Multi-resistance in *E. coli* - an underestimated therapeutic problem: Epidemiological Results from the GENARS-Project

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REVISED ABSTRACT

Objectives *E. coli* strains are naturally sensitive for most clinically used antibiotics, except for those used only for infections with gram positive bacteria. Statistics on bacterial resistance usually focus only on the percentage of resistance of a species to single drugs. In these statistics resistance to ampicillin, tetracyclin and cotrimoxazole is usually high but resistance to 3rd generation cephalosporins, aminoglycosides and even fluorinated quinolones are usually rather low, suggesting that *E. coli* does not cause therapeutic problems due to the development of resistance. However multi-resistant strains become more and more common, causing severe therapeutic problems. Therefore we wanted to analyse the datapool of the GENARS project for the incidence of multi-resistant *E. coli* strains.

Methods Analysis was based on first isolates of *E. coli* from six laboratories, collected from January 2002 to June 2004. Minimal inhibitory concentrations (MICs) were determined by broth microdilution method for ceftazidime (CAZ), cefotaxime (CTX), ciprofloxacin (CIP), gentamicin (GEN), meropenem (MER) and piperacillin (PIP). Resistance patterns were evaluated by using breakpoints according to DIN, grouping susceptible and intermediate as non-resistant; multi-drug resistance was defined as resistance to at least four of the six agents.

Results A total of 13,544 isolates was analysed. 30.7% of these isolates were resistant to at least one agent. The ranking of the four most frequent resistance patterns was: PIP (17.1%), PIP/CIP (4.5%), CIP (3.7%) and PIP/CIP/GEN (1.6%). 0.4% of the strains were classified as multi-resistant. Multi-resistance rates tend to be higher among ICU patients (0.7%) than among non-ICU inpatients or outpatients (0.3%).

Conclusions Multi-resistant, untreatable *E. coli* strains are still not too common. In the hospitals under investigation, no outbreaks with multi-resistant strains could be observed. These strains seem to develop in individual patients with severe underlying diseases. However, it cannot be excluded, that such strains become commensals of more patients in their gut flora and then can be selected during any antibiotic treatment. Therefore these strains need significant attention in order to prevent their spread.

INTRODUCTION AND PURPOSE

E. coli strains are naturally sensitive for most clinically used antibiotics, except for those used only for infections with gram positive bacteria. Statistics on bacterial resistance usually focus only on the percentage of resistance of a species to single drugs. In these statistics resistance to ampicillin, tetracyclin and cotrimoxazole is usually high but resistance to 3rd generation cephalosporins, aminoglycosides and even fluorinated quinolones are usually rather low, suggesting that *E. coli* does not cause therapeutic problems due to the development of resistance. However multi-resistant strains become more and more common, causing severe therapeutic problems. Therefore we wanted to analyse the datapool of the GENARS project for the incidence of multi-resistant *E. coli* strains.

METHODS

GENARS – funded by the German Federal Ministry of Health and Social Security – is a national network for antimicrobial resistance surveillance. At present, six laboratories affiliated to university hospitals are collecting data continuously for all clinical relevant pathogens in a widely standardized and quality controlled way (1). Susceptibility tests are performed by determination of minimal inhibitory concentrations (MICs) by broth microdilution method according to DIN guidelines (2), one center provided data achieved by the automated system VITEK 2.

Analysis was based on first isolates of *E. coli* from six centers, collected from January 2002 to June 2004. MICs were determined for the following five class representatives: ceftazidime (CAZ), cefotaxim (CTX), ciprofloxacin (CIP), gentamicin (GEN), meropenem (MER) and piperacillin (PIP). Resistance patterns were evaluated by using breakpoints according to DIN (3); multi-drug resistance was defined as resistance to at least four of the six agents. Data analysis was executed by WHONET software (4), significance tests were computed by Epi Info™(5).

RESULTS

A total of 13,544 isolates was analysed. The number of isolates collected per center varied from 493 to 4,077 due to differences in size and structure of the hospitals. With regard to patient type the sample is composed as follows: 15.5% isolates from patients of intensive care units, 55.5% from non-ICU inpatients and 20% from outpatients, for the remaining 9% information was missing. Of the isolates, 45.6% were from urine, 12.3% from respiratory specimens, 6.9% from blood, and 35.1% from other sites or unknown origin.

Antimicrobial	MIC breakpoints S (<=)	MIC breakpoints R (>)	S%	I%	R%
Piperacillin	1	4	59.6	15.5	25.0
Ciprofloxacin	4	16	88.5	0.3	11.2
Gentamicin	2	8	90.0	5.6	4.4
Cefotaxime	4	16	98.1	0.7	1.2
Ceftazidime	1	2	98.3	0.9	0.7
Meropenem	4	32	99.9	0.1	0.0

Table 1: MIC breakpoints according to DIN and susceptibility rates of *E. coli* (N=13,544)

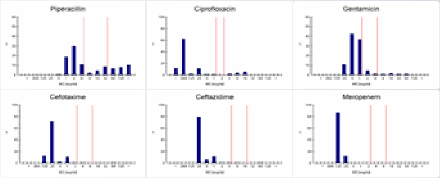

Figure 1: Distributions of MICs for *E. coli* (red lines indicate DIN breakpoints)

Basic information about susceptibility of the *E. coli* isolates tested is given in terms of SIR proportions (table 1) and more detailed as distributions of MICs (figure 1):

Rates of susceptibility were highest with meropenem (99.9%) followed by the cephalosporins (CAZ 98.3%, CTX 98.1%). In contrast, the highest rates of resistance were found with piperacillin (25.0%) and ciprofloxacin (11.2%, see table 1).

Table 2a shows the results of the analysis of resistance patterns. 9,383 isolates (69.3%) were not resistant to any of the selected antibiotics, for the remaining 4,161 isolates 28 different resistance patterns were detected: The ranking of the four most frequent resistance patterns was: PIP (17.1%), PIP/CIP (4.5%), CIP (3.7%) and PIP/CIP/GEN (1.6%). 48 isolates (0.4%, see table 2b) were classified as multi-resistant according to our definition – resistance to at least four agents – none of the strains was resistant to all six antibiotics.

a) resistance pattern	No.	%
none	9383	69.3
PIP	2320	17.1
CIP	498	3.7
GEN	118	0.9
CAZ	10	0.1
CTX	8	0.1
PIP - CIP	608	4.5
CIP - GEN	128	0.9
PIP - GEN	81	0.6
PIP - CTX	44	0.3
PIP - CAZ	7	0.1
CTX - CAZ	5	< 0.1
CIP - CAZ	2	< 0.1
CIP - CTX	1	< 0.1
GEN - CAZ	1	< 0.1
PIP - CIP - GEN	218	1.6
PIP - CTX - CAZ	22	0.2
PIP - CIP - CTX	16	0.1
PIP - GEN - CTX	10	0.1
GEN - CTX - CAZ	8	0.1
PIP - CIP - CAZ	6	< 0.1
PIP - GEN - CAZ	1	< 0.1
CIP - GEN - CAZ	1	< 0.1
PIP - CIP - CTX - CAZ	16	0.1
PIP - CIP - GEN - CTX	10	0.1
PIP - GEN - CTX - CAZ	7	0.1
PIP - CIP - GEN - CAZ	5	< 0.1
PIP - CIP - GEN - CTX - CAZ	9	0.1
PIP - GEN - CTX - CAZ - MER	1	< 0.1
b) number of resistances		
none	9383	69.3
one	2954	21.8
two	877	6.5
three	282	2.1
four to six = multi-resistant	48	0.4
total no. of isolates	13544	

Table 2: resistance patterns and number of resistances in *E. coli*

a) Patient type	%	sample size
icu patients	0.7	2106
inpatients	0.3	7522
outpatients	0.3	2712
total	0.4	12340

b) Center	%	sample size
center 1	0.0	493
center 2	1.2	1411
center 3	0.2	4077
center 4	0.5	1366
center 5	0.3	2133
center 6	0.2	4064
total	0.4	13544

Table 3: multi-resistance rates in *E. coli*
a) by patient type
b) by center

Significant differences in multi-drug resistance rates were associated with patient type (table 3a): While 0.7% of the isolates from ICU patients were resistant to four or more drugs the rate was 0.3% for inpatients as well as among out-patients (Chi²=7.89, df=2, p<0.02).

Furthermore, multi-resistance rates varied between the centers involved (table 3b) with a range from 0.0% to 1.2%. Part of the differences might be caused by different strategies in treating urine samples: Center 2 and 4 report very few results from urine samples as they perform disk diffusion as routine method for all strains from urine samples and proceed to MIC testing only if indicated. The GENARS database contains only isolates with MIC measurements. Therefore, *E. coli* isolates for urine are underrepresented for those centers. Lower proportions of strains from urine coincide with higher multi-resistance rates.

Center	multi-resistant (%)	sample size	percentage of urine samples
center 1	0.0	493	15.8
center 2	1.2	1411	3.5
center 3	0.2	4077	64.3
center 4	0.5	1366	0.8
center 5	0.3	2133	55.0
center 6	0.2	4064	55.3
total	0.4	13544	45.6

Table 4: multi-resistance rates in *E. coli* by center

CONCLUSIONS

Multi-resistance in *E. coli* is still rare, but exists. 10 strains were resistant to 5 of the six antibiotics tested. Nevertheless, this low number of multi-resistant strains is alarming, not only since *E. coli* is a common pathogen but especially because *E. coli* is able to colonise the intestinal tract of patients. Even if these strains represent a low proportion of the intestinal tract, with each antibiotic treatment they can be selected and thus could cause infections in this specific patient. In addition these strains may spread in the hospital environment.

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