# Neželjeni učinci lijekova u hitnoj medicini

# Side-effects of Medications in Emergency Medicine

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**SAŽETAK:** Rizični čimbenici za razvoj neželjenih događaja vezanih uz lijekove jesu polifarmacija, komorbiditetne bolesti, starija životna dob i ženski spol. Bubrezi su nezaobilazan organ u odstranjenju ksenobiotika, kao i produkata staničnog metabolizma. Bubrezima se izlučuju brojni lijekovi. U slučaju bubrežnog oštećenja nastaju problemi u vezi s izlučivanjem lijekova, čime se povećava koncentracija aktivnih tvari u krvi s mogućnošću neželjenih učinaka lijekova u bolesnika s kroničnom bolesti bubrega. Najčešći uzrok neželjenih učinaka lijekova, prema Rawlins-Thompsonovoj klasifikaciji, jest tip A ili tip ovisan o dozi. Riječ je o neprilagođenoj dozi lijeka, što je moguće prevenirati jer su farmakokinetika i farmakodinamika poznate. Neželjeni učinci lijekova mogu uzrokovati znatne troškove za zdravstveni sustav i rastući su problem s obzirom na sve stariju populaciju s komorbiditetnim bolestima.

**SUMMARY:** The risk factors for adverse drugs reactions are polymedication, comorbidities, old age, and female sex. Kidneys are the most important organs in the excretory system, especially for clearance of xenobiotics and products of cell metabolism. Kidney insufficiency leads to the accumulation of active metabolites of many drugs in blood and can cause drug toxicity. In patients with chronic kidney disease, it is very important to pay attention to side effects. The most common cause of inappropriate drug dosage is type A according to the Rawlins-Thompson classification. Type A or dose-related side-effects is preventable by applying the correct dosing of medications. Side-effects of drugs represent a large problem due to the cost of treatment and are very common in the senior population with comorbidities.

**KLJUČNE RIJEČI:** neželjeni učinci lijekova, kronična bolest bubrega, kardiovaskularni komorbiditeti.

**KEYWORDS:** adverse drugs reactions, chronic kidney disease, cardiovascular comorbidities.

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Rawlins-Thompsonova klasifikacija neželjene događaje vezane za lijekove najčešće razvrstava u dva tipa: A i B. Tip A uključuje reakcije povezane s dozom lijeka, odnosno, što je doza lijeka veća, može uzrokovati veći neželjeni događaj. Tip A povezan je s farmakodinamikom lijeka. Tip B karakteriziraju neočekivane reakcije koje ne možemo predvidjeti farmakodinamikom lijeka i nisu ovisne o dozi.[1] Rjeđi oblici uključuju tipove C, D i E. Obilježje kroničnog tipa ili tipa C jest pojavnost reakcije nakon uzimanja lijeka tijekom duljeg vremena. Tip D (zakašnjeli tip) nastaje nakon završetka ekspozicije lijeka. Obilježje reakcije prema tipu E jest pojavljivanje nakon što se prestane uzimati lijek.[2] Podjela neželjenih događaja (engl. *adverse event*) prilikom primjene lijekova (ADR, prema engl. *adverse reaction of*

The Rawlins-Thompson classification usually classifies adverse drug reactions into two types: A and B. Type A includes reactions associated with medication dosage, with larger doses having the potential to cause more significant adverse events. Type A depends on the pharmacodynamics of a particular medication. Type B adverse drug reactions are characterized by unexpected reactions that cannot be predicted by examining the pharmacodynamics of a drug and are not dose-dependent.[1] Rarer adverse drug reactions comprise types C, D, and E. The characteristic of the chronic type, i.e. type C, is the development of the adverse reaction after the medication has been taken for a longer period. Type D (delayed type) takes place after exposure to the medication has ended. The characteristic

*drugs*) prema tipovima korisna je, no nije potpuna jer postoji mogućnost preklapanja reakcija. Stoga je razvijena tehnika ovisna o dozi (engl. *dose-related*), gdje se ovisnost o dozi promatra prema krivulji. Smatra se da je ADR prihvatljiva kada je doza u terapijskim vrijednostima. ADR i preosjetljivost pojavljuju se kada je doza manja od terapijske. Toksičnost lijeka nastaje kada je doza veća od terapijske. Gledajući vremensku pojavnost, razlikujemo sljedeće ADR: brzonastupajuće, koje nastaju pri prvoj dozi lijeka, rane ADR, srednjeg nastanka, kasnog nastanka i zakašnjele ADR. Osjetljivost bolesnika na ADR ovisi o dobnoj skupini, spolnoj pripadnosti, interreakcijama lijekova (DDR, prema engl. *drug-drug reaction*), epigenetskim obilježjima i komorbiditetima, a istodobno uzimanje različitih lijekova znatno pridonosi višem riziku od potencijalnih problema vezanih za lijekove (DTP, prema engl. *drug therapy problems*).[3] Potencijalno neželjeni učinci ili događaji uz primjenu lijekova česti su upravo u bolesnika s kroničnom bubrežnom bolesti (KBB) koji najčešće umiru od kardijalnog uzroka, odnosno iznenadne srčane smrti prije nego se u njih razvije završni stadij KBB-a i započnu s nadomjesnim bubrežnim liječenjem. Osnovni cilj liječenja bilo koje kronične nezarazne bolesti pa tako i KBB-a jest omogućiti kvalitetu života, usporiti ili zaustaviti daljnje pogoršanje oštećenja funkcije organa, u slučaju bubrežne bolesti praćenjem glomerularne filtracije (GF), te usporiti progresiju kardiorenovaskularnog remodeliranja. Problem nastaje kada se pri liječenju bolesnici koriste sve većim brojem različitih lijekova koji se eliminiraju bubrezima, a sniženje bubrežne funkcije uzrokuje i farmakološke promjene u dinamici i kinetici lijekova koji se izlučuju putem bubrega.[4] Stoga bi svako sniženje GF-a trebalo uključivati i prilagođivanje doze lijeka u svrhu prevencije neočekivanih nuspojava lijekova, kao i neželjenih događaja posebno u skupini bolesnika s KBB-om koji su skloni DTP-u.[4] Kronična bubrežna bolest neovisni je čimbenik rizika ne samo za kardiovaskularnu bolest nego i za ostale pridružene bolesti, poput infekcija koje često pogađaju stariju populaciju, što dodatno pridonosi nastanku DDR-a i potenciranje mogućih DTP-a, posebice u kombinaciji antimikrobnih lijekova, oralnih antikoagulantnih lijekova i lijekova protiv boli poput nesteroidnih antiinflamatornih lijekova (NSAIL).[5,6]

## Učestalost neželjenih učinaka lijekova u hitnoj medicini i tijekom hospitalizacije

Istraživanja navode kako su ADR prema uzroku smrtnosti svrstani na visoko peto mjesto, s pojavnošću između 5 i 10 % među ukupno hospitaliziranim bolesnicima.[7] Pojavnost ADR-a u osoba mlađih od 18 godina iznosi 0,8 %, no povećava se s dobi, pa u osoba starijih od 80 godina iznosi 3,2 %.[8] Uzimanje sve više lijekova posebno u starijoj životnoj dobi zbog prisutnih komorbiditeta vodi polifarmaciji, a to je dodatni čimbenik koji pridonosi ADR-u.[7,8] Danas je poznato da su rizični čimbenici za nastanak ADR-a polifarmacija (svakodnevno uzimanje više od 5 različitih lijekova u populaciji, no za bolesnike s popuštanjem srca i bubrežnom bolešću preporučuje se definicija koja uključuje više od 10 lijekova na dan), starija dob, ženski spol i pridružene komorbiditetne bolesti.[3] Smatra se da su ADR u modernome društvu odgovorni za sve veći broj nepotrebnih hospitalizacija i visokih troškova liječenja.

U radu Giardina *i sur.* broj komplikacija uzrokovanih ADR-om tijekom hospitalizacije (unutarbolnički ADR) i broj hitnih hospitalizacija zbog ADR-a uspoređen je s bolesnicima koji

of type E is that the adverse reaction manifests after treatment with the drug has ended.[2] This classification of adverse events during adverse drug reactions (ADR) is useful but incomplete, since the reactions can overlap. Consequently, a dose-related technique was developed, where dose dependence is defined based on a curve. ADR is considered acceptable when the dose is within treatment values. ADR and over-sensitivity are present when the dose is lower than the treatment dose, whereas drug toxicity is considered to be present when the dose is higher than the treatment value. With regard to time-dependence, we can distinguish the following types of ADR: rapid onset ADR, appearing at the first dose of the medication, early onset ADR, moderate time-to-onset, late onset, and delayed ADR. Sensitivity of patients to ADR depends on the age group, sex, drug-drug reactions (DDR), and epigenetic characteristics and comorbidities, with simultaneous use of different drugs significantly contributing to higher risk of potential drug therapy problems (DTP).[3] Potentially adverse effects or events with the use of medications are particularly common in patients with chronic kidney disease (CKD), in whom death most often has a heart-related cause, namely sudden cardiac death before the development of the final stages of CKD and before kidney replacement treatment has been initiated. The basic goal in the treatment of any chronic, non-infectious disease, including CKD, is enabling quality of life, slowing down or preventing further deterioration of organ functions, which in the case of the kidneys means monitoring glomerular filtration (GF) rate, and slowing down the progression of cardiac and renovascular remodeling. Problems arise when physicians introduce more and more different medications that are all eliminated via the kidneys, with reduced kidney function also causing pharmacological changes in the dynamics and kinetics of the drugs excreted via the kidneys.[4] Every reduction in GF should thus also result in adjustment of drug dosage in order to prevent unexpected side-effects as well as adverse events, especially in the population of patients with CKD, who are prone to DTP.[4] Chronic kidney disease is an independent risk factor not only for cardiovascular diseases but for other associated diseases as well, such as infections that often effect the older population, which additionally contributes to the development of DDR and exacerbates potential DTP, especially in combination with antimicrobial drugs, oral anticoagulant drugs, and analgesics such as non-steroidal anti-inflammatory drugs (NSAID).[5,6]

## Frequency of adverse drug effects in emergency medicine and during hospitalization

Studies have found that ADR are the fifth most frequent cause of death, with an incidence between 5% and 10% in hospitalized patients.[7] The incidence of ADR in persons below the age of 18 is 0.8%, but it increases with age and is 3.2% in persons above 80 years of age.[8] Taking more and more different drugs at an older age due to comorbidities leads to polypharmacy, which is an additional factor that contributes to ADR.[7,8] It is now known that the risk factors for the development of ADR are polypharmacy (daily intake of 5 different drugs in the general population, but definition of more than 10 different medications per day is recommended for patients with heart failure and kidney disease the), older age, female sex, and comorbidities.[3] It is believed that ADR are responsible for a growing amount of unnecessary hospitalization and high treatment costs in modern society.

nisu imali ADR.[7] Prevalencija unutarbolničkih ADR-a iznosila je 3,2 %, dok je prevalencija ADR-a u hitnoj službi koji su bili razlog bolničkog liječenja iznosila 6,2 %. U objema skupinama čimbenici povezani s ADR-om bili su ženski spol i polifarmacija. U populaciji hospitaliziranih bolesnika ADR su od najrjeđih prema najčešćima kliničkim očitovanjima klasificirani kao kardijalni (11,5 %), generalni (13,4 %), vaskularni (13,4 %) i najčešći kožni (27 %) poremećaji. Lijekovi koji su uzrokovali ADR pripadali su od najrjeđih (kardiovaskularni lijekovi, antidijabetički lijekovi), lijekova iz skupine antihipertenziva (inhibitori renin-angiotenzin-aldosteronskog sustava / RAAS inhibitori i diuretika), do mnogo češćih koji su pripadali skupini antitrombotskih lijekova s učestalošću od 21,7 % te skupini antimikrobnih lijekova s najvećom učestalošću ADR-a od 38,2 %. U skupini lijekova antimikrobnoga djelovanja najčešće su bili primjenjivani kinoloni i penicilini. Klasifikacija ozbiljne ADR bila je u 46 % slučajeva, od kojih se 95 % bolesnika potpuno oporavilo. U bolesnika primljenih u hitnu službu ADR su bile najčešća posljedica neadekvatnog uzimanja lijekova zbog nerazumijevanja, nehotičnog uzimanja prevelike doze lijeka (pogreška u primjeni lijeka) ili bolesnikova namjernog uzimanja prevelike doze u svrhu zlouporabe. Najčešća klinička novonastala stanja, odnosno poremećaji očitovali su se na gastrointestinalnom (27,7 %) i hematološkom sustavu (26,5 %). Utvrđeno je također 18,1 % novonastalih metaboličkih i 16,1 % neuroloških poremećaja. Prema učestalosti slijede lijekovi iz skupina antitrombotskih (39 %), RAAS inhibitora (13,9 %), NSAIL-a (11,9 %) i diuretika (9 %). Potpuno se oporavilo u 87 % bolesnika, no 2,9 % bolesnika imalo je dugotrajne zaostale posljedice. U radu je navedeno da je od svih unutarbolničkih slučajeva ADR-a njih 69,4 % bilo moguće spriječiti, 24,2 % nije bilo nikako moguće predvidjeti, odnosno spriječiti, a njih 6,4 % bilo je preventabilno. U bolesnika hitno primljenih zbog ADR-a, u njih 63,9 % vjerojatno je bilo moguće spriječiti ADR, a 23,2 % slučajeva ADR-a sigurno su se mogli predvidjeti i spriječiti neželjeni događaj.[7] Drugi autori opisuju kako je većina bolesnika koja je pregledana u hitnim službama bila primljena zbog krvarenja, i to 8,6 % slučajeva, nakon čega su po učestalosti slijedile ADR (3,6 %), hipoglikemija (3,1 %), povišena temperatura bila je razlog u 2,8 % slučajeva, a slijede s 2,2 % agranulocitoza te naposljetku u 2,1 % slučajeva dehidracija.[8] Lijekovi koji su uzrokovali ADR bili su iz skupine antikoagulantnih lijekova (17,8 %), citostatika (14,8 %), diuretika (8,0 %), antidijabetika (4,4 %), salicilata (4,2 %) i antireumatika (4,1 %). U istraživanjima se navode različite incidencije ADR-a, kao i smrtnih ishoda vezanih za ADR (FADR, prema engl. *fatal adverse drug reaction*), ovisno o tome je li riječ o bolesnicima koji su primljeni putem hitne službe ili se nalaze na bolničkom liječenju. Incidencija FADR-a u populaciji bolesnika primljenih kroz hitne službe iznosi od 0,05 i 0,44 %, dok je unutarbolnički FADR bio 0,05 i 0,19 %.[9] Istraživanje provedeno u Švedskoj ističe učestalost FADR-a od 3,1 % te da je većina navedenih slučajeva uzrokovana krvarenjima. U navedenom je istraživanju najučestalija bila primjena lijekova iz skupine antitrombotskih lijekova i lijekova iz skupine NSAIL-a.[9] Rezultati istraživanja u Hrvatskoj koja su proveli Marušić *i sur.* o incidenciji ADR-a nakon otpusta iz klinike pokazali su pojavnost ADR-a od 30 % (72 od 209 bolesnika). U navedenom su istraživanju najčešća klinička očitovanja bila krvarenja zbog oralnih antikoagulantnih lijekova (varfarin) i niske razine glukoze (hipoglikemija) uzrokovane lijekovima iz skupine antidijabetika, od čega je 5 bolesnika imalo tešku

In a study by Giardina et al., the number of complications caused by ADR during hospitalization (in-hospital ADR) and the number of emergency hospitalizations due to ADR were compared to patients who did not have ADR.[7] The prevalence of in-hospital ADR was 3.2%, while the prevalence of ADR in emergency services which were the reason for hospitalization was 6.2%. Polypharmacy and female sex were factors associated with ADR in both groups. In the population of hospitalized patients, ADR were classified based on clinical manifestations from the least to the most common as follows: cardiac (11.5%), general (13.4%), vascular (13.4%), and skin disorders (27.0%) as the most common. The medications that caused ADR ranged from those that were least common (cardiovascular drugs, antidiabetic drugs), drugs from the antihypertensive group (renin-angiotensin-aldosterone system / RAAS inhibitors and diuretics), to those that resulted in ADR much more often, which included antiplatelet medication with a frequency of 21.7% and antimicrobial drugs with the highest ADR frequency of 38.2%. In the antimicrobial drug group, the most commonly applied drugs were quinolones and penicillin. Classification of serious ADR was present in 46% of cases, among which 95% of patients fully recovered. Of the patients admitted to the emergency room, ADR were most frequently the consequence of improper drug intake due to misunderstanding, accidental intake of an overly large dose (mistake in drug application), and patients deliberately taking a dose that was too large due to misuse. The most common newly-developed clinical conditions and disorders manifested in the gastrointestinal (27.7%) and hematological system (26.5%). 18.1% newly-developed metabolic disorders and 16.1% new neurological disorders were also found. Based on ADR frequency, the medications were from the antiplatelet group (39%), RAAS inhibitors (13.9%), NSAID (11.9%), and diuretics (9%). Total recovery was achieved in 87% of patients, but 2.9% had long-term lingering effects. The study states it would have been possible to prevent 69.4% of the total in-hospital ADR, 24.2% could not have been predicted or prevented in any way, and 6.4% were preventable. Among patients admitted to emergency services due to ADR, ADR likely could have been prevented in 63.9%, while 23.2% of ADR cases could have certainly been predicted and prevented.[7] Other authors have reported that most patients examined in emergency services were admitted due to bleeding, in 8.6% of cases, followed by ADR (3.6%), hypoglycemia (3.1%), elevated body temperature in 2.8% cases, agranulocytosis in 2.2% cases, and finally dehydration in 2.1% of cases.[8] The medications that caused ADR were from the group of anticoagulant drugs (17.8%), cytostatics (14.8%), diuretics (8.0%), antidiabetics (4.4%), salicylates (4.2%), and antirheumatics (4.1%). Studies have reported different incidence rates for ADR and fatal adverse drug reactions (FADR), depending on whether the study examined patients admitted through emergency services or those who were in hospital treatment. FADR incidence in the population admitted through emergency services was between 0.05% and 0.44%, whereas in-hospital FADR was 0.05 and 0.19%.[9] A study conducted in Sweden reported a FADR frequency of 3.1% and that most of these cases were caused by bleeding. In this study, antiplatelet drugs and NSAIDs were the most commonly used drugs among ADR cases.[9] The results of a study in Croatia conducted by Marušić et al. on the incidence of ADR after discharge from the clinic showed an incidence of ADR of 30% (72 out of 209 patients). In this study, the most common manifestations were bleeding due to oral anticoagulant drugs (warfarin) and low glucose levels (hypoglycemia) caused by an-

kliničku sliku.[10] U svim navedenim istraživanjima promatrana je pojavnost ADR-a u općoj populaciji, no što se događa u populaciji s KBB-om? Istraživanje Hellden *i sur.* promatralo je učinke ADR-a u skupini bolesnika s KBB-om.[11] Proučavano je 1425 osoba, korisnika kućne njege, dobne skupine od 65 i više godina. Njih 16 % pregledano je u bolnici, a 10,8 % (154) bilo je hospitalizirano. Od hospitaliziranih bolesnika u 14 % (22) primarni uzrok hospitalizacije bio je ADR. U 7 od 22 bolesnika s ADR-om (32 %) primjenjivani su lijekovi koji se ne preporučuju u KBB-u zbog kontraindikacije, pa je stoga posrijedi bila medicinska pogreška.[11] Najčešći simptomi i uzroci hospitalizacije bili su nizak tlak u stajanju (ortostatska hipotenzija), kao i vrtoglavica s neželjenim padovima u 5 bolesnika. Pojavnost krvarenja utvrđena je u 4 bolesnika, a konfuzno stanje i sediranost u 3 bolesnika, od čega je najčešće primjenjivani lijek bio tramadol. Bitno je znati da se tramadol i metaboliti (kao aktivni spojevi) izlučuju bubrezima. Stoga KBB produljuje poluvrijeme izlučivanja te povećava koncentraciju tramadola u plazmi i pojavnost ADR-a. Istraživanje je pokazalo kako su ženski spol, polifarmacija, starost viša od 80 godina i KBB čimbenici koji pridonose nastanku ADR-a.[11] U ispitivanoj skupini bolesnika s ADR-om prosječan broj lijekova bio je sedam, što ističe problem polifarmacije, na koji treba misliti posebno u skupini starijih bolesnika. Prosječna GF iznosila je 40 mL/min/1,73 $m^2$, odnosno kretala se unutar stadija G3b.[11] Većina ADR-a pripadala je tipu A, no opisana je jedna reakcija tipa B, anafilaktoidna reakcija na primjenu lijekova iz skupine inhibitora angiotenzin konvertirajućeg enzima (ACEI). Dodatni problem na koji upućuje ovo istraživanje jest da starija populacija ima sniženu bubrežnu rezervu, na što treba misliti pri odabiru lijekova. Druga činjenica proistekla iz ovog istraživanja jest da najveći broj u svakodnevici zbrinjavanja u hitnim službama, kao i u ambulantnim djelatnostima primarne, sekundarne i tercijarne zdravstvene zaštite čini populacija sve starijih osoba.[11]

U istraživanju koje je provedeno u Italiji, pratila se povezanost KBB-a i ADR-a tijekom hospitalizacije.[12] Istraživanje je zamišljeno tako da su starije bolesnike podijelili u 3 skupine ovisno o GF-u i razini serumskog kreatinina (K). Prva skupina ispitanika imala je vrijednosti GF i K unutar referentnih vrijednosti. Druga skupina imala je GF unutar referentnih vrijednosti, ali povećane vrijednosti K, te je nazvana skupinom s prikrivenim bubrežnim problemima. Treća skupina imala je snižene vrijednosti GF-a i povišen K, te je nazvana skupinom s KBB-om. Lijekovi topljivi u vodi (hidrosolubilni) uzrokovali su 301 slučaj ADR-a, dok su nehidrosolubilini uzrokovali 640 slučajeva ADR-a. Najčešći ADR zbog hidrosolubilnih lijekova bili su nizak tlak ili hipotenzija (uzrokovano lijekovima iz skupine RAAS sa 17,9 % i diureticima s 15,3 %), bradikardija (uzrokovana digitalisom 16,3 %), hipoglikemija zbog liječenja antidijabeticima u 13,9 % slučajeva i hipokalemija zbog liječenja diureticima. Slijede lijekovi s očitovanjem gastrointestinalnih simptoma (antitrombotski lijekovi s 8,0 %), usporenost i pospanost (uz psiholeptike, 7,6 %), simptomi glavobolje i hipotenzije zbog liječenja nitratima (13,7 %). Autori su pokazali da lijekovi topljivi u vodi povećavaju rizik od nastanka ADR-a u grupi bolesnika s prikrivenim bolestima bubrega s OR 1,78 za hidrosolubilne lijekove, u odnosu prema ostalim lijekovima s OR 0,92. Navedeno upućuje na to da hidrosolubilni lijekovi povećavaju rizik od pojavnosti ADR-a u toj skupini bolesnika.[12] Dodatni čimbenici rizika bili su pridružene bolesti, polifarmacija, kao i duljina hospitalizacije.[12] Dobne skupine

tidiabetic drugs, with 5 patients presenting a severe clinical picture.[10] All the studies described above examined the incidence of ADR in the general population, but what happens in the population of patients with CKD? A study by Hellden et al. examined the effects of ADR in a group of patients with CKD.[11] The study included 1425 persons receiving home care aged 65 and above. 16.0% were examined at the hospital and 10.8% (154) were hospitalized. Among the hospitalized patients, ADR was the primary cause of hospitalization in 14% (22). In 7 of the 22 patients with ADR (32%), medications had been administered that are not recommended for CKD, indicating medical error.[11] The most common symptoms and causes of hospitalization were orthostatic hypotension as well as vertigo with accidental falls in 5 patients. Incidence of bleeding was found in 4 patients, and a confused state and sedation was observed in 3 patients, with the most frequently administered drug being tramadol. It is important to know that tramadol and metabolites (as active compounds) are excreted through the kidneys. CKD thus increases excretion half-life and plasma concentrations of tramadol, as well as incidence of ADR. The study showed that female sex, polypharmacy, age over 80, and CKD are risk factors that contribute to the development of ADR.[11] The average number of prescribed medications in the group of patients with ADR was seven, which emphasizes the problem of polypharmacy that should be considered in treatment, especially in the population of older patients. Average GF was 40 mL/min/1.73 $m^2$, which means it was in stage G3b.[11] Most ADR belonged to type A, but one type B reaction was described, an anaphylactoid reaction to the application of drugs from the angiotensin converting enzyme inhibitors (ACEI). An additional problem indicated by this study is that the older population has diminished renal reserve, which should be considered when selecting medication. Another fact stemming from this study is that the majority of patients treated in emergency services as well in ambulance service for primary, secondary, and tertiary care are of increasingly advanced age.[11]

A study conducted in Italy examined the association between CKD and ADR during hospitalization.[12] The study divided older patients into 3 groups depending on GF and serum creatinine (C) values. The first group of participants had GF and C within reference values. The second group had GF within reference values, but elevated C values, and was classified as the group with concealed kidney problems. The third group had lowered GF values and elevated C, and was classified as the CKD group. Medications dissolvable in water (hydrosoluble) caused 301 cases of ADR, while non-hydrosoluble medications caused 640 cases of ADR. The most common ADR due to hydrosoluble medications were low blood pressure or hypotension (caused by drugs from the RAAS group at 17.9% and diuretics at 15.3%), bradycardia (caused by digitalis, 16.3%), hypoglycemia due to treatment with antidiabetics in 13.9% of cases, and hypokalemia due to treatment with diuretics. These were followed by drugs causing gastrointestinal symptoms (antithrombotic medications, 8.0%), sluggishness and drowsiness (with psycholeptics, 7.6%), and headache and hypotension due to nitrate treatment (13.7%). The authors demonstrated that medications soluble in water increase risk of ADR in the group of patients with concealed kidney disease with a OR of 1.78 for hydrosoluble medications, in comparison with OR 0.92 for other medications. This indicated that hydrosoluble medications increase risk of ADR in this group of

nisu se pokazale kao statički značajan čimbenik pojavnosti ADR-a. Autori istraživanja ističu važnost procjene GF-a uz prilagođivanje doze lijekova, čime se može spriječiti najveći broj ADR-a.[12]

Pojedinačna istraživanja ističu važnost prilagođivanja i smanjenja doze lijekova za gotovo 30 % od uobičajene propisane doze ako je riječ o starijoj populaciji s KBB-om.[13] No postoji li način adekvatne procjene koji bi to bolesnik bio u rizičnoj grupi za nastanak ADR-a? Istraživanje iz Dubaija procijenila je rizik kojim bi se pravodobno dijagnosticirala KBB i smanjila mogućnost nastanka ADR-a.[13] U istraživanju su praćene sljedeće karakteristike bolesnika: dob, spol, pridružene bolesti, bio je uključen fizikalni pregled te laboratorijski parametri, kao i lijekovi koje su bolesnici uzimali. Incidencija ADR-a iznosila je 12,1 % (95 % CI, 9,2 – 14,9), odnosno među 512 bolesnika u osnovi 62 hospitalizacijske komplikacije bio je ADR. Najčešći ADR bilo je krvarenje zbog antikoagulantnih lijekova (70 % svih ADR-a): po učestalosti slijede heparin (28 %), enoksaparin (26 %) i varfarin (13 %). Sljedeći ADR bila je hipoglikemija zbog liječenja sulfonilurejom (6 % slučajeva). I ovdje se polifarmacija pokazala najvažnijim faktorom rizika za nastanak ADR-a, posebice ako je bolesnik uzimao više od 8 lijekova, a, prema istraživanju podatak o polifarmaciji ocijenjen je s četiri boda. Dob viša od 65 godina i ženski spol ocijenjeni su jednim bodom. Završni stadij KBB-a, albumin u serumu <3,5 g/dL, povišen upalni parametar C-reaktivni protein (hs-CRP) >10 mg/L i kardiovaskularne bolesti označeni su svaki kao dva boda. Analizom podataka utvrđeno je da deset i više bodova ima gotovo 47 % bolesnika s ADR-om. Navedenim bi se podatcima rutinski mogla provesti procjena bolesnika s povišenim rizikom od nastanka ADR-a s kompliciranim liječenjem, produljenim liječenjem u bolnici i povećanim dodatnim troškovima zdravstvenog sustava općenito.[14]

## Mogućnosti dijagnostike i liječenja te prevencije neželjenih učinaka lijekova

Pristup zbrinjavanju bolesnika u hitnim službama (*airway, breathing, circulation, disability* i *exposure*, odnosno ABCDE) radi procjene kliničkoga stanja ne uključuje procjenu funkcije bubrega. U slučaju nastanka ADR-a, zbog čega je bolesnik došao u hitnu službu, važno je posumnjati i prepoznati koji bi lijek mogao biti uzrok ADR-a, te točno znati vrijeme uzimanja prethodne, zadnje doze lijeka. Ako postoji mogućnost primjene antidota za lijek koji je uzrokovao ADR, bitno ga je primijeniti odmah. U slučaju akutnog bubrežnog oštećenja ili akutizacije otprije poznate KBB, klirens lijekova koji se izlučuju bubregom mijenja se, odnosno smanjuje, o čemu treba razmišljati i prilagoditi doze lijekova uz praćenje diureze, prevenirati poremećaje elektrolita (posebno hiperkalemiju), kao i acidozu. Nova saznanja danas omogućuju jednostavnije i sigurnije propisivanje doza lijekova nego prije, a posebno se misli na vrijeme bez internetske pismenosti, uz individualnu prilagodbu lijekova određenom bolesniku gledajući pridružena stanja, odnosno bolesti, uz praćenje ne samo ADR-a nego i različitih DDR-ja najčešće zbog nehotične medicinske pogreške uzrokovane primjenom dvaju ili više lijekova koji nepovoljno međusobno djeluju ili stvaraju toksične metabolite. Današnje mogućnosti pružaju izbor lijekova koji su povezani s manje ADR-a pri dozi prilagođenoj bubrežnoj funkciji, što treba primijeniti na pojedinačnog bolesnika, u sve kraćem vremenskom okviru, a to je pak svakodnevni izazov u zbri-

patients.[12] Age groups were not a statistically significant factor for incidence of ADR. The authors emphasized the importance of GF assessment with dose adjustment, which can prevent the majority of ADR.[12]

Individual studies have emphasized the importance of adjusting and reducing drug dosage by almost 30% of the typically prescribed doses in older populations with CKD.[13] But is there a way to adequately assess which patient would be in an at-risk group for ADR? A study from Dubai assessed the risk that would allow timely diagnosis of CKD and reduce the likelihood of ADR.[13] The study examined the following patient characteristics: age, sex, and comorbidities, and included a physical examination and laboratory parameters as well as the medications the patients were taking. ADR incidence was 12.1% (95% CI, 9.2-14.9), which means ADR was the underlying cause in 62 hospitalization complications among 512 patients. The most common ADR was bleeding due to anticoagulant medication (70% of all ADR), followed by heparin (28%), enoxaparin (26%), and warfarin (13%). The next most frequent ADR was hypoglycemia due to sulphonylurea treatment (6% of cases). Polypharmacy was once again shown to be the most important risk factor for ADR development, especially if the patient was taking more than 8 medications, and the study graded the polypharmacy data with four points. Age above 65 and female sex were graded with one point. End-stage CKD, serum albumin <3.5 g/dL, elevated high-sensitivity C-reactive protein (hsCRP) >10 mg/L, and cardiovascular diseases were graded with two points each. Data analysis determined that almost 47% of patients with ADR had ten or more points. These data could be used to conduct a routine assessment of patients with increased ADR risk with complicated treatment, extended hospital treatment, and increased additional costs for the healthcare system in general.[14]

## Options for diagnosis, treatment, and prevention of adverse drug effects

The current treatment approach to patients in emergency rooms (airway, breathing, circulation, disability, and exposure, i.e. ABCDE) for the assessment of the patient's clinical condition does not include assessment of kidney function. If ADR is the reason that the patient presented to emergency services, it is important to suspect and recognize drugs that might be the cause of ADR and know the exact time when the last dose was taken. If there is an option to apply an antidote for the drug that caused ADR, it is important to administer it immediately. In case of acute kidney damage or progression of previously diagnosed CKD into the acute phase, clearance of medications excreted via the kidneys will be reduced, which should be taken into consideration, adjusting medication dosage with diuresis monitoring and preventing electrolyte imbalances (especially hyperkalemia) and acidosis. Today, new insights have allowed simpler and safer drug prescription, especially in comparison with the time before Internet literacy, with additional individual adjustment of the medications to patients, considering their comorbidities and monitoring not only ADR but also different DDRs, usually caused by medical error resulting from the application of two or more medications that have an adverse reaction with one another or which cause toxic metabolites. We now have the capacity to select medications that are associated with less ADR at a dose adjusted to kidney function, which should be applied to individual patients in as short a timeframe as possible, which in turn represents a daily challenge in pa-

njavanju naših bolesnika.[15,16] Stoga je nezaobilazna važnost suradnje različitih struka u brizi za bolesnike s komorbiditetima poput KBB-a i popuštanja srca, pri čemu se uključivanjem kliničkog farmaceuta može znatno smanjiti problem polifarmacije i neprilagođenih doza lijekova na svim razinama zdravstvene zaštite, počevši od primarne razine, te pravodobno uputiti na liječenje ADR na višu razinu sekundarne i tercijarne zdravstvene zaštite, što je dokazano u radu Brajković *i sur.*[17]

## Zaključak

Neželjeni ADR obuhvaćaju pojavnost od minimalnih do životno ugrožavajućih stanja. Polifarmacija znatno pridonosi većoj pojavnosti ADR-a. Zbog kombinacije više vrsta lijekova veća je učestalost i DDR-a. Uzimajući u obzir globalno starenje populacije i kontinuiran porast incidencije kroničnih nezaraznih bolesti, potrebno je osvijestiti problem DDR-a i prepoznavanje neželjenih događaja vezanih za primjenu lijekova. Da bismo unaprijedili kvalitetu zbrinjavanja i nastojali prevenirati ADR, jedna od mjera poboljšanja u budućnosti jest uključenje kliničkih farmaceuta u svakodnevno zbrinjavanje bolesnika, posebno onih starijih s komorbiditetima.

tient care.[15,16] The cooperation of different medical fields is thus paramount in the care for patients with comorbidities such as CKD and heart failure, where the inclusion of a clinical pharmacist can significantly reduce the issue of polypharmacy and unadjusted drug dosage at all levels of healthcare, starting with the primary level, and indicate timely referral for ADR treatment at secondary and tertiary healthcare levels, as demonstrated in the paper by Brajković et al.[17]

## Conclusion

Unwanted ADR range from minimal to life-threatening conditions. Polypharmacy significantly contributes to higher incidence of ADR. Combining multiple different medications also increases the incidence of DDR. Considering the global aging of the population and the continuous rise in chronic non-infectious diseases, it is important to be aware of the growing issue of DRR and recognize unwanted events associated with the application of different medications. One of the measures that can be introduced in order to improve quality of care and prevent ADR is the inclusion of clinical pharmacists in everyday patient care, especially for older patients with comorbidities.

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