Urine bactericidal activity against resistant *Escherichia coli* in an *in vitro* pharmacodynamic model simulating urine concentrations obtained after 2000/125 mg sustained-release co-amoxiclav and 400 mg norfloxacin administration

Luis Alou, Lorenzo Aguilar, David Sevillano, María-José Giménez, Fabio Cafini, Eva Valero, María-Teresa Relaño and José Prieto*

**Microbiology Department, School of Medicine, Universidad Complutense, Avda. Complutense s/n, 28040 Madrid, Spain**

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**Objectives:** To explore the urine bactericidal activity of co-amoxiclav and norfloxacin against *Escherichia coli* in an *in vitro* pharmacodynamic model simulating the human urinary concentrations observed after administration of a single oral dose of 2000/125 mg sustained-release co-amoxiclav and 400 mg norfloxacin.

**Methods:** Six *E. coli* isolates exhibiting amoxicillin/clavulanic acid MICs of 4/2 (two strains), 8/4, 16/8, 32/16 and 64/32 mg/L and norfloxacin MICs of ≤0.25 mg/L (three strains), 32, 64 and 256 mg/L were used. Colony counts were determined over 12 h and differences between the bacterial counts of initial inocula and the bacterial counts at each sampling time-point were calculated.

**Results:** With co-amoxiclav, bactericidal activity (≥3 log₁₀ reduction) was obtained against the susceptible (MIC ≤ 8/4 mg/L) and intermediate (MIC = 16/8 mg/L) strains from 3 to 12 h, and from 3 to 10 h against the resistant strains (MIC ≥ 32/16 mg/L), which exhibited a 2 log₁₀ reduction at 12 h. With norfloxacin, bactericidal activity was obtained against the susceptible strains from 4 to 12 h and from 8 to 12 h against the resistant strain with an MIC of 32 mg/L. Regrowth, with respect to initial inocula, occurred from 8 h onwards with the strain with MIC = 64 mg/L and from 3 h onwards with the strain with MIC = 256 mg/L.

**Conclusions:** While regrowth occurs after exposure of high norfloxacin-resistant *E. coli* to urine physiological concentrations of norfloxacin, this study suggests that clavulanic acid can be given twice daily (to protect amoxicillin activity) with respect to uncomplicated cystitis due to *E. coli* exhibiting amoxicillin/clavulanic acid MICs up to 64/32 mg/L.

**Keywords:** pharmacodynamic modelling, *E. coli*, urine bactericidal activity, amoxicillin, clavulanic acid

**Introduction**

The incidence of amoxicillin resistance in *Escherichia coli* clinical isolates exceeds 50% in many parts of the world, and in Spain only ~42% of *E. coli* community urinary strains are susceptible to ampicillin. Most of these isolates are resistant due to production of β-lactamase, and addition of clavulanic acid increases the ampicillin/amoxicillin susceptibility rate to 90–98%. Quinolone resistance in *E. coli* has spread in Spain, with resistance rates in the community reaching 22.8% in urinary isolates and 24% and 26% in faecal isolates from healthy adults and children, respectively.

A new oral pharmacokinetically enhanced formulation of co-amoxiclav has been developed that prolongs the duration of adequate amoxicillin concentrations after dosing. In previous studies the pharmacodynamic potential of this new formulation against amoxicillin non-susceptible *Streptococcus pneumoniae* was shown, and *ex vivo* serum bactericidal activity was determined in healthy volunteers. The serum bactericidal activity was determined using kill curves, where fresh inoculum was added to the serum sample (containing antibiotic) at each time-point. However, in infections, the infecting organism is exposed to changing antibiotic concentrations, and for this reason *in vitro* pharmacodynamic simulations mimicking this *in vivo* situation.
were performed against amoxicillin non-susceptible pneumococcal strains.8

Although it is relatively simple to undertake a pharmacodynamic analysis for systemic infections, the situation is more complex when considering urinary tract infections, and particularly when β-lactamase-producing pathogens are being tested against co-amoxiclav. In a previous Phase I study,9 significant antibacterial activity was obtained up to 12 h for the susceptible (8/4 mg/L) and intermediate (16/8 mg/L) strains and up to 8 h with the resistant (32/16 and 64/32 mg/L) strains with the new co-amoxiclav formulation. However, bacterial activity (>3 log_{10} reduction; >99.9% killing) was obtained only up to 8 h for the susceptible and intermediate strains and at the 2–4 h interval for the resistant strains.9 Results of the study may have been influenced by the fact that a fresh inoculum was exposed to each urine sample. This poorly reflects the in vivo situation, where bacteria in the urine are contained in the bladder and exposed to changing antibiotic concentrations over time. In this situation, the reduction in bacterial density would result in a reduction in the β-lactamase level, and in turn prolongation of the in vivo bactericidal activity beyond that obtained ex vivo. This has been suggested in experiments using animal models to measure serum bactericidal activity against β-lactamase-producing E. coli after co-amoxiclav treatment.10

This study evaluates the urine bactericidal activity of co-amoxiclav against E. coli in an in vitro model simulating urine concentrations obtained in humans up to 12 h after administration of a single dose in comparison with norfloxacin.

Materials and methods

Bacterial strains

Six E. coli clinical isolates from community-acquired cystitis were studied in this in vitro pharmacodynamic model. Four of them (FJ8, FJ16, FJ32 and FJ64) were those previously used in ex vivo determinations in a Phase I study.9

Antibiotics

Amoxicillin trihydrate and lithium clavulanate laboratory reference standards were supplied by GlaxoSmithKline (Worthing, UK). The norfloxacin laboratory reference standard was purchased from Sigma Chemical Co. (St Louis, MO, USA).

MIC determination and β-lactamase gene sequencing

MICs were determined by a microdilution method following CLSI methodology11 prior to and after the simulation process. All determinations were performed five times and modal values are presented. Amplification of TEM, SHV and CTX-M β-lactamase genes was performed by PCR as described previously.12 The PCR products were purified using a QIAquick PCR purification kit (Qiagen, Valencia, CA, USA) and then sequenced using a 3730 DNA Analyser (Perkin Elmer Applied Biosystems, Foster City, CA, USA). Sequences obtained were compared with the NCBI BLAST database.

In vitro kinetic model

The changing antibiotic urine concentrations were simulated in a model based on a two-compartment model described previously.8 The extra-capillary space and the intra-dialyser circulating tubing of the peripheral unit (FX50, Fresenius Medical Care S.A., Barcelona, Spain) represented the infection site. The exponential decay of concentrations was obtained by a continuous dilution–elimination process using computerized peristaltic pumps (Masterflex, Cole-Parmer Instrument Co., Chicago, IL, USA) at rates of 3.5 mL/min (period 0–3 h) and 1 mL/min (period 3–12 h) to simulate the clearance of norfloxacin and at a rate of 4.7 mL/min for the co-amoxiclav combination. Additional pumps circulated the antibiotic-medium mixture at a 50 mL/min rate between the central and peripheral compartment and at a rate of 20 mL/min within the extra-capillary space through external tubing. A computer-controlled syringe pump (402 Dilutor Dispenser; Gilson S.A, Villiers-le-Bel, France) allowed the simulation of concentrations in urine, by infusion of the antibiotic into the central compartment until the C_{max} was reached.

Kinetic simulations

Pharmacokinetic urine profiles in healthy volunteers of co-amoxiclav corresponding to the new co-amoxiclav 2000/125 mg SR formulation6 and of 400 mg norfloxacin13 were simulated over 12 h. Linear decay of both antimicrobials in urine was estimated using the mean concentration of each documented interval in Phase I studies.9,13 This approximation resulted in a biphasic clearance of norfloxacin from urine and was achieved by synchronization of the peristaltic pumps using the Win Lin software (Cole-Parmer Instrument Co., Chicago, IL, USA). The co-amoxiclav profile was simulated by the clearance of clavulanic acid from urine and supplementation of the amoxicillin concentration from time 3 to 10 h to mimic the amoxicillin concentrations obtained in urine with the new formulation. The target concentrations in urine were: 167, 85 and 30 mg/L at 1, 3 and 12 h, respectively, for norfloxacin; 814.7, 141 and 21 mg/L at 3, 10 and 14 h, respectively, for amoxicillin; and 41 and 1.5 mg/L at 3 and 10 h, respectively, for clavulanic acid. Figure 1 shows target and experimental concentrations of norfloxacin, amoxicillin and clavulanic acid.

Killing curves and the pharmacokinetic analysis

Bacterial suspensions in Mueller–Hinton broth supplemented with Ca^{2+} (25 mg/L) and Mg^{2+} (50 mg/L) were allowed to grow to a density of 5 × 10^7 cfu/mL, as measured by a UV-spectrophotometer (Hitachi U-1100). An aliquot of 60 mL of this inoculum was introduced into the peripheral compartment. Samples (0.5 mL) from the peripheral compartment were collected at 0, 1, 3, 4, 8, 10 and 12 h, and, if necessary, serially diluted in 0.9% sodium chloride. At least four dilutions of each sample were spread onto Mueller–Hinton agar plates supplemented with 5% sheep blood and incubated at 37°C, and colonies were counted after 24 h. The limit of detection was 5 × 10^5 cfu/mL, and each experiment was performed in triplicate.

In addition, aliquots were taken from the central compartment at 0, 1, 3, 4, 6, 8, 10 and 12 h, and stored at −50°C for the measurement of simulated urine concentrations. Samples were assayed by bioassay using Micrococcus luteus ATCC 9341 and Klebsiella pneumoniae NCTC 11228 as indicator organisms for amoxicillin and clavulanic acid, respectively. E. coli NCTC 10418 was used as the indicator organism for norfloxacin.14 Standards and samples were prepared and diluted in Mueller–Hinton broth as required. The limit of detection was 0.015, 0.125 and 0.25 mg/L for norfloxacin, amoxicillin and clavulanic acid, respectively. The intra-day and inter-day coefficients of variation between assays were 3.8% and 2.25% for norfloxacin, 2.1% and 4.3% for amoxicillin, and 7.3% and 4.3% for clavulanic acid, with internal control concentrations of 0.75 mg/L for norfloxacin and clavulanic acid and of 0.3 mg/L for amoxicillin. The
pharmacokinetic analysis was based on a non-compartmental approach (WinNonlin, Pharsight, Mountain View, CA, USA).

Statistical analysis

Differences in log_{10} colony counts at each sampling time with respect to initial inocula were calculated. Inter-strain differences at each time-point were determined using Tukey’s multiple comparison test. P < 0.001 was considered statistically significant. The P value was adjusted by the Bonferroni correction method, taking into consideration the multiple comparisons performed in the analysis.

Results

Table 1 shows the β-lactamase profile and MICs of co-amoxiclav and norfloxacin for the E. coli strains used in this study. Three

![Graphs and tables]( figure1.png)

Table 1. β-Lactamases and MICs (mg/L) for the six E. coli strains used in this study

<table>
<thead>
<tr>
<th>Strain</th>
<th>β-Lactamase</th>
<th>Amoxicillin/ clavulanic acid MIC</th>
<th>Norfloxacin MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR110</td>
<td>TEM-1</td>
<td>4/2</td>
<td>256</td>
</tr>
<tr>
<td>MR61</td>
<td>TEM-116</td>
<td>4/2</td>
<td>64</td>
</tr>
<tr>
<td>FJ8</td>
<td>TEM-1</td>
<td>8/4</td>
<td>32</td>
</tr>
<tr>
<td>FJ16</td>
<td>TEM-1</td>
<td>16/8</td>
<td>≤0.25</td>
</tr>
<tr>
<td>FJ32</td>
<td>TEM-1</td>
<td>32/16</td>
<td>≤0.25</td>
</tr>
<tr>
<td>FJ64</td>
<td>TEM-1</td>
<td>64/32</td>
<td>≤0.25</td>
</tr>
</tbody>
</table>

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Table 2. Simulated co-amoxiclav urine concentrations (mean ± SD) after a single 2000/125 mg dose, *E. coli* initial inocula reduction over time (log₁₀ cfu/mL initial inocula – log₁₀ cfu/mL at the corresponding sampling time) and mean urine $t > MIC$

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (mg/L)$^a$</th>
<th>0 h</th>
<th>1 h</th>
<th>3 h</th>
<th>4 h</th>
<th>8 h</th>
<th>10 h</th>
<th>12 h</th>
<th>Mean $t &gt;$ MICb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR110</td>
<td>4/2</td>
<td>0.0 ± 0.0</td>
<td>0.5 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>4.7 ± 0.2</td>
<td>4.4 ± 0.5</td>
<td>5.9 ± 0.2</td>
<td>100</td>
</tr>
<tr>
<td>MR61</td>
<td>4/2</td>
<td>0.0 ± 0.0</td>
<td>2.8 ± 0.7</td>
<td>3.6 ± 0.2</td>
<td>3.8 ± 0.4</td>
<td>5.7 ± 0.9</td>
<td>5.2 ± 0.4</td>
<td>5.5 ± 0.4</td>
<td>100</td>
</tr>
<tr>
<td>FJ8</td>
<td>8/4</td>
<td>0.0 ± 0.0</td>
<td>2.4 ± 1.3</td>
<td>4.3 ± 0.8</td>
<td>5.3 ± 0.7</td>
<td>5.9 ± 0.6</td>
<td>6.0 ± 1.1</td>
<td>5.5 ± 1.9</td>
<td>100</td>
</tr>
<tr>
<td>FJ16</td>
<td>16/8</td>
<td>0.0 ± 0.0</td>
<td>2.3 ± 0.4</td>
<td>4.3 ± 0.4</td>
<td>4.7 ± 0.3</td>
<td>5.5 ± 0.7</td>
<td>5.1 ± 1.4</td>
<td>4.6 ± 1.8</td>
<td>100</td>
</tr>
<tr>
<td>FJ32</td>
<td>32/16</td>
<td>0.0 ± 0.0</td>
<td>1.0 ± 0.9</td>
<td>3.4 ± 0.4</td>
<td>4.1 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>4.1 ± 0.1</td>
<td>2.0 ± 0.3</td>
<td>100</td>
</tr>
<tr>
<td>FJ64</td>
<td>64/32</td>
<td>0.0 ± 0.0</td>
<td>0.9 ± 0.4</td>
<td>3.9 ± 0.8</td>
<td>3.4 ± 1.3</td>
<td>5.0 ± 0.2</td>
<td>4.1 ± 0.5</td>
<td>2.0 ± 0.1</td>
<td>92</td>
</tr>
<tr>
<td>Amoxicillin concentration (mg/L)</td>
<td>–</td>
<td>462.4 ± 7.0</td>
<td>821.8 ± 19.2</td>
<td>583.1 ± 17.1</td>
<td>252.3 ± 2.6</td>
<td>124.5 ± 3.5</td>
<td>40.8 ± 6.2</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Clavulanate concentration (mg/L)</td>
<td>–</td>
<td>ND</td>
<td>42.2 ± 3.1</td>
<td>26.4 ± 1.9</td>
<td>4.0 ± 0.3</td>
<td>1.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

ND, not determined.

$^a$Amoxicillin/clavulanic acid MIC.

$^b$> MIC = % dosing interval (12 h) where amoxicillin concentrations in urine exceed amoxicillin/clavulanic acid MIC.

Table 3. Simulated norfloxacin urine concentrations (mean ± SD) after a single 400 mg dose, *E. coli* initial inocula reduction over time (log₁₀ cfu/mL initial inocula – log₁₀ cfu/mL at the corresponding sampling time) and mean urine AUC₀−12/MIC

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (mg/L)$^a$</th>
<th>0 h</th>
<th>1 h</th>
<th>3 h</th>
<th>4 h</th>
<th>8 h</th>
<th>10 h</th>
<th>12 h</th>
<th>Mean AUC₀−12/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FJ64</td>
<td>≤0.25</td>
<td>0.0 ± 0.0</td>
<td>1.7 ± 0.3</td>
<td>3.3 ± 0.3</td>
<td>3.9 ± 0.4</td>
<td>6.1 ± 0.5</td>
<td>6.3 ± 0.4</td>
<td>6.0 ± 0.3</td>
<td>≥3092.43</td>
</tr>
<tr>
<td>FJ16</td>
<td>≤0.25</td>
<td>0.0 ± 0.0</td>
<td>1.3 ± 0.6</td>
<td>2.9 ± 0.6</td>
<td>3.5 ± 0.5</td>
<td>5.8 ± 0.6</td>
<td>5.7 ± 0.3</td>
<td>6.0 ± 0.4</td>
<td>≥3092.43</td>
</tr>
<tr>
<td>FJ32</td>
<td>≤0.25</td>
<td>0.0 ± 0.0</td>
<td>0.8 ± 0.7</td>
<td>1.8 ± 1.3</td>
<td>2.1 ± 1.1</td>
<td>3.1 ± 1.3</td>
<td>3.5 ± 1.5</td>
<td>3.8 ± 1.3</td>
<td>≥3092.43</td>
</tr>
<tr>
<td>FJ8</td>
<td>32</td>
<td>0.0 ± 0.0</td>
<td>0.1 ± 0.1</td>
<td>1.1 ± 0.8</td>
<td>2.1 ± 0.7</td>
<td>3.9 ± 0.4</td>
<td>4.0 ± 0.3</td>
<td>3.5 ± 0.4</td>
<td>24.16</td>
</tr>
<tr>
<td>MR61</td>
<td>64</td>
<td>0.0 ± 0.0</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.3$^b$</td>
<td>-0.1 ± 0.1$^c$</td>
<td>-0.2 ± 0.2$^c$</td>
<td>-0.8 ± 0.3$^c$</td>
<td>12.08</td>
</tr>
<tr>
<td>MR110</td>
<td>256</td>
<td>0.0 ± 0.0</td>
<td>0.5 ± 0.8</td>
<td>-1.6 ± 0.3$^b$</td>
<td>-2.6 ± 0.3$^b$</td>
<td>-2.8 ± 0.4$^c$</td>
<td>-2.9 ± 0.3$^c$</td>
<td>-3.0 ± 0.1$^c$</td>
<td>3.02</td>
</tr>
<tr>
<td>Concentration (mg/L)</td>
<td>–</td>
<td>152.5 ± 13.5</td>
<td>79.3 ± 11.1</td>
<td>71.6 ± 13.5</td>
<td>47.3 ± 7.2</td>
<td>39.7 ± 6.7</td>
<td>29.3 ± 2.7</td>
<td>773.10 ± 68.60</td>
<td>–</td>
</tr>
</tbody>
</table>

Negative values (given in bold) correspond to regrowth with respect to initial inocula.

$^a$P < 0.001 versus FJ64 and FJ16.

$^b$P < 0.001 versus all other strains.

$^c$P < 0.001 versus FJ64, FJ32, FJ16 and FJ8.

concentrations fell below the MIC for the isolate. This occurred at 3 h in the case of the strain with an MIC of 256 mg/L and at 8 h in the case of the strain with an MIC of 64 mg/L. The AUC₀−12/MIC ratio was <24 in those strains that showed regrowth (norfloxacin MICs of 64 and 256 mg/L). Bactericidal activity (>3 log₁₀ reduction) was generally observed from 4 to 12 h for the susceptible strains (norfloxacin MICs ≤ 0.25 mg/L) and from 8 to 12 h for the strain with a norfloxacin MIC of 32 mg/L, but was never observed for the strains with norfloxacin MICs of 64 and 256 mg/L.

Bactericidal activity (against all strains with co-amoxiclav and against four strains with norfloxacin) was observed at earlier time-points with co-amoxiclav than with norfloxacin (3 h versus 4–8 h).

Isolates recovered at the end of the experiments exhibited amoxicillin/clavulanic acid MIC values equal to those prior to co-amoxiclav exposure. However, after norfloxacin exposure, the strain FJ8 exhibited an MIC of 256 mg/L (three dilutions higher than the one pre-exposure: 32 mg/L) while the remaining strains exhibited the same MIC values.

**Discussion**

Owing to the high prevalence of resistance to amoxicillin or ampicillin in *E. coli*,¹⁶,¹⁷ their use in cystitis is not advocated without a β-lactamase inhibitor.¹⁸ Susceptibility rates of *E. coli* to amoxicillin/clavulanic acid are ~90% in Spain³ and have remained at this level over time because hyperproduction of TEM-1 β-lactamase (or its derivative IRT) has a low frequency in Spain.³ Extended-spectrum β-lactamases are not often found in *E. coli* from outpatient urine culture in Spain (1.4%), and those that are found are not usually TEM derivatives.¹² It has been suggested that fluoroquinolones are a logical choice for empirical therapy of uncomplicated cystitis,¹⁹ and in early studies norfloxacin was associated with good efficacy in the treatment of uncomplicated cystitis.¹⁹,²⁰ However, this was at a time when resistance rates were not higher than 15% in Spain, and since then an ~1% per annum increase in the resistance rate for *E. coli* to fluoroquinolones has occurred.¹⁷ As a consequence, resistance rates in *E. coli* to norfloxacin now exceed the 20% level in many parts of Spain.

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In the assessment of an antibiotic for uncomplicated cystitis, bactericidal activity in urine is a relevant pharmacodynamic parameter because the gradual decrease in antibiotic concentration (which is not possible to mimic in standard in vitro testing) could lead to concentrations below the MIC, permitting bacterial regrowth that may result in therapeutic failure. One of the earlier attempts to use in vitro dynamic models to simulate bladder infections measured the effects of antibiotics by photometrically studying bacterial growth in artificial media and simulating micturition by alterations of the volume and flow rate of the medium. Despite criticisms that such spectrophotometric measurements included both non-viable and viable bacteria and that they were not reliable for dense bacterial populations (10⁹–10¹⁰ CFU/mL), this bladder model correlated well with mouse infection protection models and provided realistic simulations of the response seen in patients in clinical trials.

In the present pharmacodynamic simulation, the system used was closed (bacteria were not eliminated with alterations in the flow rate), and the changes in bacterial counts resulted solely from the action of the antimicrobial agent. Although generally bacteria grow more quickly in Mueller–Hinton broth than in urine, fluoroquinolone activity can be decreased in urine due to magnesium concentrations present. In this study the Mueller–Hinton broth used was supplemented with Ca²⁺ and Mg²⁺ to better simulate the urinary situation.

In this study bactericidal activity with norfloxacin was obtained from 4 to 12 h against strains with MIC values of ≤32 mg/L, but regrowth (with respect to the initial inoculum) occurred when concentrations were below the MIC for resistant strains with MICs ≥ 64 mg/L. Moreover, with the strain with an MIC of 32 mg/L the survival bacterial population at the end of the simulation exhibited an increased MIC (256 mg/L). This suggests that despite the original bactericidal activity obtained against this strain with norfloxacin, categorization of this strain as resistant is correct taking into account the highly resistant subpopulation selected, as may occur in vivo.

The results obtained in this study with co-amoxiclav contrast with those obtained previously in a Phase I study in healthy volunteers, where the bactericidal activity against four of the six strains used in this study (those strains with MICs of 8/4, 16/8, 32/16 and 64/32 mg/L) was assessed. In the earlier study, bactericidal activity (>3 log₁₀ reduction) was obtained for up to 8 h against the susceptible and intermediate strains, and up to 10 h against the resistant strains. In the present in vitro simulation, bactericidal activity was obtained up to 12 h (the whole dosing interval) against the susceptible and intermediate strains, and up to 10 h against the resistant strains. We believe that the difference between the two studies is due to the fact that in the Phase I study a fresh inoculum was exposed to the urine sample (containing the antibiotic) at each time-point, while in this simulation the same inoculum is exposed to changing concentrations over time, which better mimics the in vivo situation.

In previous in vitro and ex vivo studies in animal models and in humans, where fresh E. coli inocula were exposed to fixed co-amoxiclav concentrations at different time-points (static experiments), a clavulanic acid threshold for the activity of amoxicillin was observed. In contrast, in this study, where exposure of the same inocula to changing co-amoxiclav concentrations was used, this threshold was not observed. From this perspective the results of this study suggest that clavulanic acid can be given twice daily (to protect amoxicillin activity) in the treatment of uncomplicated cystitis due to E. coli exhibiting amoxicillin/clavulanic acid MICs up to 64/32 mg/L. This is a higher value than those found for strains with β-lactamase hyperproduction. In contrast, quinolone treatment should be used with caution in countries such as Spain, where resistance rates are higher than 15%.

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Transparency declarations

None to declare.

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