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Resistance to mecillinam and nine other antibiotics for oral use in *Escherichia coli* isolated from urine specimens of primary care patients in Germany, 2019/2020

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Disclosures

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Background

Urinary tract infections (UTIs) are among the most common bacterial infections in humans. *Escherichia coli* is the leading cause of community acquired UTI.[1]

Pivmecillinam, the oral prodrug of the penicillin derivative mecillinam (amdinocillin), was re-introduced in Germany in March 2016.

This study aimed to evaluate the prevalence of resistance to mecillinam in comparison to nine other antibiotics used for oral treatment in *E. co*li urine isolates after the re-introduction of pivmecillinam for first-line treatment of uncomplicated lower UTI.

Methods

Isolates were collected prospectively at 23 laboratories between October 2019 and March 2020. Verification of species identification and susceptibility testing were performed at a reference laboratory.

MICs were determined by either agar dilution (mecillinam) or broth microdilution (amoxicillin, amoxicillin-clavulanic acid, cefuroxime, cefpodoxime, cefixime, ciprofloxacin, trimethoprim-sulfamethoxazole, fosfomycin, nitrofurantoin), and interpreted by EUCAST criteria (v.12.0).[2]

Isolates with a confirmed extended-spectrum beta-lactamase (ESBL) phenotype were screened for presence of beta-lactamase genes by PCR.[3]

Results

A total of 460 isolates were collected. Forty-six isolates (10.0%) produced an ESBL of the CTX-M family, 25 of which also harboured one or more other beta-lactamase gene.

Of the 460 isolates, 49.1% were fully susceptible to all antimicrobials. Sixty-seven isolates (14.6%) were resistant to one drug class, 70 (15.2%) to two drug classes and 97 isolates (21.1%) to more than two drug classes.

Resistance to amoxicillin was most widespread, followed by resistance to trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, and cefuroxime, and least widespread to fosfomycin, nitrofurantoin and mecillinam (**Table**).

Resistance to mecillinam was detected in 24 isolates (5.2 %). The concentrations of mecillinam needed to inhibit 50 / 90 % of the ESBL producing isolates and the remaining isolates were 1 / 4 mg/L, and 0.5 / 4 mg/L, respectively. All but one mecillinam-resistant isolates showed cross-resistance to amoxicillin and amoxicillin-clavulanic acid.

Conlusions

Overall, the degree of resistance to oral antibiotics in uropathogenic *E. coli* from outpatients seems to be favorable. The frequency of resistance to individual drugs, however, varied.

Resistance rates were below 10% for fosfomycin, nitrofurantoin and mecillinam, all of which are recommended for first-line treatment of uncomplicated lower UTI by international guidelines.

References

Naber KG et al., Eur Urol 2008;54(5):1164-75
The European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2022. Breakpoint tables for interpretation of MICs and zone diameters, Version 12.0
Schuster CF et al., J Antimicrob Chemother 2021; https://doi.org/10.1093/jac/dkab407

Table: *In-vitro* activity of ten oral antibiotics against urinary *E. coli* isolates (n=460)

Antibacterial agent	Breakpoint (mg/L) [1]	MIC-50 (mg/L)	MIC-90 (mg/L)	Percent of isolates		
				S	I	R
Amoxicillin	> 8	4	≥ 64	56.7	-	43.3
Amoxicillin-clavulanic acid	> 8	4	16	82.0	-	18.0
Mecillinam	> 8	0.5	4	94.8	-	5.2
Cefuroxime	> 8	4	≥ 64	88.7	-	11.3
Cefixime	> 1	0.25	4	89.3	-	10.7
Cefpodoxime	> 1	0.5	≥ 8	88.9	-	11.1
Ciprofloxacin	> 0.5	≤ 0.06	8	86.3	2.6	11.1
Trimethoprim-sulfamethoxazole	> 4	≤ 0.25	≥ 32	72.2	0.9	27.0
Fosfomycin [2]	> 8	2	8	92.6	-	7.4
Nitrofurantoin	> 64	≤ 16	32	98.9	-	1.1

S (susceptible at standard dose), I (susceptible at increased exposure), R, resistant.
[1] EUCAST breakpoints for orally administered antibiotics. [2] Resistance was confirmed by agar dilution.

Background & Methods

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– *Escherichia coli* is the leading cause of community acquired UTI.

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– EUCAST criteria (v.12.0) were applied for interpretation.

– Isolates with a confirmed extended-spectrum beta-lactamase (ESBL) phenotype were screened for presence of beta-lactamase genes by PCR.

Results & Conclusions

Table: *In-vitro* activity of ten oral antibiotics against urinary *E. coli* isolates (n=460)

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– ESBL producing isolates
  • 10 % (n=46): all CTX-M family
  • One or more additional beta-lactamase (n=25)

– Antimicrobial susceptibility of the isolates
  • Fully susceptible to all antimicrobials: 49.1%
  • Resistant to one drug class: 14.6% (n=76)
  • Resistant to two drug classes: 15.2% (n=70)
  • Resistant to more than two drug classes: 21.1% (n=97)
  • Most widespread: resistance to amoxicillin, followed by resistance to trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, and cefuroxime
  • Least widespread: resistance to fosfomycin, nitrofurantoin and mecillinam
  • Mecillinam-resistant: 5.2 % (n=24)
  • MIC 50 / 90 % of mecillinam for ESBL producing isolates: 1 / 4 mg/L
  • MIC 50 / 90 % of mecillinam for remaining isolates: 0.5 / 4 mg/L
  • All but one mecillinam-resistant isolates showed cross-resistance to amoxicillin and amoxicillin-clavulanic acid.

➡ Overall, the degree of resistance to oral antibiotics in uropathogenic *E. coli* from outpatients seems to be favorable. The frequency of resistance to individual drugs, however, varied. Resistance rates were below 10% for fosfomycin, nitrofurantoin and mecillinam, all of which are recommended for first-line treatment of uncomplicated lower UTI by international guidelines.