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Antibiotic resistance patterns of more than 120 000 clinical *Escherichia coli* isolates in Southeast Austria, 1998–2013

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Abstract

Antibiotic resistance patterns of more than 120 000 clinical *Escherichia coli* isolates were retrospectively analysed. Isolates originated from both hospitalized patients and outpatients from the region of southeast Austria from 1998 to 2013. Except for amoxicillin/clavulanic acid, nitrofurantoin and piperacillin/tazobactam, all of the antibiotics analysed showed increasing proportions of resistant isolates over time, which were most prominent for ampicillin (from 25.4% in 1998 to 40% in 2013), cefotaxime (0.1% to 6.7%), ceftazidime (0.3% to 14.2%), ciprofloxacin (4.3% to 16.7%) and trimethoprim/sulfamethoxazole (14.6% to 24.8%). There was a marked increase in extended-spectrum β-lactamase–positive isolates (0.1% to 6.3%) starting in 2005, with male patients and hospital-related patients showing a higher increase than female patients and outpatients. Proportions of resistant isolates for most antibiotics were generally higher for male patients and hospital-related patients. Amikacin, nitrofurantoin and trimethoprim/sulfamethoxazole showed a marked increase in resistance proportions among male subjects aged 10 to 19 years which were absent for female subjects, indicating a strong modulation potential of host characteristics.

Keywords: Antibiotic resistance, Austria, epidemiology, ESBL, *Escherichia coli*
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Introduction

Escherichia coli belongs to the physiological intestinal flora of both humans and other mammals, and depending on its pathogenic properties, it can cause various intestinal and extraintestinal infections [1]. *E. coli* is the leading pathogen causing bacteremia and urinary tract infections in both hospitalized patients and outpatients, and it is a common cause of peritonitis as well as skin and soft tissue infections. It can also lead to sepsis among newborns, and it belongs to the most frequent causes of enteric/diarrhoeal diseases globally [2].

E. coli is a highly versatile microorganism which is able to easily acquire genetic elements responsible for antimicrobial resistance. Empirical therapy for *E. coli* infections has become increasingly difficult as a result of growing resistance rates to first-line antibiotics [3]. Multi-drug-resistant *E. coli* producing extended-spectrum β-lactamases (ESBL) have become a substantial health issue. The production of ESBL confers resistance to third-generation cephalosporins and monobactams, but not to cephamycins and carbapenems; β-lactamase inhibitors usually remain effective *in vitro* [4]. The emergence of carbapenem resistance in *E. coli* due to metallo- and serine-type carbapenemases raises concern for public health at a global level [5].

There are numerous studies presenting antibiotic resistance data of *E. coli* and Gram-negative pathogens. However, most of

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them involve specific infections, anatomic locations or resistance problems [6–11]. Surveillance studies focusing exclusively on *E. coli* and covering a large number of isolates acquired over a long period of time are of great importance in order to specify resistance patterns according to different patient-related factors and to determine emerging resistance developments.

Here we present what is to our knowledge one of the most comprehensive antibiotic resistance studies about *E. coli* from a specific region. The aim of the study was to retrospectively analyse the antibiotic resistance patterns of more than 120 000 clinical *E. coli* isolates originating from both hospitalized patients and outpatients from southeast Austria from 1998 to 2013. The large number of isolates allows statistical analysis of antibiotic resistance data according to patient location (community, hospital), age, gender and culture site. Moreover, annual changes in resistance prevalence are described, with a special focus on ESBL-producing isolates.

Materials and methods

In this retrospective observational study, antibiotic resistance patterns of a total of 135 878 clinical *E. coli* isolates were analysed. Data were retrieved from the Laboratory of Medical Bacteriology and Mycology of the Medical University of Graz, Austria from January 1998 to December 2013. Inpatient isolates origin from our 1500-bed medical university center which covers all medical disciplines (approximately 85 000 inpatients per year) and from 24 smaller regional hospitals in the federal province of Styria. Outpatient isolates origin from medical practices throughout the federal province of Styria (1.2 million inhabitants; 16 400 km^2). In the case of multiple isolates from one person in a year showing identical resistance patterns, only the first one was considered. A total of 15 843 isolates were thus excluded; 120 035 remained and were considered for statistical analysis. For each isolate, patient-related data (age, gender), patient location (community/hospital) and culture site were obtained. Culture sites were subdivided into the following categories: blood, genital tract, urinary tract, respiratory tract, wounds and others; patient age was categorized as follows: <1, 1 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79 and ≥80 years.

All isolates had been tested in the routine microbiology laboratory for antibiotic susceptibilities, in general isolates of community origin with the disk diffusion method and isolates of hospital origin automatically using a Vitek 2 system (bioMérieux, Marcy l'Etoile, France). From 1 January 1998 to 31 May 2011, results were interpreted using the criteria recommended by the Clinical and Laboratory Standards Institute (CLSI), formerly known as National Committee for Clinical Laboratory Standards (NCCLS) [12]. From 1 June 2011, results were interpreted using the criteria recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST breakpoint tables v1.2, 2011) in its respective current version (http://www.eucast.org/clinical_breakpoints/). For this retrospective study, resistance to the following 12 antibiotics was analysed: amikacin, ampicillin, amoxicillin/clavulanic acid, cefotaxime, ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem, nitrofurantoin (analysed for urinary tract isolates only), piperacillin/tazobactam and trimethoprim/sulfamethoxazole. Resistant and intermediate resistant isolates were combined. ESBL phenotype confirmation was done either by the Etest ESBL screen method using strips with cefotaxime, ceftazidime and cefepime or an ESBL confirmatory test that involves testing cefotaxime and ceftazidime alone and in combination with clavulanic acid.

Statistical analysis

For the complete data set, proportions of isolates resistant to the respective antibiotic were determined for each of the following covariates: culture site, patient location, age group, gender, year of isolate acquisition and ESBL phenotype. They are reported as percentages and frequencies. The proportion of ESBL-positive isolates was also determined per covariate and is presented in the same way. Resistance and ESBL trends over time were inspected graphically on a purely descriptive level (Figs. 1 and 2).

Additionally, the influence of the aforementioned covariates on the proportion resistant was further investigated by multivariate logistic regression methods. Each covariate except for culture site was entered linearly into the model, and no interactions were taken into consideration. To determine the significance of culture site, the full model containing all covariates including culture site was compared to the model without culture site.p values of <0.05 are considered statistically significant. Because all analyses are of an exploratory nature, no correction for multiplicity was applied. All analyses were carried out for each antibiotic separately. Statistical analysis was performed by the R software package (version 3.0.1) [13].

Ethics statement

The study was approved by the ethics committee of the Medical University of Graz (26-238 ex 13/14); patient records were anonymized and deidentified before analysis.

Results

In total, 120 035 clinical *E. coli* isolates were included in the statistical analysis. The number of isolates analysed per year

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