# 14. KONGRES FARMAKOLOGA I 4. KONGRES KLINIČKE FARMAKOLOGIJE SRBIJE
sa međunarodnim učešćem

# 14th SERBIAN CONGRESS OF FARMACOLOGISTS AND 4th SERBIAN CONGRESS OF CLINICAL PHARMACOLOGY
with international participation

*Organizator*
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## GENDER-RELATED DIFFERENCES IN GASTROINTESTINAL ADVERSE EFFECTS AFTER MYCOPHENOLIC ACID THERAPY IN RENAL TRANSPLANT RECIPIENTS

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The most immunosuppressive regimens include mycophenolic acid (MPA) after renal transplantation, which is associated with gastrointestinal (GIT) adverse effects. The objective was the evaluation of GIT adverse effects within renal transplant recipients under MPA treatment with respect to gender. This research was performed in 77 Serbian renal recipients who received MPA, prednisone and Tacrolimus or Cyclosporin A. The patients were treated in the Clinic of Nephrology (Clinical Center of Nis, Serbia). The MPA trough concentration in human plasma was determinated by validated high performance liquid chromatography method. In order to observe gastrointestinal adverse effects of MPA, we used an adverse effect scoring system developed by nephrologists within the University of Buffalo Nephrology/Transplant Program. This study showed that 57% of stable renal transplant recipients experienced gastrointestinal symptoms, even when they received a proton pump inhibitor or ranitidine. The obtained data showed that women had a statistically higher MPA dose and MPA plasma trough concentration compared to male renal recipients (990mg ± 304.92 vs 849.06mg ± 212.91; p=0.044 and 4.31μgmL$^{-1}$ ± 3.19 vs 2.71μgmL$^{-1}$ ± 2.26; p=0.037, respectively). Female patients demonstrated higher gastrointestinal adverse effects score within the same MPA dosing regimens and this was particularly evident for the occurrence of diarrhea (41.7 vs 17.0; p=0.038). Women had statistically higher MPA dose and concentrations compared to the men and demonstrated higher GIT score within the same MPA dosing regimens. Gender differences in MPA pharmacokinetic could be accounted for by adjusting doses in order to minimize the adverse effects and improve graft outcomes.

## UTICAJ JONA BAKRA NA ANTIBAKTERIJSKU AKTIVNOST B-LAKTAMSKIH ANTIBIOTIKA

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Joni bakra mogu uticati na aktivost antibiotika stupajući u redoks i koordinativne interakcije i dovesti do izmenjene antibakterijske aktivnosti.
Cilj rada je analiza interakcije jona bakra i β-laktamskih antibiotika (penicilin G, ampicilin, amoksicilin, cefaleksin, cefaklor, ceftazidim, ceftriakson i meropenem) i posledičnih promena inhibitornih efekata antibiotika na sojevima *Escherichia coli* i *Staphylococcus aureus*.
Korišćene su sledeće tehnike: UV/vis spektrofotometrija, EPR spektroskopija, polarografija, ciklična voltametrija i test za određivanje minimalne inhibitorne koncentracije antibiotika.
Penicilin G ne stupa u interakcije sa $Cu^{2+}$. Ampicilin, amoksicilin i cefaleksin grade oktaedraelni kompleks tetragonalne distorzije sa jonom bakra pomoću primarne amino grupe bočnog lanca i dovode do porasta koncentracije rastvorljivog $Cu^{2+}$ u fosfatnom puferu. Slične geometrije je i kompleks ceftazidima i $Cu^{2+}$, a samo vezivanje se verovatno odigrava preko atoma kiseonika u deprotonovanoj karboksilnoj grupi cefalosporinskog prstena što je praćeno stvaranjem organskog radikala. Iz EPR spektra ceftriakson-$Cu^{2+}$ zaključujemo da je kompleks drugačije geometrije od prethodno pomenutih. Svi ispitivani kompleksi su 1:1 stehiometrijskog odnosa. Cefaklor redukuje $Cu^{2+}$ do $Cu^{1+}$ koji potom reaguje sa kiseonikom i dovodi do stvaranja vodonik peroksida, dok se meropenem razgrađuje u prisustvu $Cu^{2+}$. Analizom minimalne inhibitorne koncentracije na sojevima *E. coli* i *S. aureus* uočava se da prisustvo $Cu^{2+}$ slabi antimikrobni potencijal ampicilina, amoksicilina, ceftriaksona i meropenema, dok je delovanje cefaleksina i cefaklora blago poboljšano.
Imajući u vidu da je koncentracija jona bakra u infektivnim stanjima povišena, opisani *in vitro* mehanizmi interakcija $Cu^{2+}$ sa β-laktamskim antibioticima upućuju na oprez prilikom primene pomenutih antibiotika.

## THE IMPACT OF COPPER IONS ON ANTIBACTERIAL ACTIVITY OF B-LACTAM ANTIBOTICS

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Copper ions can affect antibiotics via redoxs reactions or by formation of coordinative bonds and consequently lead to changes in antibacterial activity.
The aim of this study was to analyze interactions of copper ions with β-lactam antibiotics (penicillin G, ampicillin, amoxicillin, cephalexin, cefaclor, ceftriaxone, ceftazidime and meropenem), and the resulting impact on the antimicrobial activity of the mentioned antibiotics against *Escherichia coli* and *Staphylococcus aureus*.

The experiments were conducted using the following methods: UV/vis spectrophotometry, electron paramagnetic resonance spectroscopy, cyclic voltammetry, polarography and determination of antibiotic inhibitory concentration on selected bacterial strains.
Penicillin G does not interact with $Cu^{2+}$. Ampicillin, amoxicillin and cephalexin form stable complexes with $Cu^{2+}$ with octahedral coordination environment and tetragonal distortion with the primary amine group on the side-chain as the site of the coordination. These three antibiotics increase the solubility of $Cu^{2+}$ in the phosphate buffer. Ceftazidime and $Cu^{2+}$ form a complex with a similar geometry, $Cu^{2+}$ binds to cephalosporin ring which has deprotonated carboxyl group and leads to radical formation. EPR spectar of ceftriaxone- $Cu^{2+}$ complex implies that the complex might have a diffrent geometry compared to previously described. All complexes showed 1:1 stoichiometry. Cefaclor reduces $Cu^{2+}$ to $Cu^{1+}$ that further reacts with molecular oxygen and produces hydrogen peroxide; while meropenem underwent degradation in the presence of copper. The analysis of the minimum inhibitory concentration against *E. coli* and *S. aureus* showed that the effects of ampicillin, amoxicillin, ceftriaxone and meropenem were significantly hindered in the presence of copper ions, while the effects of cephalexin and cefaclor were slightly increased.
Having in mind that copper is mobilized in infections, the described mechanisms of copper interactions with β-lactam antibiotics call for caution in the application of these antibiotics.

## *IN VIVO* PRIMENJIVOST FARMAKODINAMSKIH DETERMINANTI RAZVOJA REZISTENCIJE NA ANTIBIOTIKE

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Jedna od predloženih farmakodinamskih mera, razvijena za usporavanje razvoja otpornosti prema antibioticima, koja opisuje odnos između farmakodinamike antibiotika i razvoja resiztencije je tkz. prozor selekcije rezistentnih sojeva (PSR). CIlj ovog rada je da se opiše concept PSR sa osvrton na klinički značaj i primenjivost. Pretraživanje PubMed baze pomoću različitih ključnih reči dalo je 450 rezultata, nakon provere naslova i 181 sažetaka, 84 članaka u punom tekstu uključeno je u istraživanje. Koncept PSR je prvobitno ispitan za fluorhinolone, 1999. godine, a potom i za beta-laktame, polimiksine, makrolide i aminoglikozide, *in vitro*. Unutar osetljive bakterijske populacije izložene antibioticima, deo ćelija ostaje nepogođen dejstvom antibiotika. Umnožavanje ove otporne subpopulacije odvija se u rasponu koncentracija između minimalne inhibitorne koncentracije (MIK) osetljivih ćelija i MIK-a najmanje osetljive subpopulacije, koja se naziva koncentracija prevencije rasta rezistentnih sojeva (MPK). Ovaj raspon koncentracija odgovara prozoru selekcije rezistentih sojeva (PSR). Tradicionalni režimi doziranja često daju antibakterijske koncentracije unutar PSR-a, omogućavajući selektivno umonažavanje rezistentnih bakterija. Za fluorohinolone, PSR određen *in vitro* primenjiv je za optimizaciju režima doziranja u cilju smanjenja mogućnosti razvoja rezistencije i u kliničkim uslovima. Potrebna su dalja istraživanja kako bi se utvrdila *in vivo* primenljivost PSR za druge grupe antibakterijskih lekova.

## *IN VIVO* APPLICATION OF PHARMACODYNAMIC DETERMINANTS OF ANTIBIOTIC RESISTANCE DEVELOPMENT