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Increasing Rates of Extended-Spectrum Beta-Lactamase (ESBL) Producing Strains among Community Urinary Isolates and Impact of Patient Age on ESBL Prevalence and Resistance Rates: A Five-Year Study

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ABSTRACT

Background: Monitoring resistance of ESBL-producing organisms is critical for guiding appropriate empiric antimicrobial therapy. As most infections caused by ESBL producers in the community involve the urinary tract, we investigated the prevalence of community urinary ESBL-producing *Escherichia coli* and *Klebsiella* strains over the past 5 years and determined their resistance to four commonly used oral antimicrobials.

Methods: *E. coli* and *Klebsiella* isolates from urine cultures obtained from April 2006 to March 2011 were tested by the double-disk synergy method to identify ESBLs, and disk diffusion with ciprofloxacin (CIP), nitrofurantoin (FM), norfloxacin (NOR) and trimethoprim/sulfamethoxazole (TMP/SMX) in accordance with CLSI guidelines. A subset (n = 201) was tested by PCR for ESBL-encoding genes. Data were analyzed by age groups.

Results: Of the total of nonduplicate 18,759 *E. coli* and 1,872 *Klebsiella* spp., 642 (3.4%) *E. coli* and 27 (1.4%) *Klebsiella* spp. were identified as ESBL producers by the double-disk synergy method. The ESBL rates in *E. coli* increased over 5 years from 1.8% to 4.0% (P < 0.01) and from 0.4% to 1.7% in *Klebsiella* spp. (P < 0.01). Of the ESBL-producing strains, 8.2%, 11.1%, 23.2%, 24.2%, and 33.3% were isolated from patients who were ≤18, 19-30, 31-50, 51-65, and >65 years of age, respectively. bla_{CTX-M}, bla_{OXA-1}, bla_{SHV}, and bla_{TEM} genes were present in 94%, 35%, 13%, and 44% of PCR-tested strains, respectively, with bla_{CTX-M} found in 97% of the *E. coli* strains and bla_{SHV} in 92% of the *Klebsiella* strains. Resistance rates for CIP, FM, NOR, and TMP/SMX were 62%, 5%, 62%, and 57%, respectively. There was a trend for higher resistance rates against CIP and NOR with increasing age.

Conclusions: There has been a steady increase in ESBL rates in community urinary isolates over the past 5 years, with a trend towards higher rates in older patients. ESBL-producing *E. coli* and *Klebsiella* spp. were often multi-drug resistant, but most isolates remained susceptible to FM. bla_{CTX-M} was the predominant ESBL among urinary *E. coli* isolates in the community.

INTRODUCTION

Serious infections due to organisms harbouring extended-spectrum β-lactamases (ESBLs) have been reported worldwide with significant morbidity and mortality. Although ESBLs typically do not hydrolyze 7-α-methoxy-cephalosporins and are inactivated by β-lactamase inhibitors, recent reports suggest that treatment of infections due to ESBL producing organisms with cephamycins or β-lactam/β-lactamase inhibitor combinations may result in clinical failure, thus further limiting therapeutic options, already rendered more difficult by the emergence or co-production of resistance to other antimicrobials.[7]

Dissemination of infections caused by ESBL-producing and other multidrug-resistant organisms has recently been described as a significant threat of global crisis proportions.[4] Although most urinary tract infections (UTIs) are uncomplicated, serious ESBL-associated infections (e.g., ESBL-associated bacteraemia) are known to originate frequently from the urinary or biliary tract.[8] As most infections caused by ESBL producers in the community involve the urinary tract, we investigated the prevalence of community urinary ESBL-producing *Escherichia coli* and *Klebsiella* strains over the past 5 years and determined their resistance to four oral antimicrobial agents, ciprofloxacin (CIP), nitrofurantoin (FM), norfloxacin (NOR) and trimethoprim/sulfamethoxazole (TMP/SMX), commonly used for the treatment of UTIs in the community.

METHODS

Over a 5 year period, from April 1st, 2006 to March 31st, 2011, all positive urine cultures yielding ≥ 10^4 CFU/ml of one or two organisms were investigated to obtain the isolate identification and its susceptibility to appropriate antimicrobials. Non-duplicate isolates of *E. coli* and *Klebsiella* species were tested for ESBL production by the double-disk synergy test, and their antimicrobial susceptibility profiles were determined for CIP, FM, NOR and TMP/SMX, using the disk diffusion method, in accordance with current guidelines of the Clinical and Laboratory Standards Institute (CLSI).[1]

Among the ESBL-producing strains, a subset (n = 201) was tested by PCR for ESBL-encoding genes (bla_{CTX-M}, bla_{OXA-1}, bla_{SHV}, and bla_{TEM}). Data were analysed by patient age, which was defined according to previously described inclusion parameters (≤18; 19 – 30; 31 – 50; 51 – 65; and >65 years of age).[3]

RESULTS & DISCUSSION

Five-Year ESBL Rates: Of the 229,181 urine specimens submitted for culture, a total of 18,759 non-duplicates of *E. coli* and 1,872 non-duplicates of *Klebsiella* spp. were isolated. Of these, there were 642 (3.4%) *E. coli* and 27 (1.4%) *Klebsiella* spp. that were ESBL-producing. Over the study five year period, the ESBL rates in *E. coli* increased from 1.8% to 4.0% (P < 0.01) and from 0.4% to 1.7% in *Klebsiella* spp. (P < 0.01). Figure 1 shows the number of ESBL-producing strains per year analysed by patient age group. Over the study period, 8.2%, 11.1%, 23.2%, 24.2%, and 33.3% of the ESBL-producing strains were isolated from patients who were ≤18, 19-30, 31-50, 51-65, and >65 years of age, respectively, suggesting a trend towards higher ESBL rates with increasing age.[3]

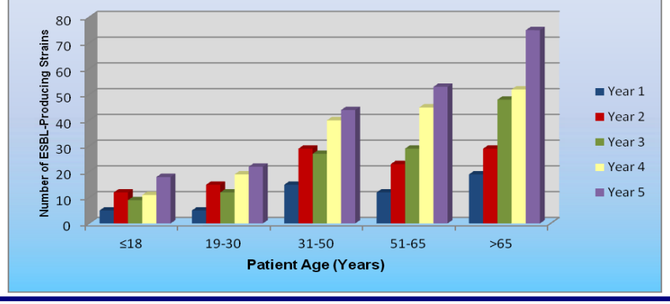
Gene Distribution: bla_{CTX-M}, bla_{OXA-1}, bla_{SHV}, and bla_{TEM} genes were present in 94%, 35%, 13%, and 44% of PCR-tested strains, respectively, with bla_{CTX-M} found in 97% of the *E. coli* and bla_{SHV} in 92% of the *Klebsiella* strains.

Table 1: Antimicrobial Resistance Rates (Year 1 – Year 5) by Age Group

Age Group (yr)	No. tested (n)	CIP n = 614	FM n = 669	NOR n = 614	TMP/SMX n = 669
		No. (%R*)	No. (%R)	No. (%R)	No. (%R)
≤18	55	NT	2 (3.6)	NT	36 (65.4)
19 – 30	74	41 (55.4)	4 (5.4)	41 (55.4)	39 (52.7)
31 – 50	155	91 (58.7)	3 (1.9)	91 (58.7)	82 (52.9)
51 – 65	162	103 (63.6)	11 (6.8)	103 (63.6)	103 (63.6)
>65	223	148 (66.4)	12 (5.4)	148 (66.4)	120 (53.8)
Overall Resistance	669	383 (**62.4**)	32 (**4.8**)	383 (**62.4**)	380 (**56.8**)

* %R, resistance rate (%); CIP, ciprofloxacin; FM, nitrofurantoin; NOR, norfloxacin; NT, not tested for patients ≤ 18 yr; TMP/SMX, trimethoprim/sulfamethoxazole.

Figure 1: Number of ESBL-Producing Strains per Year Analysed by Patient Age Group



Antimicrobial Resistance: Table 1 summarizes the resistance rates of ESBL-producing isolates by patient age group for the five year period. Three of the four non-beta-lactams tested in this study, namely CIP, NOR, and TMP/SMX, were associated with high resistance rates, as previously reported.[3,6] Among the PCR-tested isolates, bla_{CTX-M} producing strains were more likely to be resistant to CIP and NOR, but less likely to be resistant to FM, than non-producers. FM was the most likely of the oral agents tested in this study to have a favourable antibacterial effect against community urinary ESBL producers.

Effect of Age on Resistance: The trend for higher resistance rates observed with increasing age over the five years was consistently seen with CIP and NOR, but not with FM or TMP/SMX (Figure 2).[3] The identification of age groups with increasing fluoroquinolone resistance rates has been recommended for surveillance of resistance.[5]

Year-to-Year Resistance Rates: Figure 3 shows the year-to-year resistance rate for each antimicrobial agent tested during each interval. The resistance rate for each agent appears to have remained relatively stable over time.

Figure 2: Rates of ESBL Resistance to CIP, FM, NOR, or TMP/SMX Analysed by Patient Age

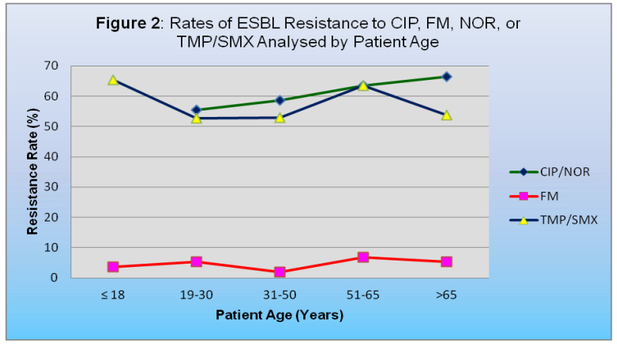
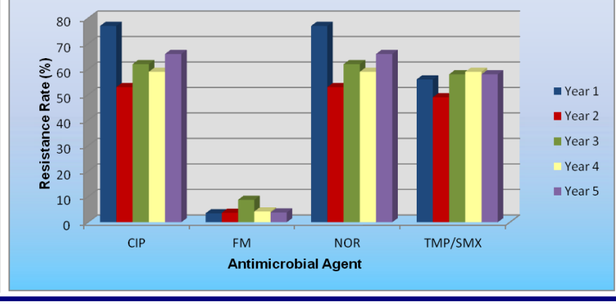


Figure 3: Antimicrobial Resistance Rates for Each Agent Over Time (Year 1- Year 5)



CONCLUSIONS

- There has been a steady increase in ESBL rates in community urinary isolates over the past 5 years, with a trend towards higher rates in older patients.
- ESBL-producing *E. coli* and *Klebsiella* spp. were often multi-drug resistant, but most isolates remained susceptible to FM.
- bla_{CTX-M} was the predominant ESBL among urinary *E. coli* isolates in the community.
- bla_{CTX-M} producing strains were more likely to be resistant to CIP and NOR, but less likely to be resistant to FM, than non-producers, among community urinary isolates.

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