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Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA)

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Abstract

The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study determined the antibiotic susceptibility to commonly used agents for urinary tract infections of outpatient *Escherichia coli* urinary isolates obtained from various geographic regions in the USA and Canada. NAUTICA involved 40 medical centres (30 from the USA and 10 from Canada). From April 2003 to June 2004 inclusive, each centre submitted up to 50 consecutive outpatient midstream urine isolates. All isolates were identified to species level by each laboratory's existing protocol. Susceptibility testing was determined using the Clinical and Laboratory Standards Institute (CLSI) microdilution method. Ampicillin (resistant ≥32 μg/mL), sulphamethoxazole/trimethoprim (SMX/TMP) (resistant ≥4 μg/mL), nitrofurantoin (resistant ≥128 μg/mL), ciprofloxacin (resistant ≥4 μg/mL) and levofloxacin (resistant ≥8 μg/mL) resistance breakpoints used were those published by the CLSI. Of the 1142 *E. coli* collected, 75.5% (862) were collected from the USA and 280 (24.5%) were from Canada. Patient demographics revealed a mean age of 48.1 years (range, 2 months to 99 years), with female patients representing 79.4% of patients and males representing 20.6%. Overall, resistance to ampicillin was 37.7%, followed by SMX/TMP (21.3%), nitrofurantoin (1.1%), ciprofloxacin (5.5%) and levofloxacin (5.1%). Resistance rates for all antimicrobials were higher in US medical centres compared with Canadian centres ($P < 0.05$). Fluoroquinolone resistance was highest in patients ≥65 years of age ($P < 0.05$). Resistance rates demonstrated considerable geographic variability both in the USA and Canada. This study reports higher rates of antibiotic resistance in US versus Canadian outpatient urinary isolates of *E. coli* and demonstrates the continuing evolution of resistance to antimicrobial agents.

Keywords: Antibiotic resistance; *Escherichia coli*; Urinary

1. Introduction

Urinary tract infections (UTIs) such as cystitis and pyelonephritis are among the most commonly encountered infections both in community and hospital settings [1–4] and *Escherichia coli* has been established as the predominant pathogen in UTIs [5–13]. In settings where the prevalence of

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sulphamethoxazole/trimethoprim (SMX/TMP) resistance is <10–20%, the currently recommended empirical antimicrobial regimen for treating acute uncomplicated bacterial cystitis in otherwise healthy, adult, non-pregnant females is a 3-day regimen of double-strength SMX/TMP [1,3,11]. Because *E. coli* accounts for 75–90% of uncomplicated UTI isolates [5–13], resistance to SMX/TMP among clinical isolates of *E. coli* is an important indicator of whether SMX/TMP should continue to be used empirically. The prevalence of SMX/TMP resistance among urinary pathogens now equals or exceeds 10–20% in all regions of the USA [11,13] and it appears inevitable that in the future empirical treatment of uncomplicated urinary infections with SMX/TMP will be replaced by alternative therapies such as fluoroquinolones or nitrofurantoin [1,2]. A recent report by Huang and Stafford [14] suggested that many ambulatory care physicians already prescribe fluoroquinolones and nitrofurantoin to treat UTIs in women. Given that a transition in therapy is occurring, or appears imminent, clarity regarding the current susceptibilities of SMX/TMP-resistant and other antimicrobial-resistant urinary isolates of *E. coli* to fluoroquinolones and nitrofurantoin is important and will be of benefit to clinicians.

The goal of the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study was to determine the antibiotic susceptibility to commonly used agents for UTIs of outpatient *E. coli* urinary isolates obtained from various geographic regions in the USA and Canada.

2. Materials and methods

2.1. Isolate collection

NAUTICA is a UTI surveillance study involving 40 medical centres (30 from the USA and 10 from Canada) [13]. From April 2003 to June 2004 inclusive, each centre submitted up to 50 consecutive outpatient midstream urine isolates. All isolates were identified to species level by each laboratory's existing protocol. It was not known whether submitted urinary isolates came from patients with symptomatic upper or lower UTIs or from patients with asymptomatic bacteriuria; however, all submitted isolates had to be deemed significant by the participating laboratory, identified to species level and its antibiotic susceptibility reported to the submitting clinician. Isolates were transported to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) on Amies charcoal swabs. Only one isolate per patient was accepted. Upon receipt, isolates were cultured by the coordinating laboratory, stocked in skim milk and stored at −80 °C until reference antibiotic susceptibility testing. Elementary demographic information was also compiled for each isolate.

2.2. Antibiotics

All antibiotics tested were obtained as laboratory-grade powders from their respective manufacturers.

2.3. Antimicrobial susceptibility testing

Susceptibilities to ampicillin (Sigma Chemical Co., St Louis, MO), SMX/TMP (Sigma Chemical Co.), nitrofurantoin (Procter & Gamble Inc., Cincinnati, OH), ciprofloxacin (Bayer Inc., Toronto, ON) and levofloxacin (Ortho-McNeil Pharmaceuticals, Toronto, ON) were determined using the National Committee for Clinical Laboratory Standards M7-A6 broth microdilution method [15]. Cation-adjusted Mueller–Hinton broth (Ca^{2+}, 25 μg/mL; Mg^{2+}, 12.5 μg/mL) microdilution panels were prepared by the coordinating laboratory to contain antimicrobial doubling dilution concentrations appropriate for each agent tested [15]. Each final panel well volume was 100 μL with a bacterial inoculum of 5×10^5 colony-forming units/mL [15]. Panels were read following 16–20 h of incubation at 35 °C in ambient air [15]. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of antimicrobial inhibiting visible growth [15]. Quality control was performed using appropriate ATCC quality control organisms. Ampicillin (resistant ≥32 μg/mL), SMX/TMP (resistant ≥4 μg/mL), nitrofurantoin (resistant ≥128 μg/mL), ciprofloxacin (resistant ≥4 μg/mL) and levofloxacin (resistant ≥8 μg/mL) resistance breakpoints used were those published by the Clinical and Laboratory Standards Institute (CLSI) [16].

2.4. Statistical analysis

P-values were calculated using χ^2 for dichotomous variables, Mann–Whitney test for ordinal data and Student's *t*-test for continuous variables. All tests were two-tailed and a *P*-value of ≤0.05 was considered significant.

3. Results

3.1. Patient demographics

Table 1 describes the patient demographics for submitted *E. coli* outpatient urinary tract isolates. Patients were categorised into four different age groups: ≤14 years, 15–50 years, 51–64 years and ≥65 years. Total breakdown by age group was 8.7% of isolates in the ≤14 years age group, 42.8% in the 15–50 years age group, 13.8% in the 51–64 years age group and 34.7% in the ≥65 years age group. Females represented 79.4% of patients and males represented 20.6%. The mean age was 48.1 years (range, 2 months to 99 years). Of the 1142 *E. coli* collected, 75.5% (862) were collected from the USA and 280 (24.5%) were from Canada.

3.2. Antibiotic resistance in E. coli outpatient isolates

As can be seen in Table 2, overall resistance rates were: ampicillin 37.7%, SMX/TMP 21.3%, nitrofurantoin 1.1% and the fluoroquinolones ciprofloxacin and levofloxacin 5.5% and 5.1%, respectively. Resistance rates for all antimicrobials