Clinical and bacteriological efficacy of pivmecillinam treatment for uncomplicated urinary tract infections caused by ESBL-producing Escherichia coli: a prospective, multicentre, observational cohort study

Marianne Bollestad1,2*, Nils Grude1,3, Sigrid Solhaug4, Niclas Raffelsberger4, Nina Handal5, Hans-Johanny Schjelderup Nilsen6, Monica Regine Romstad7, Andreas Emmert8, Yngvar Tveten9, Arne Søraas10, Pål A. Jenum10, Synne Jenum10, Janne Møller-Stray11, Einar Tollaksen Weme11, Morten Lindbaek1 and Gunnar Skov Simonsen12 (the Norwegian ESBL UTI study group)

1The Antibiotic Centre for Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway; 2Division of Medicine, Stavanger University Hospital, Stavanger, Norway; 3Department of Medical Microbiology, Vestfold Hospital Trust, Tønsberg, Norway; 4Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø, Norway; 5Department of Microbiology and Infection Control, Akershus University Hospital, Lørenskog, Norway; 6Department of Medical Microbiology, St Olavs University Hospital, Trondheim, Norway; 7Department of Medical Microbiology, Stavanger University Hospital, Stavanger, Norway; 8Department of Medical Microbiology, Unilabs Telelab AS, Skien, Norway; 9Department of Medical Biochemistry, Telemark Hospital, Skien, Norway; 10Department of Laboratory Medicine, Vestre Viken Hospital Trust, Baerum, Norway; 11Department of Laboratory Medicine, Vestre Viken Hospital Trust, Drammen, Norway; 12Department of Microbiology and Infection Control, University Hospital of North Norway, and Research Group for Host-Microbe Interaction, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway

*Corresponding author. Stavanger University Hospital, Pb. 8100 Forus, 4068 Stavanger, Norway. Tel: +47 98488454; Fax: +47 51519906; E-mail: marianne.bollestad@med.uio.no

Received 2 February 2018; returned 12 March 2018; revised 23 April 2018; accepted 22 May 2018

Objectives: To compare the clinical and bacteriological outcomes of pivmecillinam treatment for community-acquired urinary tract infections (UTIs) caused by ESBL-producing Escherichia coli versus non-ESBL-producing E. coli in an outpatient setting.

Methods: A prospective, multicentre, observational cohort study of women aged ≥16 years, with pivmecillinam-treated community-acquired UTIs caused by E. coli with or without ESBL production, recruited from primary care, was conducted in the period from April 2013 to August 2016. Eighty-eight women (mean age 49.4 years) with community-acquired UTIs caused by ESBL-producing E. coli were compared with a control group of 74 women (mean age 50.1 years).

Trial registration: Regional Committees for Medical and Health Research Ethics (REC) in Norway, ID 2011/2214, and ClinicalTrials.gov, ID NCT01531023.

Results: The median time until symptom resolution after treatment initiation was 5 days for the ESBL cases and 3 days for the non-ESBL controls (P < 0.01). The proportion of women warranting a second antibiotic prescription in the follow-up period was higher for the ESBL cases [30/88 (34.1%) versus 10/72 (13.9%), P < 0.01]. Persistent bacteriuria was non-significantly more common among ESBL cases than in the control group [15/81 (18.5%) versus 6/67 (9.0%), P = 0.10]. A pivmecillinam dosage of 200 mg given three times daily for ≤5 days was associated with treatment failure (OR 4.77, 95% CI 1.40–19.44, P = 0.03) for the ESBL E. coli group. For the subgroup treated with 400 mg of pivmecillinam given three times daily there was no significantly increased OR for treatment failure between ESBL cases and the control group irrespective of treatment duration.

Conclusions: Pivmecillinam given at 400 mg three times daily gave comparable clinical and bacteriological cure rates in women with community-acquired E. coli UTIs irrespective of ESBL production.
Introduction

Increased antibiotic consumption and microbial resistance is a global public health challenge and has led to interest in alternative treatment options.1–4 The number of patients infected by MDR microbes is increasing and the rise in ESBL-producing Enterobacteriaceae is an especially worrying situation.1,5–7 Known risk factors for community-acquired bacteriuria caused by ESBL-producing Enterobacteriaceae include travel to high-prevalence countries, old age, recurrent urinary tract infections (UTIs), prostatic disease, prior hospitalization, recreational freshwater swimming and recent use of fluoroquinolones and penicillins, except pivmecillinam.7–12

ESBL-producing Enterobacteriaceae are often isolated from urine samples of patients with community-acquired UTIs who do not require hospitalization based on clinical findings.5,13,14 Community-acquired UTIs are the most frequent infections treated with antibiotics in primary care, and hence ensuring adequate empirical oral treatment options for community-acquired UTIs is important.15

For hospitalized patients infected with ESBL-producing Enterobacteriaceae, antibiotic treatment is usually administered intravenously and several treatment regimens have been studied.16 Oral treatment options are limited for patients infected with ESBL-producing Enterobacteriaceae; fosfomycin, pivmecillinam, amoxicillin/clavulanic acid and nitrofurantoin have been identified as potential alternatives based on antimicrobial susceptibility testing.17–21

Pivmecillinam is an amidinopenicillin with selective activity against Gram-negative bacteria. Orally administered pivmecillinam is commonly used in the Scandinavian countries and is included in internationally recommended empirical treatment guidelines for uncomplicated cystitis along with trimethoprim and nitrofurantoin.22,23 Pivmecillinam is, according to national guidelines, recommended at a dosage of 200 mg given three times daily for 3 days for acute uncomplicated cystitis and can be considered as an oral treatment option for acute pyelonephritis at a dosage of 400 mg given three times daily for 7–10 days.24

Widespread use of pivmecillinam over many years has not caused any significant increase in resistance rates among uropathogenic E. coli. Pivmecillinam has recently been suggested as an oral treatment option for community-acquired UTI caused by ESBL-producing Enterobacteriaceae owing to significantly greater antibacterial potency and higher in vitro stability to β-lactamase hydrolysis compared with other penicillins.5,24–29

Clinical studies on the efficacy of pivmecillinam treatment for community-acquired UTI caused by ESBL-producing Enterobacteriaceae are limited and have included relatively few patients.30–33 Preliminary results are inconsistent and vary from favourable bacteriological and clinical cure rates to clinical and bacteriological failure. Higher MIC values and lower dosage of pivmecillinam (200 mg) have been suggested as predictors of treatment failure.30–33

An adequately powered study was warranted to examine the clinical and bacteriological efficacy of pivmecillinam treatment against ESBL-producing E. coli causing community-acquired UTI. In this study we aimed to compare the clinical and bacteriological outcomes of pivmecillinam treatment in community-acquired UTI caused by ESBL-producing E. coli versus community-acquired UTI caused by non-ESBL-producing E. coli in an outpatient setting.

Patients and methods

Study registration

This study is registered with the Regional Committees for Medical and Health Research Ethics (REC) in Norway, ID 2011/2214, and ClinicalTrials.gov, ID NCT01531023.

Study design and data collection

This study is a prospective observational multicentre study of women with community-acquired UTI caused by E. coli. ESBL-producing E. coli were identified at eight participating microbiology laboratories. Patients were included from 76 different geographically diverse municipalities in Norway.

In collaboration with the primary care physician, the local study co-ordinators conducted preliminary screening according to the following inclusion criteria: women aged ≥16 years with symptoms of UTI; significant growth of a monoculture of ESBL-producing E. coli in urine samples (≥10⁶ cfu/mL urine); and treatment with pivmecillinam (dose and treatment length determined by the treating physician). Patients were excluded if, prior to inclusion, they had been hospitalized for >48 h during the last 90 days, had received haemodialysis or intravenous chemotherapy within the last 30 days, had received specialized medical treatment at home including change of permanent urinary catheter in the last 30 days, were unable to provide informed consent, or had a urine culture containing ESBL-producing bacteria identified within the last 6 months. No patients were included who had indwelling urinary catheters.

Candidate cases were invited by their primary care physician to a consultation 2 weeks after the end of treatment, which represented the follow-up period. At this consultation they were informed about the study. If willing to participate, a signed informed consent was obtained before registration of clinical data in a standardized clinical registration form (see Supplementary data, available at JAC Online). Treatment failure was defined as persistent symptoms leading to a second antibiotic prescription during the follow-up.

For all patients, a clean-catch morning urine control sample was analysed no later than 2 weeks after end of treatment, but in case of clinical treatment failure the urine sample taken at the time of initiation of alternative treatment was included for analysis. The primary and control urine culture results as well as the clinical registration forms were sent to the study coordinator.

Women with community-acquired UTI caused by non-ESBL-producing E. coli were recruited as controls and followed up according to the same protocol as the ESBL cases. Inclusion criteria were identical for both groups with respect to antibiotic treatment, geographical origin and time period of inclusion. Initially, ESBL cases and non-ESBL controls were also matched 1:1 for age (±5 years), but the inclusion of non-ESBL controls proved to be challenging. Eligible control cases were identified in the participating microbiological laboratories; however, the clinical registration forms that were sent to the treating physician were more often not returned compared with the ESBL cases. The study coordinators were not informed that the women did not wish to participate, and hence it is more probable that the women were not contacted by their general practitioner and invited to be a part of the study. Therefore, after approval by the regional ethics committee, matching by age was abandoned, whereas the other inclusion criteria remained unchanged. There were 27 matched cases and controls included according to the initial protocol.

Laboratory analyses

Urine samples were cultured and species identified according to the respective laboratory procedures based on Norwegian guidelines.36 Uropathogens were quantified in cfu/mL. Significant bacteriuria of E. coli was defined according to current European guidelines for patients with symptomatic UTI as ≥10⁵ cfu/mL for primary pathogens.37 Antibiotic susceptibility testing was performed according to the laboratories’ standard
procedures. E. coli that were resistant to third-generation cephalosporins were examined for ESBL production. Nordic clinical breakpoints are in accordance with EUCAST. ESBL-positive isolates were stored at −70°C for future molecular testing. Isolates from non-ESBL controls were not frozen for further studies.

At the end of the inclusion period, ESBL-producing isolates were sent from the primary laboratories to the microbiological laboratory at Stavanger University Hospital, Norway. Verification of species identification was performed by use of MALDI-TOF MS (Bruker Daltonics, Germany) according to the manufacturer’s instructions. The MIC of pivmecillinam was determined using the MIC gradient test (Liofilchem, Italy) according to EUCAST methodology and clinical breakpoints.

ESBL production was confirmed by the double disc synergy test using cefotaxime with and without clavulanic acid and ceftazidime with and without clavulanic acid (Becton Dickinson, USA), according to the manufacturer’s procedure.

Statistical analyses

Statistical power was calculated based on 60% efficacy among ESBL cases versus 80% efficacy among non-ESBL controls for complete symptom resolution by day three. This gives a relative difference of 25% with 80% and a 5%. Sample size calculation indicated that 82 patients in each group were needed, which was increased to 100 persons in each group to cover for possible drop-outs.

Kaplan–Meier and log-rank tests were used to analyse time until symptom resolution. Treatment failure was analysed using a binary logistic regression model (a type of generalized linear regression model). A two-way interaction term for treatment length and group (treatment) was used to understand the effect of treatment over time. The modelling process proceeded in two steps. Firstly, crude estimates of OR were obtained from logistic models adjusted for clinical factors. All models were fitted using Stata SE 14 and the significance level was set at \( P = 0.05 \). A conditional logistic regression model was also performed but did not yield valid results owing to the relatively low number of matched cases and controls. All \( P \) values were two-tailed and a \( P \) value \(<0.05\) was considered significant. Collected data were analysed by the use of SPSS version 24.

Results

Demographics

A total of 88 ESBL cases and 74 non-ESBL controls were included in the study, all treated with oral pivmecillinam. Demographic data are summarized in Table 1. Cases and controls were similar in age (mean age for ESBL cases was 49.4 years compared with 50.1 years for non-ESBL controls, \( P = 0.82 \)) and clinical presentation, including the presence of frequent urinary incontinence, haematuria, dysuria, fever and abdominal and back pain. Reduced general condition was noted for a significantly greater proportion of ESBL cases than for non-ESBL controls (37.9% versus 22.9%, \( P = 0.04 \)). No differences in relevant comorbidities (diabetes mellitus, immunosuppression, pregnancy and urinary tract malformations) were found.

Thirty-seven of 87 ESBL cases (42.5%) were treated with 200 mg of pivmecillinam given three times daily versus 48/73 (65.8%) among non-ESBL controls. The remaining patients were treated with 400 mg given three times daily. For one of the ESBL cases and one of the non-ESBL controls pivmecillinam dosages were not registered.

| Table 1. Demographic and clinical characteristics of the study population |
|---------------------------------|-----------------|-----------------|--------|
|                               | ESBL (N = 88)\(^a\) | non-ESBL (N = 74)\(^a\) | \(P\) value |
| Age, years, mean (SD)          | 49.4 (17.7)      | 50.1 (19.2)      | 0.82   |
| Symptoms                        |                 |                 |        |
| increased frequency of urination| 75/87 (86.2)    | 68/74 (91.9)    | 0.25   |
| haematuria                      | 12/86 (14.0)    | 13/72 (18.1)    | 0.48   |
| painful urination               | 69/88 (78.4)    | 65/74 (87.8)    | 0.11   |
| self-reported fever             | 14/85 (16.5)    | 7/71 (9.9)      | 0.23   |
| reduced general condition       | 33/87 (37.9)    | 16/70 (22.9)    | 0.04   |
| abdominal pain                  | 28/86 (32.6)    | 24/71 (33.8)    | 0.87   |
| back pain                       | 20/86 (23.3)    | 22/72 (30.6)    | 0.30   |
| Comorbidity                     |                 |                 |        |
| diabetes                        | 6/88 (6.8)      | 3/74 (4.1)      | 0.44   |
| immunosuppression               | 3/88 (3.4)      | 4/74 (5.4)      | 0.70   |
| pregnancy                       | 1/88 (1.1)      | 1/74 (1.4)      | 1.00   |
| urinary tract malformations     | 3/88 (3.4)      | 1/74 (1.4)      | 0.63   |
| Number of UTIs in previous year, | 1.4 (2.3)      | 1.4 (1.8)       | 0.95   |
| mean (SD)                       |                 |                 |        |
| Pivmecillinam dosage            |                 |                 |        |
| 200 mg given three times daily  | 37/87 (42.5)    | 48/73 (65.8)    | <0.01  |
| 400 mg given three times daily  | 50/87 (57.5)    | 25/73 (34.2)    | <0.01  |
| Treatment length                |                 |                 |        |
| \(\leq5\) days                  | 42/88 (47.7)    | 38/72 (52.8)    | 0.52   |
| \(>5\) days                     | 46/88 (52.3)    | 34/72 (47.2)    | 0.52   |

All values shown are numerator/denominator (%), unless otherwise specified. \(^a\)The respective denominators show the number of included patients with registered data for the specific parameter.

Clinical response

ESBL cases had a median duration of symptom of 5 days compared with 3 days for non-ESBL controls (log-rank test, \( P < 0.01 \)) (Figure 1). Subsequent stratification according to pivmecillinam dose (200 versus 400 mg) also showed longer symptom duration for the ESBL cases compared with the non-ESBL controls (log-rank test, \( P < 0.01 \) for both cohorts) (Figure 2). Compared with controls, symptoms persisted in a larger proportion of ESBL cases 2 weeks after end of treatment (32/87 (36.8%) versus 11/72 (15.3%), \( P < 0.01 \), warranting a second antibiotic prescription (30/88 (34.1%) versus 10/72 (13.9%), \( P < 0.01 \)). One patient in the ESBL group was admitted to hospital in the follow-up period and treated with ampicillin and gentamicin for pyelonephritis.

Reduced general condition was associated with increased risk of treatment failure both in univariate (OR 3.19, 95% CI 1.50–6.80, \( P < 0.01 \)) and multivariate (OR 2.84, 95% CI 1.18–6.84, \( P = 0.02 \)) analysis (Table 2). The presence of other clinical factors (fever, increased frequency of urination, haematuria, dysuria and abdominal and back pain), the presence of relevant comorbidities (diabetes mellitus, immunosuppression and urinary tract malformations), pregnancy, previous UTIs in the last 12 months or increasing age was not associated with increased risk of treatment failure.
The vast majority of ESBL cases showed signifi-
cantly higher rates of treatment failure for the ESBL cases or the non-ESBL controls regardless of treatment duration (≤5 days, OR 2.17, 95% CI 0.31–14.64, P = 0.43; >5 days, OR 2.16, 95% CI 0.32–14.65, P = 0.43).

Subgroup analysis demonstrated that treatment with 200 mg of pivmecillinam given three times daily and treatment duration ≤5 days predicted failure (OR 4.77, 95% CI 1.40–19.44, P = 0.03) for ESBL cases compared with the control group.

Performing the analysis without stratification according to pivmecillinam dosage gave findings comparable with those of the subgroup analysis of the cohort treated with 200 mg given three times daily. ESBL cases who received treatment lasting ≤5 days had increased risk of treatment failure compared with non-ESBL controls (OR 5.20, CI 1.19–22.67, P = 0.03) (Table 3).

**Bacteriological findings**

There was a non-significantly higher rate of persistent bacteriuria at follow-up for ESBL cases compared with non-ESBL controls [15/81 (18.5%) versus 6/67 (9.0%), P = 0.10].

The *E. coli* isolates from ESBL cases showed similar levels of in vitro resistance to pivmecillinam and nitrofurantoin compared with strains from non-ESBL controls. ESBL cases showed significantly higher rates of in vitro resistance to many other commonly used oral treatment options for UTI, including trimethoprim, trimethoprim/sulfamethoxazole and ciprofloxacin (Table 4). The vast majority of ESBL *E. coli* isolates had pivmecillinam MIC values ≤2 mg/L (84/86, 97.7%). One isolate had an MIC value of 6 mg/L and one displayed an MIC value of 256 mg/L. Both patients with MIC values >2 mg/L showed clinical response to the initial pivmecillinam treatment. The rates of treatment response for the cohorts with MIC ≤1 mg/L (47/71, 66.2%) and MIC >1 mg/L (11/15, 73.3%) were similar (P = 0.59).

**Discussion**

The time until complete symptom resolution was significantly longer for community-acquired UTIs caused by ESBL-producing *E. coli* following initial pivmecillinam treatment when compared with non-ESBL controls. A significantly larger proportion of the ESBL cases also had persisting symptoms after the initial treatment and required a second antibiotic prescription. The rate of persistent bacteriuria was higher for ESBL cases than the non-ESBL controls, but the difference did not reach statistical significance.

Shorter treatment duration (≤5 days) was associated with a significantly higher rate of treatment failure for ESBL cases versus non-ESBL controls for the subgroup treated with 200 mg given three times daily and for the cohorts as a whole without stratification for the given dose of pivmecillinam. For the subgroup who received 400 mg of pivmecillinam three times daily (n = 75) the rate of treatment failure was comparable for ESBL cases and non-ESBL controls, irrespective of treatment length.

In vitro susceptibility to pivmecillinam and nitrofurantoin among ESBL-producing *E. coli* isolates was high. ESBL isolates displayed marked co-resistance to other oral treatment options including trimethoprim, trimethoprim/sulfamethoxazole and ciprofloxacin.

Previously published data on the clinical and bacteriological efficacy of pivmecillinam treatment for ESBL-producing Enterobacteriaceae show inconsistent results and variable methodological quality. Smaller studies have reported both adequate clinical response and high rates of treatment failure. Higher MICs of pivmecillinam have been shown to be associated with increased risk of clinical treatment failure. The number of ESBL *E. coli* isolates with pivmecillinam MIC values >2 mg/L was too low to allow analysis of the relationship between clinical response rates and higher MIC values.

Our findings showed comparable rates of treatment failure for ESBL cases and non-ESBL controls when treated with 400 mg given three times daily, irrespective of treatment length. A possible explanation is that a dosage of 400 mg given three times daily compared with 200 mg given three times daily gives a higher proportion of time above the MIC (\(T_{\text{MIC}}\)), which is essential to achieve the bactericidal effect of \(\beta\)-lactam antibiotics. The study also found comparable rates of treatment failure for all subgroups treated with mecillinam for >5 days; a possible cause of this is a protracted treatment response in which the ESBL cases benefit from longer duration of treatment.

Oral treatment options for UTI caused by ESBL-producing *E. coli* are limited. Previous studies have suggested a \(\beta\)-lactam antibiotic (amoxicillin or pivmecillinam) combined with the \(\beta\)-lactamase inhibitor clavulanic acid as a possible treatment option, but clinical studies are limited. Aminoglycosides can also be used, and amikacin administered intravenously once daily has been tested as a possible agent in a small study. Fosfomycin stands out as a
A viable oral option for ESBL-producing microbes. Ertapenem administered once daily intravenously is an effective treatment option for many ESBL-producing E. coli strains causing UTI. Our data support pivmecillinam as a narrow-spectrum alternative oral treatment for women with acute uncomplicated cystitis.

Co-resistance to several oral treatment options for ESBL-producing E. coli UTI isolates is in concordance with previously published studies. The rate of pivmecillinam resistance was comparable with that in previous Norwegian data, but lower than has been reported in a study from South-East Asia.

**Table 2.** Univariate and multivariate logistic regression analysis for treatment failure and prescription of a new antibiotic treatment

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced general condition</td>
<td>3.19 (1.50–6.80)</td>
<td>0.01</td>
<td>2.84 (1.18–6.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fever</td>
<td>2.02 (0.77–5.33)</td>
<td>0.15</td>
<td>1.38 (0.46–4.11)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.56 (0.65–10.03)</td>
<td>0.18</td>
<td>2.97 (0.70–12.70)</td>
<td>0.14</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.64 (0.77–3.48)</td>
<td>0.20</td>
<td>1.41 (0.70–3.25)</td>
<td>0.42</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.03)</td>
<td>0.52</td>
<td>1.00 (0.98–1.03)</td>
<td>0.68</td>
</tr>
<tr>
<td>Increased frequency of urination</td>
<td>1.71 (0.47–6.27)</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>0.94 (0.35–2.55)</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful urination</td>
<td>0.80 (0.32–1.99)</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>1.14 (0.51–2.56)</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>2.35 (0.5–11.0)</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>3.05 (0.19–49.94)</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract malformations</td>
<td>1.0 (0.10–9.89)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of UTIs in previous year</td>
<td>0.90 (0.73–1.11)</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC (reference ≤1 mg/L)</td>
<td>0.71 (0.20–2.47)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The adjusted model is based on variables with P ≤ 0.20 from the unadjusted analysis plus age, which we identified as a clinically relevant variable.

**Table 3.** Evaluation of the relationship between treatment failure, length of treatment and dosage of pivmecillinam in ESBL cases and non-ESBL controls

<table>
<thead>
<tr>
<th>Group comparison (n = 162)</th>
<th>Unadjusted treatment ≤5 days (N = 80)</th>
<th>Unadjusted treatment &gt;5 days (N = 80)</th>
<th>Adjusted treatment ≤5 days</th>
<th>Adjusted treatment &gt;5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL cases</td>
<td>4.13 (1.22–13.97)</td>
<td>2.60 (0.82–7.02)</td>
<td>5.20 (1.19–22.67)</td>
<td>2.06 (0.39–16.42)</td>
</tr>
<tr>
<td>Treatment: pivmecillinam tid</td>
<td>1 (reference)</td>
<td>1.83 (0.47–7.17)</td>
<td>1 (reference)</td>
<td>1.51 (0.30–7.49)</td>
</tr>
<tr>
<td>Changes between the two study groups (reference: control group)</td>
<td>4.75 (0.95–23.84)</td>
<td>1.84 (0.46–7.32)</td>
<td>4.77 (1.60–19.44)</td>
<td>2.53 (0.53–12.15)</td>
</tr>
<tr>
<td>Treatment: pivmecillinam tid</td>
<td>1 (reference)</td>
<td>1.27 (0.25–6.42)</td>
<td>1 (reference)</td>
<td>0.9 (0.14–5.66)</td>
</tr>
<tr>
<td>Changes between the two study groups (reference: control group)</td>
<td>4.63 (0.75–58.56)</td>
<td>2.77 (0.47–16.21)</td>
<td>2.17 (0.31–14.64)</td>
<td>2.16 (0.32–14.65)</td>
</tr>
</tbody>
</table>

*The data presented are adjusted for the clinical factors presented in Table 2.

*For two patients the dosages were not given.

*The adjusted model is based on variables with P ≤ 0.20 from the unadjusted analysis plus age, which we identified as a clinically relevant variable.

tid, three times a day.
Table 4. *In vitro* susceptibility to antibiotics used for oral treatment of uncomplicated urinary tract infections

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Susceptible E. coli [n/N]</th>
<th>ESBL</th>
<th>non-ESBL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim</td>
<td>34/88 (38.6)</td>
<td>59/73 (80.8)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>40/88 (45.5)</td>
<td>61/71 (85.9)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>84/88 (95.5)</td>
<td>72/73 (98.6)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>86/88 (97.7)</td>
<td>72/73 (98.6)</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>47/84 (56.0)</td>
<td>14/15 (93.3)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Strengths and limitations**

This is, to our knowledge, the largest study carried out to evaluate the clinical and bacteriological efficacy of pivmecillinam treatment for ESBL *E. coli* UTI. It was a prospective, multicentre, observational, cohort study, which ensures a high quality of data representing the Norwegian population.

The inclusion of control patients proved challenging, possibly because eligible patients were not invited to participate in the study by their general practitioners. Perhaps general practitioners did not consider inclusion of controls as relevant and did not prioritize this to the same degree as the inclusion of ESBL cases. The inclusion period was terminated before the planned number of control patients was reached to ensure that the cohorts were comparable in time. The difficulty with enrolment of the control cases is a potential source of bias. The planned number of ESBL *E. coli* UTI patients was achieved.

As this was an observational study patients were not randomized to receive a specific pivmecillinam dosage or treatment length. It is unlikely that this affected the results as patients with previously known infections with an ESBL-producing microbe were not included and the presence of an ESBL-producing *E. coli* as the cause of the relevant UTI was not known at the time of treatment choice. It is noteworthy that the ESBL cases experienced significantly higher rates of reduced general condition at presentation. Pivmecillinam at a dosage of 400 mg given three times daily for 7–10 days is the recommended dosage for acute pyelonephritis that is associated with reduced general condition. This could explain why a higher proportion of the ESBL cases received treatment with pivmecillinam at this dosage.

**Implications**

Pivmecillinam given at 400 mg three times daily for >5 days is a reasonable oral treatment option for ESBL-producing *E. coli* causing uncomplicated community-acquired UTI. Comparable rates of bacteriological cure for ESBL cases and non-ESBL controls can be expected.

**Acknowledgements**

We thank the staff at the microbiological laboratories and the general practitioners and patients involved in the study. We also thank statistician Ibrahimu Mdala for help with preparing the manuscript.

**Funding**

The study was supported by The Research Council of Norway (grant number 228775/H10) and The Norwegian Surveillance System for Antimicrobial Drug Resistance (to M. B.).

**Transparency declarations**

None to declare.

**Author contributions**

M. B. wrote the protocol for the study, coordinated the collection of data, performed data analysis, drafted the manuscript and approved the final version. G. S. S. had the idea for the study together with N. G., participated in the planning of the study, revision of the manuscript and approved the final version. M. L. participated in the planning of the study, data collection, revision of the manuscript and approved the final version. All members of the Norwegian ESBL UTI study group participated in data collection, revision of the manuscript and approved the final version of the manuscript.

**Supplementary data**

The clinical registration form is available as Supplementary data at JAC Online.

**References**


**Downloaded from https://academic.oup.com/jac/article-abstract/73/9/2503/5046991 by guest on 08 June 2020**
Pivmecillinam treatment of ESBL-producing E. coli UTI


36 European Society of Clinical Microbiology and Infectious Diseases. MIC and Zone Distributions and ECOFFs. http://www.eucast.org/mic_distributions_and_ecoffs/.


