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

M Kresken¹,², Y Pfeifer ³, F Wagenlehner ⁴, G Werner ³, E Wohlfarth ¹

¹Antiinfectives Intelligence GmbH, Cologne, Germany; ²University of Applied Sciences, Cologne, Germany; ³Robert Koch Institute, FG13 Nosocomial Pathogens and Antibiotic Resistances, Wernigerode Branch, Wernigerode, Germany; ⁴Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Gießen, Gießen, Germany

Third party affiliation:
Study Group ‘Antimicrobial Resistance’ of the Paul-Ehrlich-Society for Chemotherapy

Disclosures

– The authors declare the following real or perceived conflicts of interest during the last 3 years in relation to this presentation:
  MK is a partner and CEO of Antiinfectives Intelligence GmbH (AI), a research organisation providing services to pharmaceutical companies; EW is an employee of AI.
– This study was funded by Apogepha Arzneimittel GmbH.
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

M Kresken 1,2, Y Pfeifer 3, F Wagenlehner 4, G Werner 3, E Wohlfarth 1

1Antinfectives Intelligence GmbH, Cologne, Germany; 2University of Applied Sciences, Cologne, Germany; 3Robert Koch-Institute, FG13 Nosocomial Pathogens and Antibiotic Resistances, Wernigerode Branch, Wernigerode, Germany; 4Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Gießen, Gießen, Germany. Study Group “Antimicrobial Resistance” of the Paul-Ehrlich-Society for Chemotherapy

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. coli* 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.

Conclusions
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.

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

| Antibacterial agent | Breakpoint (mg/L) | 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         | > 8              | 2             | 8             | 92.6 - 7.4          |
| Nitrofurantoin     | > 64             | ≤ 16          | 32            | 98.9 - 1.1          |

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Disclosures
MK is a partner and CEO of Antinfectives Intelligence GmbH a research organisation providing services to pharmaceutical companies; E.W. is an employee at Antinfectives Intelligence GmbH.

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1 EUCAST breakpoints for orally administered antibiotics. 2 Resistance was confirmed by agar dilution.
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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

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| Mecillinam                           | > 8               | 0.5 | 4   | 94.8 | - | 5.2  |
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| 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                           | > 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.

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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.