

Recurrent lower urinary tract infections in adults: don't think it's *E. coli*, don't choose ciprofloxacin to treat

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by Jurałowicz et al,
see p. 373

Urinary tract infections (UTI) remain the key morbidities in the general population, with a lifetime risk in women exceeding 60% (and less than 10% in men). Annual incidence of UTI in adults may be as high as 12% for women and 3% for men.¹ These figures become even higher in older adults, and become a true and worrisome epidemics in residents of the long-term care facilities (LTCF); in addition, catheter-associated UTI represent up to 40% of all hospital acquired infections.² My personal view is that—although highly prevalent by their nature—UTIs are in addition overdiagnosed (misdiagnosed) and several patients are unnecessarily treated with antibiotics just because of unspecific urine sediment abnormalities, asymptomatic bacteriuria, or even proteinuria. Urinary tract infections undergo progressive changes in epidemiology, clinical course, and approach to treatment due to rapid changes in their microbiology, patient characteristics, and increasing resistance of microorganisms to available antibiotics; lack of breakthrough discoveries in an antibiotic research makes the treatment of UTI increasingly difficult.³ Since both microbiology of UTI and the bacterial susceptibility to antibiotics are the moving targets, medical community needs to be updated with data that illustrate the current trends in these issues to successfully treat UTI.

The study by Jurałowicz et al⁴ provides us with an insight into the microbiology of UTI in a large group of patients with urine cultures. The study sample is unique since authors were able to select patients with recurrent lower UTI referred to a large academic center. In addition, they managed to identify 2 groups of patients: with complicated and uncomplicated UTI (and consequently, 2 respective groups of cultures). The analysis excluded patients with high C-reactive protein concentrations and indwelled Foley catheter as well as those with very low estimated

glomerular filtration rate values—indeed, these patients are likely to seek medical attention in hospitals. Hence, the results are of great importance and interest mostly to those practitioners who see patients in community.

There are a few messages from this study that deserve special attention. The analysis which (except for mentioned above low glomerular filtration rate, bladder catheterization, and high C-reactive protein concentrations) applied no particular inclusion / exclusion criteria (ie, is representative for the community) demonstrated that older adults comprise a main age group that suffers from recurrent lower UTI. Thus, the ratio of women to men was 5:1, that is, with proportion of women being much lower as compared with younger age groups. Only 58% of all pathogens belonged to the gram-negative group of species, with *Escherichia coli* identified in only 39.6% of episodes (and even less, only 33.6%, in complicated recurrent lower UTI). The percentage of particularly resistant strains (that is, extended spectrum β -lactamase producing, high-level aminoglycoside resistance) within both gram-positive and gram-negative species varied between 6% and 30.2%. Probably the most important message from the study is that resistance to fluoroquinolones was very high, ranging between 39.9% for *E. coli* to 93.2% for *Enterococcus faecalis* (the results were roughly similar in case of cotrimoxazole). On the other hand, high susceptibility to such oral agents as fosfomycin, nitrofurantoin, and cefuroxime was observed in case of *E. coli*, and to ampicillin, amoxicillin and nitrofurantoin for *E. faecalis* (most frequently found gram-positive strain).

The 2 key messages for the everyday practice are: forget about *E. coli* and forget about ciprofloxacin! More precisely, remember about *E. coli*, but stop thinking that most of UTIs are caused by this species (especially in older adults with recurrent

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UTI). With regard to ciprofloxacin, the data published by Jurałowicz et al⁴ clearly demonstrate that the leading species infecting the lower urinary tract are susceptible to this agent in around 50% if gram-negative, and are almost completely resistant if gram-positive.

It becomes increasingly difficult to publish universal guidelines on the empirical treatment of UTI. The landscape is changing so fast (mostly due to the changing bacterial spectrum and susceptibility to antibiotics) that it seems that only website-based, continuously updated living guidelines, such as UpToDate or UK-NICE are capable to reflect the changes. Notably, experts advise that practitioners prescribing drugs for UTI should be aware of the resistance of bacterial species to antimicrobial agents in their communities (ie, local microbiology labs). For example, the antibiotic can still be prescribed in lower UTI as an empirical treatment if local resistance to it does not exceed 20%, and in case of acute pyelonephritis, if not higher than 10%.^{5,6} While writing this comment I made a private investigation and made a few phone calls to general practitioners in my region, asking if they are familiar with the resistance / susceptibility data of most frequent pathogens infecting urinary tract in their practices and whether they follow such an information while prescribing antibiotics. Guess the answers...

What was not mentioned by Jurałowicz et al,⁴ but is important, is the series of warnings published by regulatory authorities, that is, the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) regarding ciprofloxacin and other fluoroquinolones. These warnings are essentially identical and state that fluoroquinolones may increase the risk of such severe events as: QT prolongation and torsade de pointes ventricular tachycardia, tendonitis and tendon rupture (in particular, the Achilles tendon), seizures and delirium, peripheral neuropathy, retinal detachment, and aortic aneurysm dissection (in addition to previously well-known hypersensitivity reactions, diarrhea, and the risk of infection caused by *Clostridioides difficile*, formerly *Clostridium difficile*). The risks are particularly high in older adults, and—when considering tendon complications—in those who take steroids. There is no direct relationship between the dose of fluoroquinolone, duration of treatment or time span between drug use / discontinuation and the onset of the abovementioned complications. For example, Achilles tendon rupture may develop within 48 hours of starting treatment but also after several months following its discontinuation. Based on their adverse event profile, the FDA and the EMA state that the potential benefits of using these drugs may be outweighed by their side effects; thus they must not be used in the treatment of any infection unless no alternative treatment is available.⁷⁻⁹ The FDA and the EMA warn that fluoroquinolones should not be used for the treatment

of UTIs that do not exceed the urinary bladder (relatively good prognosis of lower UTI does not justify the risk of using these drugs). I am afraid the mentioned warnings are not yet widely observed by the medical community worldwide.

Except for treatment in humans, fluoroquinolones are extensively used in the veterinary medicine and in intensive livestock farming (animal husbandries). A widely cited study published recently reported that 47% of dust samples obtained from barns (especially those housing pigs and broilers) contained fluoroquinolones. The same source also contained *E. coli* that was antibiotic-resistant in 22% of cultures. Since barn emissions contaminate the air, surfaces, water, and plants, the environmental exposure of humans to fluoroquinolones (and possibly to resistant bacteria) should be taken into account as an important factor contributing to bacterial resistance (in addition to overuse in medical practice). Although fluoroquinolones used in veterinary medicine and farming are different from those applied in humans, the cross-resistance of bacterial strains against different antibiotics from the same therapeutic group is a common phenomenon (and in addition, one of the popular vet fluoroquinolones is metabolized to ciprofloxacin).¹⁰

Data that were apparently possible to obtain but are missing in the study of Jurałowicz et al⁴ include the residence status of older adults analyzed in the study (median age of the studied group was 65 years with 60.8% being above median). This would be of paramount importance since several publications suggest high prevalence of recurrent UTI among residents of the LTCF, reaching even 20% in some reports. UTI remain the second most frequent indication for antibiotic treatment in this patient group (with respiratory infections as a leading indication).² The antibiotic consumption in those patients is very high—it has been reported that 4% of LTCF residents (at any time point) use antibiotics: 88% for documented infection and 12% as prophylaxis (in 29% and 50% of users, respectively, for treatment and prophylaxis of UTI). A cited survey found that 25% of antibiotics used in LTCF were fluoroquinolones.¹¹ Thus it would be very interesting to look at the clinical characteristics and microbiology of recurrent lower UTI in relation to the place of residency (ie, living alone vs LTCF) in Poland.

One more short comment: according to the data obtained by Jurałowicz et al,⁴ fosfomycin seems to be the great drug to treat lower UTI. It is very convenient to use in an ambulatory care and many common gram-negative species are susceptible to it (the same holds true for nitrofurantoin). But one should remember that both drugs share also another feature—they penetrate to renal parenchyma poorly and thus must not be used for the treatment of acute pyelonephritis (ie, should be restricted only for the treatment of lower UTI).¹²

In summary, the analysis of Jurałowicz et al⁴ contributes significantly to the current body of knowledge on microbiology and antibiotic susceptibility of microorganisms infecting the urinary tract and resulting in recurrent lower UTI. The study should be read carefully and its results adopted in everyday practice by practitioners who deal with patients with UTI, especially older adults in ambulatory care.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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