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Editorial

Oral treatment of acute pyelonephritis: when, with which antimicrobial agent and for how long?

Tratamiento oral de la pielonefritis aguda: ¿cuándo, con qué antimicrobiano y durante cuánto tiempo?

Acute pyelonephritis (APN) is one of the most common community-onset infections and represents more than 600 admissions a year in a tertiary 1000-bed hospital.[1] Oral antibiotics are priceless to avoid the need for intravenous therapy and hospitalizations, but although many oral antibiotics have been proven to be effective in APN, comparative studies are scarce. In addition, the emergence of global antibiotic resistance complicates its treatment. During 2014 in our centre 23% of *Escherichia coli* isolates from community acquired APN were resistant to fluroquinolones (FQ) and 34% to trimethoprim-sulfamethoxazole (TRS). In patients with recurrent urinary tract infections (UTI) or recent antibiotic exposure (during the last 3 months) those percentages were 31% and 40%, respectively.[1]

Several international guidelines including the IDSA and Spanish guidelines state that FQ or TRS are the drugs of choice for APN treatment, and that oral beta-lactam antibiotics should be used with caution and for a longer period of time (10–14 days).[2–4] Although initial studies compared the elective antibiotics (mainly FQ) with aminopenicillins, a later study compared norfloxacin with ceftibuten and showed a higher bacterial relapse rate in the beta-lactam group (the causal strain was eradicated in 75% of patients in the ceftibuten group vs 89% of patients in the norfloxacin group).[5] A recent systematic review of randomized clinical trials of oral antibiotics for APN reviewed 277 studies and found only five studies in which adult patients were treated only with oral antibiotics (no initial intravenous therapy), with clinical and microbiological follow-up at 5–9 days and at 4–6 weeks posttreatment.[6] The clinical cure rates were comparable between beta-lactams (cefaclor, loracarbef) and FQ (84 to 95% at 5–9 days, and 83 to 95% at 4–6 weeks post-treatment), but the microbiological cure rates were higher in the FQ group (85–94% for FQ vs 76% to 50% for beta-lactams at 5–9 days, and 72–87% for FQ vs 81% to 64% for beta-lactams at 4–6 weeks). For TRS, clinical success was 85% at 4–11 days and 78% at 22–48 days, and microbiological cure rates were 85% and 72%, respectively, percentages that increased to 96% and 92% in those cases with susceptible strains.[7] Evidence on lower UTI (cystitis) treatment also suggest that beta-lactams are less effective than FQ or TRS, and a longer period of antibiotic therapy is recommended (5 days for beta-lactams vs 3 days for FQ or TRS).[2,8]

Several reasons may explain why beta-lactam antibiotics might be less effective in the treatment of APN. Enterobacterales are able to penetrate into the uroepithelial cells and to remain quiescent forming a biofilm.[9] Therefore, antibiotics with intracellular and antibiofilm activity such as FQ or TRS may be more effective than beta-lactams. On the other hand, FQ and TRS have a high bioavailability, reaching after oral administration serum levels of 100% for FQ and 85–90% for TRS, whereas for beta-lactams serum levels are 10–25 times higher with the intravenous (IV) route than with the oral route. Ceftriaxone reaches a Cmax of 150 μg/ml after the administration of 1 g IV, in comparison to 4 μg/ml after 400 mg of oral cefixime and 4 μg/ml after 400 mg of oral cefditoren.[10] For cefuroxime, the Cmax is 100 μg/ml after a 1500 mg IV dose and 4–7 μg/ml after a 250–500 mg oral dose. The differences in serum peak levels between the intravenous and oral route have a direct impact on the percentage of time during the dosing interval that the free (nonprotein bound) antibiotic concentration remains above the MIC (*%T* > MIC), which is the pharmacokinetic/pharmacodynamic (PK/PD) parameter that better predicts the antibacterial effect of beta-lactams.

According to the IDSA guidelines,[3] a specific antibiotic is appropriate for APN empirical therapy if the prevalence of resistance in community uropathogens is not known to exceed a threshold of 10%. However, this recommendation is based on expert opinions and the evidence to support it is limited. We observed no differences in mortality according to whether the initial antibiotic treatment was adequate or not for APN (2.4% versus 2.8%)[1] and our impression is that there are also no differences in clinical outcome despite an inactive empirical antimicrobial treatment if it is tailored afterwards according to the uropathogen identification and the susceptibility results. Other authors have described the same clinical and microbiological outcomes despite discordant empirical treatment, even in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli (GNB).[11] A recent study in patients with APN treated empirically with cefuroxime showed that although time taken for fever defervescence after starting antimicrobial therapy was higher in the cefuroxime-resistant group than in the cefuroxime-susceptible group (51.5 vs 46 h, respectively), the clinical and the microbiological cure rates and the median duration of hospitalization were

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not significantly different between both groups.[12] Thus, we believe that to avoid an overuse of broad-spectrum antibiotics such as third generation cephalosporins or carbapenems the 10% resistant rate threshold should be reconsidered, at least in non-severe patients.

Besides, we know that relapse rates are significantly higher when definitive antimicrobial treatment is not adequate (37.1% vs 9.3% when definitive antimicrobial treatment is adequate; $P < 0.001$).[1] However, it is remarkable that in all studies on APN there is a not negligible percentage of relapses despite an adequate antibiotic therapy. The study published by Rodríguez-Gascón et al. provides interesting information on this issue.[13] They studied by means of PK/PD analysis using the Monte Carlo simulation and susceptibility data of clinical isolates form two recent studies, the adequacy of oral cephalosporins (cefuroxime axetil, cefixime and cefditoren) at different dosing regimens for uncomplicated APN treatment. They found that the likelihood of treatment success based upon the current breakpoints proposed by either EUCAST or CLSI is low. Only cefixime at a dose of 400 mg q12 h attained the PK/PD target. The results of this study arise some questions that should be pondered.

First, uropathogens' MIC values may differ between centres. Cefuroxime is the first choice for community-acquired APN treatment in our hospital and resistant rates of *E. coli* are higher than in the study by Rodríguez-Gascón et al.; among 105 *E. coli* isolates recovered from blood cultures of patients with a febrile UTI, 36% were resistant to cefuroxime according to EUCAST (MIC > 8 mg/ml),[14] 8% had a MIC of 8 mg/ml, 56% a MIC of 4 mg/ml and only 3% were highly susceptible (MIC ≤ 1 mg/ml) (unpublished data). Therefore, in our setting, since most of the strains have a MIC value close to the resistant breakpoint and considering the PK/PD data, the probability of clinical success would also be low.

Second, we are not sure how well antimicrobial breakpoints correlate with clinical response in APN treated with oral antimicrobials. In the case of Enterobacterales, EUCAST has published several clinical breakpoints that are only valid for isolates from lower UTI for cephalexin, trimethoprim and nitrofurantoin, but none of these agents have clinical breakpoints for isolates from systemic infections.[14] Fosfomycin, cefuroxime and third generation cephalosporins have specific breakpoints for oral and intravenous formulations, but oral formulations only have clinical breakpoints for lower UTI. In 2014, EUCAST introduced a urinary susceptibility breakpoint for amoxicillin-clavulanic acid of ≤32 mg/L (amoxicillin concentration plus a fixed (2 mg/L) concentration of clavulanic acid) for uncomplicated UTI.

Some authors suggest that despite there is a high number of patients with UTIs caused by strains with MICs that are close to the resistant breakpoint of a specific antibiotic, a significant number of patients are going to be cured when treated with this antibiotic.[4] However, clinical studies are needed to be sure that these cases do not have lower cure rates than patients infected with highly susceptible strains. Although we have the impression that this group of patients might have more relapses, especially in the cases of APN, we do not have studies to support it. For example, in our centre, where most UTI isolates have a cefuroxime MIC close to the resistant breakpoint, switching to third generation cephalosporins could be an alternative, with a much better PK/PD profile according to the study of Rodríguez-Gascón et al., but it might also result in an increase of the percentage of ESBL-producing Enterobacterales. However, second generation cephalosporins are also a risk factor for ESBL-producing GNB. In an Israeli study the independent risk factors for development of infections by ESBL-producing bacteria in the community setting were previous hospitalization in the past 3 months (OR = 8.95), antibiotic treatment in the past 3 months (OR = 3.23), age over 60 years (OR = 2.65), diabetes (OR = 2.57), male gender (OR = 2.47), *Klebsiella pneumoniae* infection (OR = 2.31), previous use of third-generation cephalosporins (OR = 15.8), previous use of second-generation cephalosporins (OR = 10.1), previous use of quinolones (OR = 4.1), and previous use of penicillin (OR = 4.0).[15] In the multivariate analysis of another Spanish case-control study, only previous exposure to oral cefuroxime was strongly associated with community-onset UTI due to ESBL-producing *E. coli* (OR = 21.42).[16] In fact, in our hospital, there has been an increase in the frequency of infections due to ESBL-producing bacteria from 6–7% in 2006–2008 to 19% in *E. coli* and 23% in *Klebsiella* spp. in 2019 (unpublished data), and this has happened in parallel with the progressive increase in the use of cefuroxime, mainly for UTI.

Third, the optimal antimicrobial dose might be influenced by patient's weight. Since there are no comparative studies, for overweight patients we tend to use higher doses of FQ (ciprofloxacin 750 mg q12 h or levofloxacin 750 mg q24 h) and TRS (160/800 mg, 1.5–2 tablets q12 h), particularly in complicated cases such as an acute focal bacterial nephritis or a renal abscess. In this sense and considering the PK/PD data, cefixime 400 mg q12 h could be the best beta-lactam oral option.

Therefore, before selecting an oral therapy for APN, there are some considerations. If oral treatment is started empirically (for example in outpatients), local epidemiology should guide the choice. For hospitalised patients, it seems reasonable to wait for the antimicrobial susceptibilities results or at least for a clear clinical improvement before changing from IV to oral route. In addition, the antimicrobial spectrum of each antibiotic alternative, the risk of colonization by ESBL-producing bacteria and the risk of *Clostridioides difficile* infection (CDI) should be pondered. In a retrospective multicenter study of CDI, prior antibiotic use was the dominant risk factor, and the highest-risk antibiotic was cefuroxime (OR = 6.4), followed by ceftriaxone (OR = 4), FQ (OR = 3), and TRS (OR = 2).[17] Besides, patients' weight may influence our choice, as well as the clinical picture, since in the presence of pus (like in abscesses) or debris, TRS may lose its efficacy due to a high thymidine input.[18] Considering all these points, for a patient with an uncomplicated APN our order of oral antibiotic preferences would be TRS, FQ, and, lastly, beta-lactams. If an oral beta-lactam is needed, considering the susceptibility of uropathogens in our community, the PK/PD data, the risk of colonization by ESBL-producing bacteria, the risk of CDI with both second and third generation cephalosporins, and our experience in daily practice, we would rather prefer to use cefixime 400 mg q24 h or q12 h depending on the weight of the patient. We agree with the Spanish guidelines[8] that cefuroxime should be reserved to treat highly susceptible strains and if used, high doses (500 mg q8 h with meals) may be preferable.

Finally, apart from the above concerns about the best oral antibiotic choice for APN treatment, it is not known for sure which is the optimal duration of the antibiotic therapy, since strong evidence is lacking. The duration of treatment should be adjusted according to the disease severity and the treatment response. Based on old studies, the IDSA and Spanish guidelines[3,4] recommend a 7-day course of ciprofloxacin (500 mg q12 h) or levofloxacin (500 mg q24 h) or a 5-day course of levofloxacin (750 mg q24 h) for uncomplicated, non-severe, and rapidly responding APN. For patients with severe disease or slow clinical response 10 days of FQ are recommended; for complicated cases such as patients with an acute focal bacterial nephritis or a renal abscess the recommendation is 3 and 4–6 weeks of FQ, respectively.

For TRS, a 14-day course at a dose of 160/800 mg q12 h is recommended, based in a study performed in 2000.[7] However, the Spanish guidelines suggest that 10 days could be enough in uncomplicated cases.[4] Recently, one study compared 81 patients that received a 7-day course of TRS, at standard doses, with 191 that received a 7-day course of ciprofloxacin 500 mg q12 h, and the likelihood of a recurrent UTI within 30 days of treatment was similar.[19] This data favours a shorter duration of TRS for uncomplicated APN

cases with rapid clinical improvement[20] and, in fact, it is our usual approach.

For beta-lactams, no comparative studies are available; while some authors suggest a 7–10-day course of antibiotic therapy,[4,20] others recommend 10–14 days.[2,3] Two recent observational studies with each of these regimens have shown similar outcomes. One study that included 328 patients treated with cefuroxime for a median of 7 days observed a microbiological cure rate of 93% at 7–14 days of follow-up,[12] and in another study that compared a 14-day course of cefuroxime versus cefotaxime followed mainly by oral FQ the microbiological cure rates were comparable (88% vs 95%).[21] Until further prospective studies are available, we prefer to use beta-lactams for 10 days in patients with a short duration of symptoms before starting treatment and with a rapid clinical response, and to prolong treatment (14 days) if the clinical response is slow. If beta-lactams are used for the treatment of acute focal bacterial nephritis, prolonged parenteral antibiotic therapy is recommended until data on the efficacy of oral therapy is available.

In summary, for the therapy of uncomplicated APN, a 10-day course of TRS or 7 days of a FQ may be reasonable options if the UTI isolate is susceptible. Beta-lactams should be used with caution, particularly in those cases with MICs close to the resistant breakpoint, and patients should be followed-up closely to detect relapses. In these circumstances, cefixime is probably the best option. Further randomized prospective studies are needed to clarify if beta-lactams might be a first-line oral option for APN patients.

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Conflict of interest

The authors certify that there are no potential conflicts of interest regarding this study.

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