, USA) were used for antimicrobial susceptibility and ESBL testing in this study. The disks were tested daily and met NCCLS standards for accurate performance against quality control organisms. Suspensions of test organisms were prepared to a concentration equivalent to 0.5 McFarland standard and inoculated onto Mueller-Hinton agar plates (PML Microbiologicals, Mississauga, ON, Canada) using standard methods. Interpretation of disk zone diameters was performed in accordance with NCCLS interpretive criteria.

ESBL Screening:

Isolates were screened according to NCCLS guidelines by cefpodoxime disk (10 g) (Primary Screen), followed if screen-positive, by further screening (Secondary Screen) with ceftazidime (CAZ, 30 g), cefotaxime (CTX, 30 g), ceftriaxone (CRO, 30 g), and aztreonam (ATM, 30 g) disks. SecondaryScreen-positive isolates were subsequently referred to Public Health Laboratories for confirmatory testing.

ConfirmatoryTesting:

An isolate was confirmed as an ESBL producer by the NCCLS Phenotypic Confirmatory Test (Disk Diffusion). An increase in zone diameter of 5 mm for either CTX or CAZ tested in combination with clavulanic acid versus its zone diameter when tested alone was considered confirmatory of ESBL production. If the isolate expressed no synergy with clavulanic acid, was resistant or intermediate to cefoxitin, and the CTX or CAZ zone diameters were 27 mm or 22 mm, respectively, this was considered indicative of the presence of AmpC.

Profile Analysis:

Antimicrobial susceptibility profiles were analyzed for six oral antimicrobials, ampicilin, cephalothin, ciprofloxacin, nitrofurantoin, norfloxacin, and trimethoprim-sulfamethoxazole.

RESULTS & DISCUSSION

A total of 9,128 *E. coli* and 926 *Klebsiella* urinary isolates were screened for ESBL production, in accordance with NCCLS guidelines. Of these 10,054 isolates, 98 were potential broad-spectrum -lactamase producers. Confirmatory testing detected 81 strains that were either ESBL- or AmpC- producing isolates, all *E. coli*.

The mean age of patients with ESBL- or AmpC-positive organisms was 47.9 years, with a range of <1 to 94 years. More isolates were recovered from females (0 - 21 years, n = 10; 22 - 65 years, n = 49; > 65 years, n = 13) than from males (0 - 21 years, n = 1; 22 - 65 years, n = 5; > 65 years, n = 3). This high female to male ratio is consistent with urinary isolation rates encountered in routine practice.

As can be seen in Figure 1, the number of confirmed ESBL/AmpC-producing *E. coli* isolates increased significantly during the study period. At consecutive six month intervals, the number of isolates were 4, 13, 32, and 32. The increase in the isolation rates of broad-spectrum -lactamase producing organisms is consistent with studies showing increasing prevalence of infections caused by these types of resistance.

Table 1 summarizes the susceptibility profiles of the 81 isolates. Since the source of isolation was urine, where drugs are physiologically concentrated, the intermediate category in the susceptibility profile may imply clinical applicability.

At the low resistance rate of 2.5%, nitrofurantoin was significantly more active *in vitro* than the other antimicrobials in this study (P = 0.04). The generally low aquired resistance of nitrofurantoin has been attributed to the broad-based nature of its mode of action by inactivating or altering ribosomal proteins and other target macromolecules, thus inhibiting essential biochemical processes of protein synthesis and nucleic acid synthesis.

ESBL- and AmpC-producing *E. coli* strains are often multidrug resistant. In this study, nitrofurantoin was found to be the most active agent tested against these strains. Therefore the use of nitrofurantoin as an oral antibiotic may be a good option for the empiric treatment of this type ofcommunity-aquired uncomplicated lower UTIs.

CONCLUSIONS

- There has been an increase in the isolation of community-acquired UTI-associated broad-spectrum ß-lactamase producing *E. coli* over the past two years.
- This study demonstrated the efficacy of nitrofurantoin as significantly more active *in vitro* than ampicillin, cephalothin, ciprofloxacin, norfloxacin, or trimethoprim-sulfamethoxazole against ESBL- or AmpC-producing *E. coli*.
- Due to its high *in vitro* activity, nitrofurantoin may be a good option for the empiric treatment of uncomplicated lower UTIs caused by ESBL- or AmpC-producing *E. coli*.