Major article

Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: A 7-year surveillance study

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Background: We conducted a retrospective analysis on the identification and antibiogram of all bacteria isolated from urine samples with microbiological confirmation of urinary tract infection (UTI) in a Spanish reference hospital over a 7-year period.
Methods: A retrospective analysis was performed of the identification and antibiogram data.
Results: A total of 31,758 uropathogens were isolated. *Escherichia coli* accounted for the majority (55.2%) of these, followed by *Enterococcus faecalis* (18.0%) and *Klebsiella* spp (10.3%). The highest *E coli* susceptibility rates were to imipenem (93.0%-99.8%), amikacin (97.3%-99.5%), nitrofurantoin (96.7%-98.9%), and fosfomycin (95.3%-100%), and the lowest were to cefuroxime (67.8%-86.4%), ciprofloxacin (61.2%-69.8%), and co-trimoxazole (55.0%-65.5%). We highlight the overall high activity of imipenem, piperacillin-tazobactam, nitrofurantoin, and fosfomycin on isolates versus the low activity of fluoroquinolones, co-trimoxazole, or cephalosporins. The activity of amoxicillin-clavulanic acid and fosfomycin decreased significantly over the 7-year study period.
Conclusions: Imipenem and piperacillin-tazobactam appear to be good options for the empiric treatment of UTI acquired in hospital or requiring hospitalization, whereas nitrofurantoin and fosfomycin can be first-choice antibiotics for the treatment of uncomplicated community-acquired cystitis. However, surveillance studies are required to detect resistance to these antibiotics, given that an increase in uropathogen resistance rates may contraindicate its future use in empiric UTI therapy.

Urinary tract infections (UTIs) are caused by a limited number of bacterial species, more than 95% of which are monomicrobial. *Escherichia coli* is the most frequently implicated uropathogen reported by virtually all epidemiologic studies worldwide. Other pathogens of the genera *Enterococcus, Klebsiella, Enterobacter, Proteus, Morganella, Citrobacter, Serratia, Pseudomonas, Streptococcus,* and *Staphylococcus,* and fungi, such as *Candida* spp, are also isolated with variable frequency.[1]

The high incidence of UTIs and their usually mild character call for empiric antibiotic treatment in most cases.[2] Providing rational empiric treatment requires identifying the microorganisms involved and establishing their antibiotic susceptibility patterns to the largest possible number of agents; this is especially important for *E coli*, the most frequently isolated uropathogen.[1,3]

The objectives of the present study were to identify the bacteria most frequently responsible for UTIs in our area and their susceptibility profiles, using a standardized work procedure, and to evaluate the activity on all isolates of antibiotics widely used for the treatment of community- and hospital-acquired UTIs.

MATERIALS AND METHODS

A retrospective analysis was performed of the identification and antibiogram data for all consecutive bacteria isolated from urine samples with microbiological confirmation of UTI at the

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Microbiology Department of Virgen de las Nieves Hospital Complex, Granada, in southern Spain, between January 2006 and December 2012.

All urine cultures were analyzed by calibrated loop seeding in usual media. A count $\geq 10^5$ colony-forming units (CFU)/mL was considered to indicate significant bacteriuria. A count of $>10^4$ CFU/mL of a single microorganism was considered positive in the presence of >40 leukocytes/μL in noncentrifuged urine. Urine cultures with growth of more than 2 microorganisms were considered contaminated. The WIDER system (Francisco Soria Melguizo, Madrid, Spain) was used for identification and antibiogram profiling of all bacteria from positive urine cultures up to March 2012, when it was replaced with the MicroScan system (Siemens Healthcare Diagnostics, Spain). Duplicate positive urine cultures (ie, of the same genus or species obtained sequentially from the same UTI episode) were excluded. Furthermore, if a subject contributed more than 1 urine sample, regardless of the origin (community or hospital), then an interval of at least 30 days had to pass before the second sample was considered a significant finding and included in the report. This was done to avoid duplicate isolates from a single UTI episode.

Amikacin, amoxicillin-clavulanic acid, cefepime, cefotaxime, ceftazidime, cefuroxime, ciprofloxacin, fosfomycin, gentamicin, imipenem, nitrofurantoin, piperacillin-tazobactam, tobramycin, and co-trimoxazole were tested against Enterobacteriaceae. The presence of extended-spectrum beta-lactamase (ESBL) producers among enterobacteria was considered only from January 2010, when the Clinical and Laboratory Standards Institute (CLSI) modified the susceptibility cutoff points to cephalosporins. Amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, imipenem, piperacillin-tazobactam, tobramycin, and co-trimoxazole (not for *Pseudomonas* spp) were tested against *Pseudomonas* spp and *Acinetobacter* spp. Ampicillin, levofloxacin, fosfomycin, nitrofurantoin, and co-trimoxazole (only against *Streptococcus agalactiae*) were tested against *Enterococcus* spp and *S agalactiae*; and amikacin, levofloxacin, fosfomycin, gentamicin, nitrofurantoin, oxacillin, tobramycin, and co-trimoxazole against *Staphylococcus* spp.

Isolates were classified as susceptible, intermediate, or resistant to each antibiotic according to CLSI recommendations.[4] The clinical categorization of all isolates against nitrofurantoin and of *S agalactiae* against co-trimoxazole followed the recommendations of the European Committee on Antimicrobial Susceptibility Testing.[5] For each study year and each bacterial species identified in ≥ 5 isolates/year, the proportion of susceptible organisms was calculated by dividing the number of urinary isolates susceptible to each antibiotic by the number of organisms tested against that antimicrobial agent. (Intermediately resistant and resistant organisms were grouped together.)

The activity of each antibiotic was evaluated on all bacteria isolated during the study period. The following assumptions were made: (1) Each of the aforementioned antibiotics is potentially active against enterobacteria; (2) fosfomycin, nitrofurantoin, amoxicillin-clavulanic acid, cefotaxime, and cefuroxime have no activity against nonfermenting gram-negative bacilli, and *Pseudomonas aeruginosa* is intrinsically resistant to co-trimoxazole; (3) among staphylococci, oxacillin predicts the response to all beta-lactam antibiotics indicated for ITUs; (4) among enterococci, ampicillin predicts the response to amoxicillin-clavulanic acid, piperacillin-tazobactam, and imipenem, and cefepime, cefotaxime, ceftazidime, cefuroxime, amikacin, gentamicin, tobramycin, and co-trimoxazole are not clinically active against these microorganisms[6]; (5) fluoroquinolone activity can be determined from the activity of ciprofloxacin on gram-negative bacilli and of levofloxacin on gram-positive cocci; (6) the activity of fosfomycin on enterobacteria and gram-positive cocci can be assessed using the cutoff points recommended by the CLSI for this antibiotic against *E coli* and *Enterococcus faecalis*, respectively[7,8]; and (7) the activity of nitrofurantoin on enterobacteria can be assessed using the cutoff points recommended by the European Committee on Antimicrobial Susceptibility Testing for this antibiotic in *E coli*. Data for *S agalactiae* were excluded owing to the absence of antibiograms for this microorganism between 2006 and 2010.

A descriptive statistical analysis was performed, and differences in susceptibility rates were analyzed using Pearson's χ^2 test and contingency tables with Fisher's exact test. SPSS version 18.0 (SPSS, Chicago, IL) was used for all analyses. A P value $<.05$ was considered significant for all tests.

RESULTS

The 31,758 bacteria identified included 24,813 (78.1%) gram-negative bacilli and 6945 (21.9%) gram-positive cocci. Over the 7-year study period, there was no significant change in the frequency of the types of bacteria identified, with *E coli* the most frequently identified UTI agent in each year (55.2% of all isolates; range, 50.1%-59.4%) in both community (55.6%; range, 51.5%-59.4%) and hospital (54.2%; range, 50.1%-57.4%) isolates, followed by *E faecalis* (18.0%; range, 14.7%-22.1%) and *Klebsiella* spp (10.3%; range, 7.2%-12.9%). Together, other bacteria (*Proteus mirabilis*, *Enterobacter* spp, *Morganella morganii*, *Citrobacter koseri*, *Citrobacter freundii*, *P aeruginosa*, *Acinobacter baumannii*, *Staphylococcus aureus*, *Staphylococcus saprophyticus* , and *S agalactiae*) accounted for only 15.3% of commuity isolates and 16.8% of hospital isolates.

Antibiotic susceptibility of the isolated bacteria

E coli showed high susceptibility to imipenem, amikacin, fosfomycin, and nitrofurantoin, with annual resistance rates $<5\%$, whereas resistance to cefuroxime, ciprofloxacin, and co-trimoxazole, key antibiotics in the treatment of community-acquired UTIs, was recorded in $>20\%$-30% of isolates in most years. Compared with community isolates, hospital isolates of *E coli* species were significantly more resistant to amoxicillin-clavulanic acid ($P < .001$), cefepime ($P < .001$), cefotaxime ($P < .001$), ceftazidime ($P = .011$), and piperacillin-tazobactam ($P = .003$), but significantly more susceptible to cefuroxime ($P < .001$), fosfomycin ($P < .001$), and nitrofurantoin ($P = .019$). There were no significant differences between the community and hospital isolates for imipenem ($P = .520$), ciprofloxacin ($P = .152$), amikacin ($P = .054$), gentamicin ($P = .829$), tobramycin ($P = .344$), or co-trimoxazole ($P = .219$).

In 2010, the prevalence of ESBL-producing *E coli* among the community and hospital isolates was 7.5% and 5.0%, respectively. In 2011, these respective prevalences were 7.4% and 9.8%, and in 2012, they were 8.6% and 10.8%. This increase in prevalence was especially marked in isolates of hospital origin. Considered together, these bacteria had high susceptibility rates to imipenem (98%-100% susceptible isolates), piperacillin-tazobactam (87%-94%), amikacin (92%-100%), fosfomycin (88%-93%), and nitrofurantoin (93%-98%), but much lower susceptibility rates to amoxicillin-clavulanic acid (52%-68%), ciprofloxacin (13%-24%), and co-trimoxazole (39%-52%).

The community isolates of *Klebsiella pneumoniae* and *Klebsiella oxytoca* species were highly susceptible, whereas the hospital isolates were significantly more resistant to all antibiotics tested ($P \leq.001$ in all cases) except fosfomycin ($P = .872$) and imipenem ($P = .722$). The respective prevalences of ESBL-producing *Klebsiella* spp among community and hospital isolates were 4.4% and 8.6%, respectively, in 2010, 5.9% and 31.8% in 2011, and 6.6% and 7.3% in 2012. Overall, these bacteria showed high susceptibility rates only to imipenem (91%-100% susceptible isolates) and amikacin (66%-100%). Susceptibility was lower to other antibiotics, including

piperacillin-tazobactam (33%-84%), amoxicillin-clavulanic acid (6%-50%), ciprofloxacin (6%-50%), fosfomycin (40%-78%), nitrofurantoin (16%-78%), and co-trimoxazole (7%-67%).

In *P mirabilis,* the highest resistance rates were to ciprofloxacin and co-trimoxazole, and community isolates of this bacteria were significantly more resistant to co-trimoxazole compared with hospital isolates (*P* = .001). *M morganii* was the member of the Enterobacteriaceae family with the highest resistance to fosfomycin and very low susceptibility to amoxicillin-clavulanic acid, cefotaxime, cefuroxime, ciprofloxacin, and co-trimoxazole. The resistance rates of these bacteria against co-trimoxazole were higher in community isolates (*P* = .043), but there was no difference against any other antibiotic between community and hospital isolates.

Enterobacter spp (*Enterobacter aerogenes* and *Enterobacter cloacae*) had low susceptibility to amoxicillin-clavulanic acid, cefotaxime, ceftazidime, and cefuroxime. Hospital isolates were significantly more resistant than community isolates to cefepime (*P* = .004), cefotaxime (*P* < .001), ceftazidime (*P* < .001), gentamicin (*P* = .002), piperacillin-tazobactam (*P* < .001), tobramycin (*P* = .005), and co-trimoxazole (*P* = .004) and significantly more susceptible to fosfomycin (*P* = .045) and imipenem (*P* = .022).

Compared with community isolates, hospital isolates of *C koseri* were significantly more resistant to amikacin (*P* = .041), ciprofloxacin (*P* = .001), gentamicin (*P* = .008), and imipenem (*P* = .044), whereas hospital isolates of *C freundii* were more resistant to ceftazidime (*P* = .014), gentamicin (*P* = .002), and tobramycin (*P* = .009).

P aeruginosa exhibited high susceptibility in general, although the hospital isolates were significantly more resistant to cefepime (*P* = .002), ceftazidime (*P* = .001), gentamicin (*P* = .012), imipenem (*P* = .006), piperacillin-tazobactam (*P* = .007), and tobramycin (*P* = .014) compared with the community isolates. Hospital isolates of *A baumannii* were significantly more resistant than community isolates to all tested antibiotics (*P* < .001), including imipenem (*P* = .025).

We highlight the elevated frequency of *E faecalis* and its high susceptibility to fosfomycin and nitrofurantoin in both community and hospital isolates but very low susceptibility to levofloxacin, which was significantly more marked in hospital isolates (*P* < .001). *Enterococcus faecium* also showed high susceptibility to fosfomycin and nitrofurantoin but low susceptibility to ampicillin and levofloxacin, again more marked in hospital isolates (*P* < .001 in both cases).

S aureus isolates evidenced low susceptibility to fluoroquinolones, mainly among hospital isolates (*P* < .001), in which resistance to oxacillin was also significantly more frequent (*P* < .001). In general, *S saprophyticus* isolates were highly susceptible to fluoroquinolones, including levofloxacin, although they showed higher resistance rates to oxacillin compared with *S aureus*, but with no significant differences between community and hospital isolates.

Finally, before 2011, antibiograms were not performed systematically for *S agalactiae* isolates identified in urine; thus, in the present study we considered only the results for 2011 and 2012. The susceptibility of *S agalactiae* to antibiotics with anti−gram-positive activity habitually prescribed for UTIs (ie, beta-lactam antibiotics, fosfomycin, nitrofurantoin, levofloxacin, and co-trimoxazole) was high in both community and hospital isolates, with no significant differences between them.

Evolution of antibiotic activity against isolated bacteria in UTIs

Fig 1 depicts the activity of the tested antibiotics against the 31,758 bacteria isolated in urine during the study period. The activity of amikacin, gentamicin, tobramycin, amoxicillin-clavulanic acid, piperacillin-tazobactam, cefotaxime, ceftazidime, cefepime, fluoroquinolones, fosfomycin, co-trimoxazole, and nitrofurantoin was significantly higher (*P* < .001, in all cases) in the isolates of community origin compared with isolates of hospital origin. However, cefuroxime was more active against hospital isolates (*P* < .001), whereas imipenem showed no difference in activity between isolates of community and hospital origin (*P* = .327).

There was no significant change in the activity of any of the studied antibiotics over the 7-year study period with the exception of amoxicillin-clavulanic acid and fosfomycin, which showed a significant decrease in activity against isolates of both community and hospital origin (*P* < .001).

DISCUSSION

This retrospective study describes the distribution and antimicrobial susceptibility of bacterial species isolated from a large number of urine samples collected from the community and hospitalized patients over a 7-year period. Research into uropathogen resistance has centered mainly on *E coli*, the most frequently identified bacteria in UTIs, revealing a gradual increase in resistance that affects empiric treatment, especially in community-acquired cases.[1,3]

A 2001 study of urine samples of community origin from the same geographic area as the present study found resistance rates of 37% of isolates to amoxicillin-clavulanic acid, 13% to cefuroxime, 33% to co-trimoxazole, and 22% to ciprofloxacin, but only 1% to fosfomycin and 7% to nitrofurantoin.[9] Those results are similar to the findings of subsequent multicenter studies in Spain, in which fosfomycin and nitrofurantoin showed the lowest resistance rates alongside wider-spectrum antibiotics.[2,10-13] In the present study, the resistance of *E coli* to some of these antibiotics was higher than reported previously; thus, the resistance rates to cefuroxime, ciprofloxacin, and co-trimoxazole were >30%, although rates remained low for fosfomycin and nitrofurantoin. Resistance rates to beta-lactam antibiotics, quinolones, and co-trimoxazole are generally higher in Spain than in other European countries.[14-17]

A pathogen other than *E coli* was identified in approximately 45% of the bacteria isolated in the urine samples in this study. *K pneumoniae* and *K oxytoca* were detected in 10.6% of community isolates and in 9.7% of hospital isolates. Compared with the 2001 data,[9] in the present study susceptibility results were slightly higher for amoxicillin-clavulanic acid, fosfomycin, and nitrofurantoin but lower for co-trimoxazole and ciprofloxacin. Other national[2,11] and European[18] studies have reported similar results for these bacteria, although with higher resistance rates to nitrofurantoin than seen in our population.

A significant increase in ESBL-producing strains of *E coli* and *Klebsiella* spp was previously recorded in our setting.[19] Both strains showed high resistance rates to fluoroquinolones and co-trimoxazole in the present investigation, whereas carbapenems, especially imipenem and to a lesser extent piperacillin-tazobactam and amikacin, remained the most active antibiotics. Fosfomycin and nitrofurantoin also appeared to retain their activity, with low resistance rates to these antibiotics among ESBL-producing isolates, especially those of *E coli*. However, there is evidence of an increasing prevalence of ESBL-producing isolates that are resistant to these antibiotics,[20,21] especially in isolates of *Klebsiella* spp, with >20% demonstrating resistance to fosfomycin and nitrofurantoin, as in the present study.

P mirabilis represented 5.4% of community isolates and 3.9% of hospital isolates. Its susceptibility rates to some antibiotics have varied among studies; however, as in the present study, it generally has demonstrated high resistance to ciprofloxacin and co-trimoxazole, as well as natural resistance to nitrofurantoin and, in
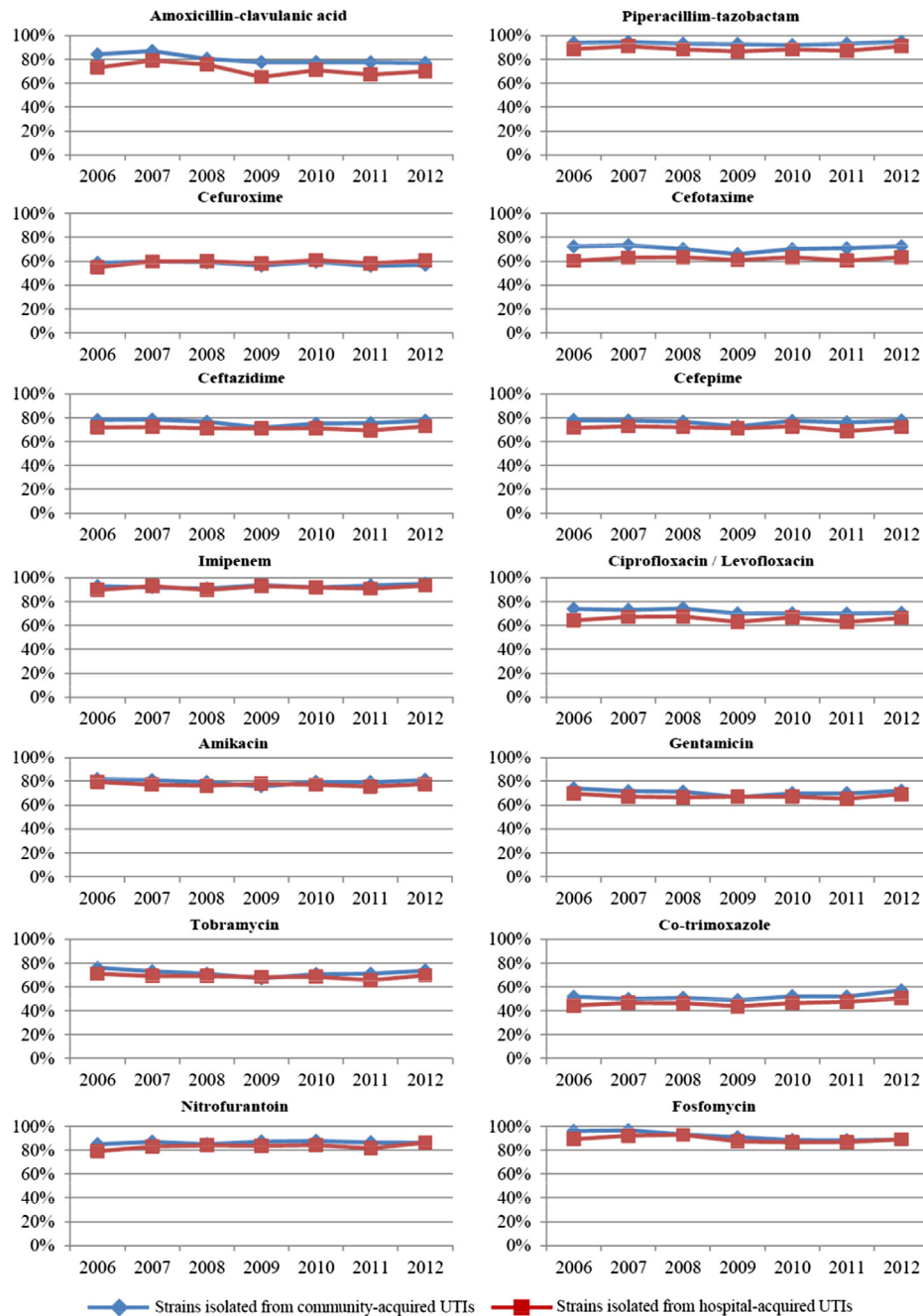
Fig 1. Activity (in %) of the various antibiotics on the total number of bacteria isolated in urine samples during 2006-2012.

some cases, imipenem.[2,9,11,18] *M morganii* represented 1.3% of community isolates and 1.0% of hospital isolates and was the enterobacteria with the highest resistance to fosfomycin, as reported previously,[21] along with a natural resistance to imipenem.

E cloacae and *E aerogenes* represented 1.6% of community isolates and 2.4% of hospital isolates, similar to recent findings in a Portuguese population,[14] demonstrating the low susceptibility of these bacteria to amoxicillin-clavulanic acid, cefuroxime, cefotaxime, and ceftazidime. Resistance generally develops in these species through production of a constitutive AmpC-type beta-lactamase.

C freundii and *C koseri* were isolated in only 1.3% of the bacterial isolates from community samples and in 0.9% of those from hospital samples. Both bacteria proved susceptible to the tested antibiotics, although *C freundii* showed higher resistance to beta-lactam antibiotics owing to its natural resistance phenotype.

P aeruginosa represented approximately 2.1% of community isolates and 5.2% of hospital isolates, and the susceptibility rates were similar to or higher than those reported in other studies.[9,14,18,21] In this same group, *A baumannii* represented 1.2% of the bacteria isolates in community samples and 1.2% of those in hospital samples. Amikacin preserved the highest activity among the tested antibiotics over the 7-year period, but resistance rates to imipenem were high, although lower than in previous studies.[21]

E faecalis represented 18.1% of community isolates and 17.9% of hospital isolates. The activity of fosfomycin and nitrofurantoin was elevated, as previously reported by Magliano et al[18] and Linhares et al,[14] but there was high resistance to fluoroquinolones. *E faecium* (0.3% of community isolates and 1.5% of hospital isolates) showed high resistance to ampicillin, mainly among hospital isolates (natural resistance owing to altered PBP5).

S aureus represented only 0.8% of community isolates and 1.1% of hospital isolates. High resistance to fluoroquinolones was seen, as previously reported in our setting,[9] especially among hospital isolates. *S saprophyticus* is reportedly the most frequent species of this genus in UTIs[10,17,22]; however, in the present study, its frequency was even lower than that of *S aureus*, representing only 0.8% of community isolates and 0.5% of hospital isolates. Resistance of *S saprophyticus* to antibiotics was low in our setting, as in other European regions.[22]

S agalactiae was isolated in 2.0% of community samples and 0.5% of hospital samples, with high susceptibility to the tested antibiotics. Identification of *S agalactiae* is especially important during pregnancy owing to its association with neonatal sepsis.

Optimal antibiotic management of UTI requires knowledge of the susceptibility profiles of the most frequently isolated uropathogens in the locality and a constant update of epidemiologic data.[2] Through this approach, the activity of any antibiotic used for empiric ITU treatment can be estimated a priori according to the incidence of different pathogens and the accumulated resistance.

Among beta-lactam antibiotics, amoxicillin-clavulanic acid and piperacillin-tazobactam showed different behaviors (Fig 1). Although therapeutic guidelines do not consider amoxicillin-clavulanic acid a first-choice treatment in UTI,[23] it is widely prescribed because of continued reports of its low resistance rates, mainly in *E coli*.[10,24] However, the rate of resistance to amoxicillin-clavulanic acid of the bacteria identified in the present study was high (>20%-25%), especially in community isolates. The significant decrease in its activity over recent years in our area and in a neighboring Spanish region[3] calls into question its usefulness as a first-line empiric treatment. In contrast, the activity of piperacillin-tazobactam has remained constant, with low resistance rates, even in ESBL-producing isolates. Although the parenteral administration of piperacillin-tazobactam impedes its use as an empiric treatment for community-acquired UTI, it remains a good therapeutic option in severe or complicated UTI cases requiring hospitalization.[21]

Oral penicillins and first-generation cephalosporins are no longer recommended for UTI treatment owing to their high microorganism resistance rate. Second-generation cephalosporins (eg, cefuroxime) have been widely used to treat UTIs, but the resistance rates are now very high, (~40%, >10 percentage points above the resistance rates of *E coli* to cefuroxime), owing to its reduced activity spectrum and inactivity against ESBL-producing isolates. Third- and fourth-generation cephalosporins are usually active against most gram-negative bacilli involved in these infections, including ceftazidime or cefepime against nonfermenting gram-negative bacilli; however, they are not usually active against ESBL-producing isolates, although their use is now permitted when in vitro activity is demonstrated, according to the new CLSI cutoff points.[4] In the present study, the global resistance of uropathogens to cefotaxime, ceftazidime, and cefepime was >20%, ruling out these agents as first-choice empiric treatment.

Among beta-lactam antibiotics, only imipenem maintained high activity (>90%) against all isolates over the study period. Imipenem has proven to be the best option for UTI in hospitalized patients because of its effectiveness in treating infections by enterobacteria nonfermenting gram-negative bacilli and some bram-positive cocci, all of which preserve high susceptibility rates to this antibiotic, as demonstrated previously.[21]

Fluoroquinolones are one of the most widely accepted antibiotic families for treating UTIs, even in complicated cases, given their broad-spectrum action, bactericidal potency, excellent oral bioavailability, good tolerance, and marked postantibiotic effect.[3,24] However, various studies have reported high resistance rates to these antibiotics (>30% in some series, including the present

study), especially among ESBL-producing isolates,[19] and some authors have opposed their use as first-line treatment for uncomplicated UTIs because of these high resistance rates.[25] Others have proposed restricting their use to severe infections in young patients, who have shown lower resistance in this situation.[10] The present results shed no light on this question, because they were not stratified by sex or age.

The percentage activity of amikacin, gentamicin, and tobramycin remained constant against all bacteria detected (roughly 80%, 70%, and 70%, respectively) but was much lower, especially for amikacin, when *E coli* alone was considered. Given their toxicity and parenteral administration, these antibiotics are not indicated for the treatment of uncomplicated UTIs and are limited to use in hospitals, where amikacin appears to be the best alternative to carbapenems among the aminoglycosides.[21]

Co-trimoxazole is not recommended for empiric treatment when the local resistance prevalence is >20%[23,26]; thus, it is not prescribed in Spain, where resistance rates >30% have been recorded.[10,13,24,27] It is frequently associated with beta-lactam antibiotic resistance in ESBL-producing isolates.[28] The global activity of co-trimoxazole in the present study (<50%) is considerably below the requirement for empiric use, and some authors have proposed its restriction to infections caused by uropathogens with demonstrated susceptibility to this antibiotic.[10]

Nitrofurantoin has conventionally been considered an excellent therapeutic option for uncomplicated cystitis in the United States[26] and in some southern European countries, where *E coli* isolates from urine have shown high resistance rates to fluoroquinolones and co-trimoxazole.[15] However, given the low parenchymatous levels achieved, nitrofurantoin is not useful for treating pyelonephritis.[24] Various studies have found a <10% rate of resistance to nitrofurantoin in *E coli*, including ESBL-producing isolates.[2,13,20,24] The global activity of this antibiotic on the uropathogens examined in the present study remained around 80%-85% of isolates throughout the 7-year period, whereas its activity against *E coli* alone was >95%. This difference is explained by the lower activity against other enterobacteria considered to be intrinsically resistant.

In general, fosfomycin has maintained excellent activity against the main community- and hospital-acquired uropathogens,[2,13] largely because it is used in UTIs alone and not in the veterinary setting, reaches high concentrations in urine (although not at a parenchymatous level), and is easy to dose. The CLSI recommends the use of fosfomycin solely in uncomplicated UTIs produced by *E faecalis* or *E coli*,[4] but fosfomycin also has demonstrated moderate activity against other gram-positive and gram-negative bacteria, especially ESBL-producing *E coli* isolates.[21] Thus, most published data, including our present results showing global activity rates >84%, endorse fosfomycin as a first-choice empiric treatment in mild and uncomplicated community-acquired UTIs.[10] This approach preserves antibiotics that are potentially useful in other indications, thereby reducing the risk of developing resistance.[28] Nonetheless, our present findings indicate a gradual but significant decrease in this activity, and an increase in resistance to this antibiotic has been reported in ESBL-producing *E coli* isolates,[20] possibly related to the increasing use of fosfomycin in the community in recent years.[29] If this trend continues, >20% of isolates may become resistant within the next 5-6 years, contraindicating this therapeutic option. Thus, it is crucial to maintain strict epidemiologic surveillance of resistance to fosfomycin, which can develop relatively quickly.[11]

The main limitation of the present study was our inability to retrospectively gather some key data for the correct interpretation of bacterial susceptibility and antibiotic activity, including patients' age, sex, and recent history of antibiotherapy. In addition, we were unable to establish whether UTIs were complicated or

uncomplicated, which is important information because microbiology laboratories receive a higher proportion of urine samples with complicated, recurrent, or treatment-resistant infections than samples with uncomplicated infections, which are usually treated empirically with a good outcome. Consequently, there may be some overestimation of uropathogen resistance.[10,30] Nevertheless, we believe that the results of our local, wide, and longitudinal study reliably reflect the evolution of antibiotic activity against these bacteria.

Our 2 main messages for professionals involved in infection control are (1) it is vital to maintain a record of changes in the susceptibility of UTI-producing bacteria to antibiotics, and (2) some of the antibiotics investigated in the present study are clinically useful in the empiric treatment of UTIs. The control of infection requires knowledge of the epidemiology of resistance to antibiotics, especially given the limitations in therapeutic options currently threatened by multiresistant staphylococci, glycopeptide- and fosfomycin-resistant enterococci, and gram-negative bacilli resistant to carbapenems and third-generation cephalosporins, among others. Informing the medical community about the evolution of these resistances over time, as seen in the present study, is crucial to support the adequate management of patients with these infections.

In conclusion, *E coli* was the most frequently isolated bacteria in our study of community- and hospital-acquired UTIs; however, other bacteria represented a large percentage of the etiologic agents detected, although the frequency of each was much lower. Thus, it is important to consider the resistance patterns of non—*E coli* bacteria when empiric antibiotic treatment is initiated. Imipenem, piperacillin-tazobactam, and, to a lesser extent, amikacin are good options for the empiric treatment of patients with hospital-acquired UTIs or requiring hospitalization, because they maintain high activity rates against the main uropathogens; however, certain antibiotics with resistance rates >30% (eg, cefuroxime, cefotaxime, ceftazidime, cefepime, gentamicin, tobramycin, cotrimoxazole, fluoroquinolones) should be limited to situations of demonstrated or highly probable susceptibility in the hospital or community setting and never used as first-line empiric treatment. Likewise, the decreased activity of amoxicillin-clavulanic acid suggests that it should not be used as first-line empiric treatment but rather as the preferred option in community cases of complicated UTIs with parenchymatous involvement or associated risk factors. Finally, antibiotics such as nitrofurantoin, and especially fosfomycin, can be first-choice treatments for community-origin uncomplicated cystitis, especially in women; however, the use of these antibiotics, especially fosfomycin, in empiric therapy may be called into question if resistance rates continue to rise.

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