Akutno oštećenje bubrega izazvano lekovima

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Nefrološka sekcija

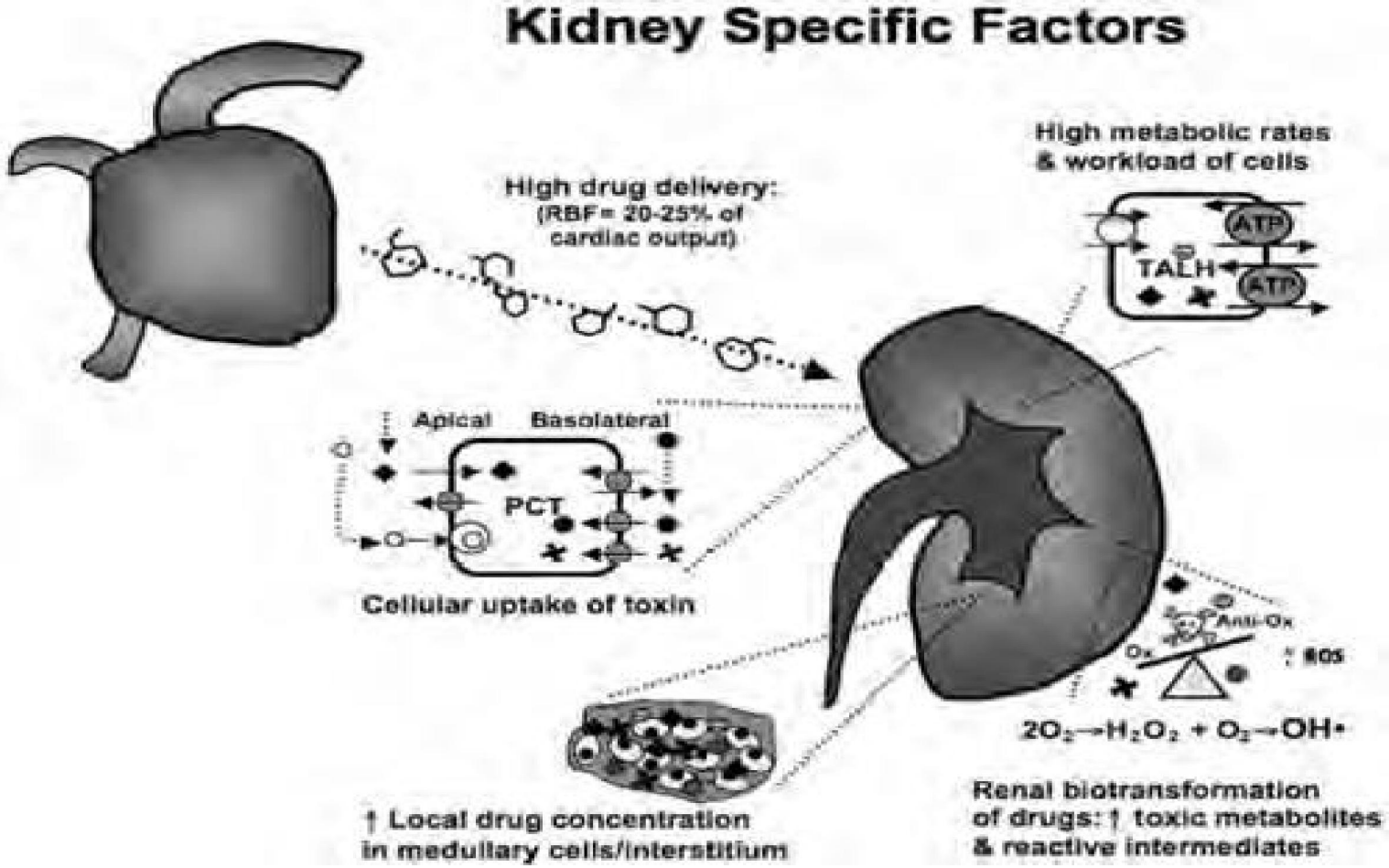
Epidemiologija

- Nefrotoksičnost je jedno od najčešćih neželjenih dejstava lekova/ interakcija lekova
- Brojni lekovi *(NSAI,antimikrobni, ACEi, hemioterapeutici, kontrasna sredstva)* udruženi sa faktorima rizika mogu da izazovu oštećenje bubrega
- 7% hospitalizovanih pacijenata razvija akutno bubrežno oštećenje (AKI)
- 20% hospitalizovanih akutnih bubrežnih insuficijencija uzrokovano lekovima
- 66% incidenca nefrotoksičnosti kod starijih osoba

Choudhury D. Acute kidney injury: current perspectives. Postgrad Med. 2010

Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 2012

Vulnerabilnost bubrega na toksično dejstvo lekova



Nephrology Self-Assessment Program. 2010
Clin J Am Soc Nephrol 2009: 4: 1275–1283

Faktori rizika za nefrotoksičnost

Faktori bolesnika

starost i pol

prethodne bolesti bubrega

komorbiditeti: diabetes, multipli mijelom, lupus

retencija natrijuma (ciroza jetre, srca, nefrotski sy)

dehidriranost

acidoza, hipokalijemija, hipomagnezijemija

hiperurikemija, hiperurikozurija

sepsa, šok

Transplantacija bubrega

Faktori leka

nefrotoksičnost

doza

trajanje,učestalost,oblik primene

ponovljeno izlaganje leku

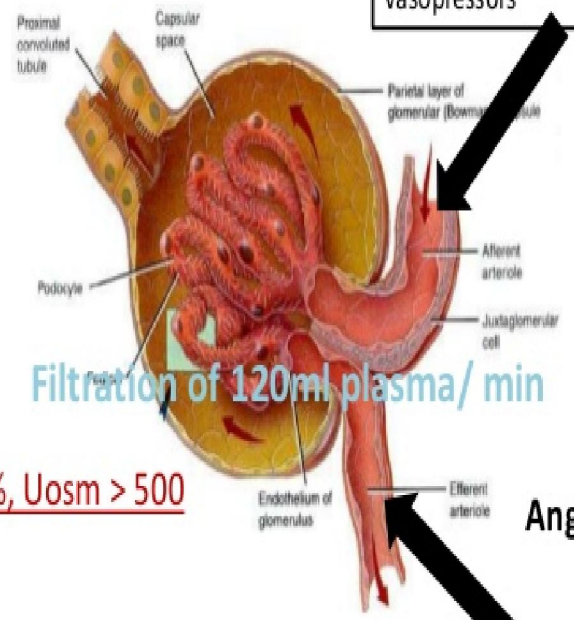
interakcije lekova

TABLE 1. DRUG CLASSES ASSOCIATED WITH RENAL FAILURE/DYSFUNCTION

- Antibiotics
- Analgesics
- Anticonvulsants
- Antivirals
- Amphotericin B
- Antineoplastics
- Antihypertensives
- Drugs of abuse
- Diagnostic agents
- Herbal supplements
- HMG-CoA reductase inhibitors
- Immune globulin
- H_2-antagonists
- Lithium
- Proton pump inhibitors
- Others

AKI : 3% - 23% in Bilateral RAS
or 38% in solitary RAS

Afferent Arteriolar Vasoconstrictors:
Vasodilatory PG Inhibitors: NSAIDs
Direct Afferent Vasoconstrictors:
CyA, Tacrolimus, Radioconstrast Media, Vasopressors



prostaglandins

Filtration of 120ml plasma/ min

➢FENa <1%, Uosm > 500

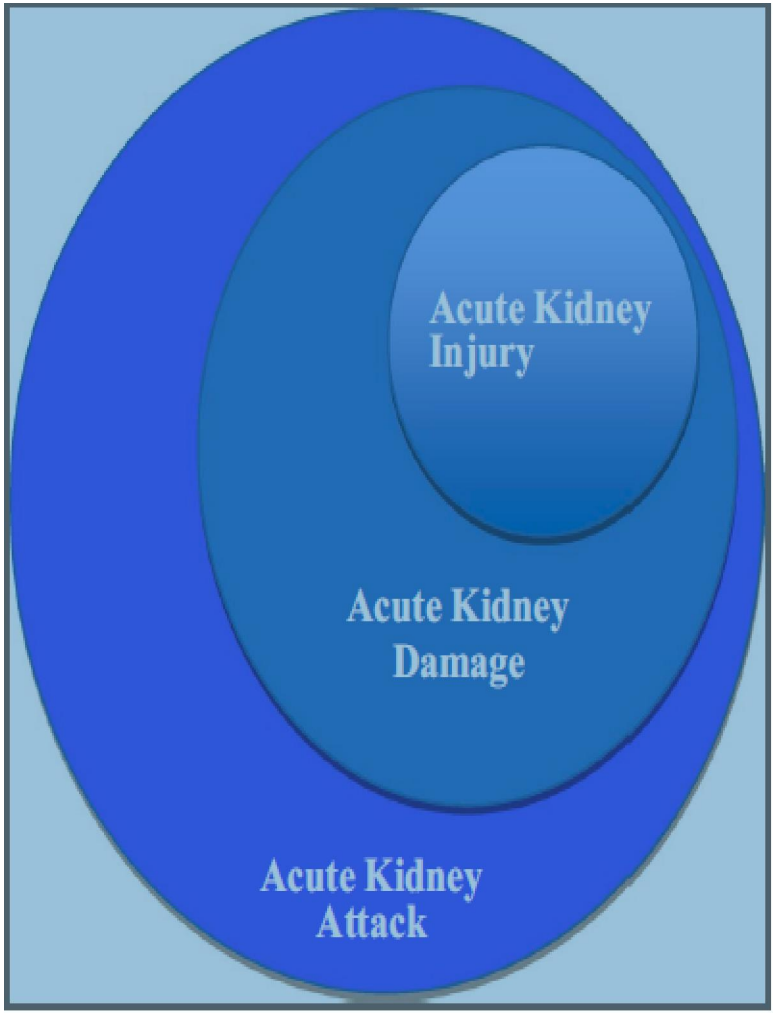
Ang II

Risk Factors:
Decreased intravascular volume (dehydration, diuretic overuse, CHF, vomiting, diarrhea)
Sepsis
Renal-artery stenosis
Polycystic kidney disease

Efferent Arteriolar Vasodilators:
RAAS: ACEI, ARB
Direct Efferent Vasodilators:
Diltiazem, Verapamil

Major nephrotoxic agents responsible for AKI in ICUs and in the perioperative period

Radiocontrast agents
Aminoglycosides
Amphotericin
Non-steroidal anti-inflammatory agents
β-Lactams (interstitial nephropathies)
Sulfamides
Aciclovir, methotrexate, cisplatin
Cyclosporin, tacrolimus
Angiotensin-converting-enzyme inhibitors (ACE)



Kliničke manifestacije nefrotoksičnosti lekova

Table 3 Potential causes of AKI and recovery expectations

	Nondrug-induced AKI	Drug-induced AKI	Recovery
Prerenal injury	Intravascular volume depletion, decreased CO, decreased SVR	NSAIDs, ACEIs, ARBs, calcineurin inhibitors (cyclosporine, tacrolimus, sirolimus), diuretics	Days to weeks
Renal (intrinsic) injury			
ATN	Prolonged or severe prerenal states, ingestion of toxins (ethylene glycol)	AGs, AmB, rifampicin, radiocontrast agents, cisplatin, cocaine, some antiretrovirals, immunoglobulin, mannitol	Weeks to months; may require temporary RRT
AIN	Papillary necrosis, pyelonephritis, renal tuberculosis, fungal nephritis, focal segmental glomerulosclerosis, various viral infections, TINU syndrome, sarcoidosis, lupus erythematosus	Antimicrobials (β-lactams, sulfonamides, quinolones, vancomycin, others), NSAIDs, PPIs, phenytoin, allopurinol, diuretics	Weeks to months; may require temporary RRT
Glomerulonephritis	Lupus	Hydralazine, NSAIDs, ampicillin, lithium	Weeks to months; may require temporary RRT Few may never fully recover
Postrenal injury	Tumor lysis syndrome, myoglobin, multiple myeloma, kidney stones, malignancy, BPH	Acyclovir, methotrexate, sulfonamides, triamterene, sulfadiazine, some antiretrovirals (indinavir, tenofovir), guaifenesin, large doses of vitamin C	Days to weeks; if reversal of obstruction is delayed, may not fully recover

Abbreviations: AKI, acute kidney injury; CO, cardiac output; SVR, systemic vascular resistance; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-II receptor blockers; ATN, acute tubular necrosis; AGs, aminoglycosides; AmB, amphotericin B; RRT, renal replacement therapy; AIN, acute interstitial nephritis; TINU, tubulointerstitial nephritis and uveitis; PPIs, proton pump inhibitors; BPH, benign prostatic hyperplasia.

Clinical Queries: Nephrology 0101 (2012) 29–33

Tubularna oštećenja izazvana lekovima

Syndrome	Description
Aminoglycosides and tetracyclines	
proximal RTA or Fanconi syndrome	Normal anion gap metabolic acidosis; hypokalemia; uric acid, glucose, amino acid, phospho-wasting
Bartter-like syndrome	Metabolic alkalosis with K^+, Ca^+, Mg^+, Na^+ wasting
Amphotericin B compounds	
distal RTA (H^+ "backleak")	Normal anion gap metabolic acidosis
hypokalemia	K^+ wasting; distal RTA
polyuria/hypernatremia	Nephrogenic diabetes insipidus
Trimethoprim	
distal RTA	Normal anion gap metabolic acidosis
blockade of ENaC	Hyperkalemia
Penicillins	
hypokalemia	High urine K^+, low urine Cl^-
hyperkalemia	High K^+ content in setting of poor kaliuresis
Linezolid and tetracyclines	
lactic acidosis	High anion gap metabolic acidosis

ENaC, epithelial sodium channels; RTA, renal tubular acidosis.

Drugs Responsible for Acute Interstitial Nephritis

ANTIMICROBIAL AGENTS

PENICILINS
- Amoxicillin
- **Ampicillin***
- Aztreonam
- Carbenicillin
- Cloxacillin
- **Methicillin***
- Mezlocillin
- Nafcillin
- Oxacillin*
- **Penicillin G* (benzylpenicillin*)**
- Piperacillin

CEPHALOSPORINS
- Cefaclor
- Cefamandole
- Cefazolin
- Cefbdm
- Cefoperazone
- Cefotaxime
- Cefotetan
- Cefoxitin
- Ceftriaxone
- Cephalexin
- Cephaloridine
- Cephalothin
- Cephapirin
- Cephradine
- Latamoxef

QUINOLONES
- **Ciprofloxacin***
- Levofloxacin*
- Moxifloxacin
- Norfloxacin

OTHERS
- Abicavir
- Acyclovir
- Atazanavir
- Azithromycin
- Clarithromycin
- Colistin
- **Cotrimoxazole***
- Erythromycin*
- Ethambutol
- Fluritromycin
- Foscarnet
- Gentamicin
- Indinavir
- Interferon
- Isoniazid
- Lincomycin
- Minocycline
- Nitrofurantoin*
- Piromidic acid
- Polymixin B*
- Quinine
- **Rifampin* (rifampicin*)**
- Spiramycine*
- **Sulfonamides***
- Teicoplamin
- Telithromycin
- Tetracycline
- Vancomycin*

NSAIDs INCLUDING SALICYLATES

SALICYLATES AND DERIVATIVES
- **Aspirin (acetyl salicylic acid)**
- Diflunisal*

PROPIONIC ACID DERIVATIVES
- Benoxaprofen
- Fenbufen
- **Fenoprofen***
- Flurbiprofen
- **Ibuprofen***
- Ketoprofen
- **Naproxen**
- Pirprofen
- Suprofen

ACETIC ACID DERIVATIVES
- **Indomethacin* (Indometacin)**
- Alclofenac
- Diclofenac
- Fenclofenac
- Sulindac
- **Zomepirac**

ENOLIC ACID DERIVATIVES
- Meloxicam
- **Piroxicam***

FENAMIC ACID DERIVATIVES
- Mefenamic acid
- Niflumic acid

COXIBS
- Celecoxib
- Rofecoxib

OTHERS
- Azapropazone
- Mesalamine (mesalazine, 5-ASA)
- Phenazone
- **Phenylbutazone**
- Sulfasalazine
- **Tolmetin**

ANALGESICS
- Aminopyrine
- Antipyrine
- Antrafenin
- Clometacin* (clometazin*)
- Dipyrone (noramidopyrine, metamizol)
- Fioctafenin*
- Glafenin*

ANTICONVULSANTS
- Carbamazepine*
- Diazepam
- Phenobarbital (phenobarbitone)
- **Phenytoin***
- Valproic acid (valproate sodium)

DIURETICS
- Chlortalidone
- Ethacrynic acid
- **Furosemide* (frusemide*)**
- Hydrochlorothiazide*
- Indapamide
- Tienilic acid*
- Triamterene*

ANTIULCER AGENTS

H2-RECEPTOR ANTAGONISTS
- **Cimetidine***
- Famotidine
- Ranitidine

PROTON PUMP INHIBITORS
- Esomeprazole
- Lansoprazole
- **Omeprazole**
- Pantoprazole
- Rabeprazole

OTHERS
- **Allopurinol***
- Alpha Methyl Dopa
- Amlodipine
- Azathioprine
- Betanidine*
- Bismuth salts
- Captopril*
- Carbimazole
- Chlorpropamide*
- Clofibrate
- Clozapine
- Cyamemazine*
- Cyclosporine
- Cytosine Arabinoside
- Desferasirox
- Diltiazem
- D-penicillamine
- Etanercept
- Fenofibrate*
- Fluindione
- Gold salts
- Griseofluvin
- Interleukin 2
- Lamotrigine*
- Linezolid
- Nicergolin
- **Phenindione***
- Phenothiazine
- Phentermine/
- Phendimetrazine
- Phenylpropanolamine
- Probenecid
- Propanolol
- Propylthiouracil
- Sorafenib
- Streptokinase
- Sulphinpyrazone
- Sunitinib
- Warfarin
- Zopiclone

Common culprits

ANTIBIOTICS
[Methicillin]
Benzylpenicillin
Ampicillin
Ciprofloxacin
Rifampicin
Sulphonamides
Co-trimoxazole

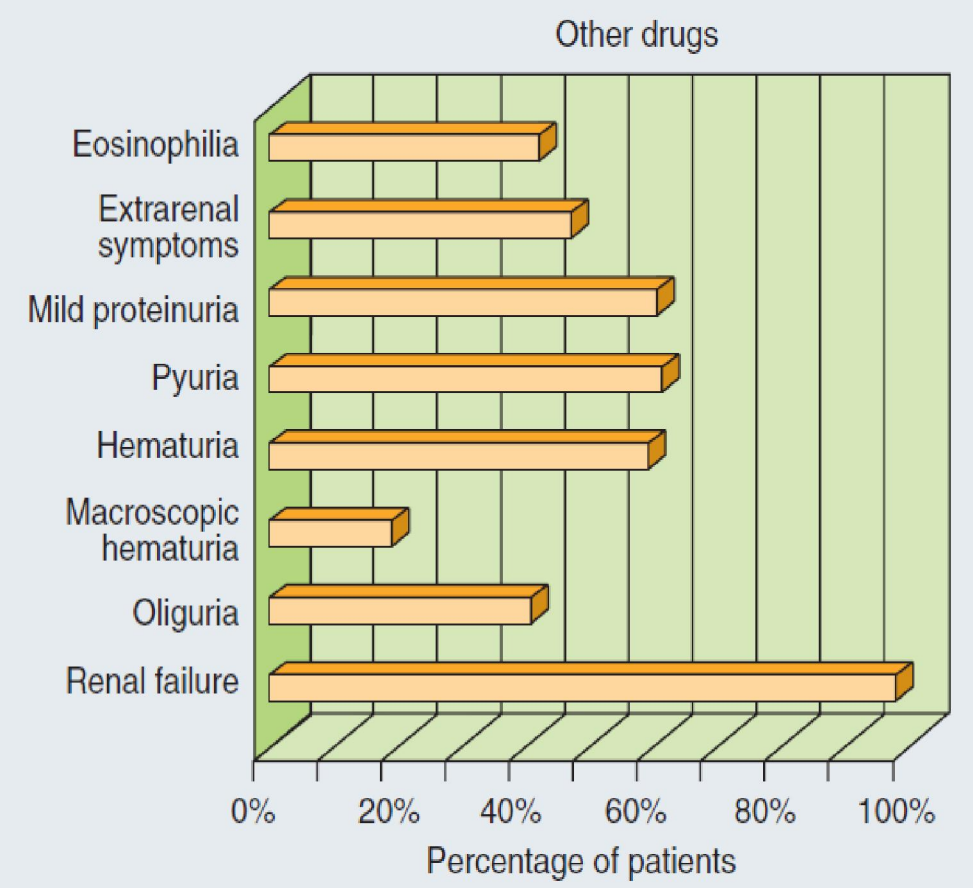
NSAIDs

Frusemide

Cimetidine
Omeprazole

Phenindione

Acute Interstitial Nephritis (AIN)
Drug induced-71%



penicilini/cefalosporini, sulfonamidi, ciprofloxacin, rifampin

Antimikrobni lekovi

- AIN – hipersenzitivna/alergijska reakcija
- Akutna renalna insuficijencija, raš, eozinofilija
- Najčešće penicilini/cefalosporini i sulfonamidi
- Ciprofloxacin (AIN, *trombotična mikroangiopatija, tubularna nekroza, apoptoza)*
- Rifampicin
- Amfotericin B (80% pacijenata razvija ABI)
- cidofovir, foskarnet, aciklovir i interferoni

Aminoglycoside Nephrotoxicity

The risk factors for the aminoglycoside nephrotoxicity.

Patient-related	Treatment-related	Concomitant drugs
• Older age	• Longer treatment	• NSAIDs
• Reduced renal function	• Higher dosages	• Higher dosage diuretics
• Pregnancy	• Split dosages	• Amphotericin
• Dehydration	• Type of aminoglycoside	• Cisplatin
• Renal mass reduction	• Elevated plasma drug concentrations	• Cyclosporin
• Hypothyroidism		• Iodide contrast media
• Hepatic dysfunction		• Vancomycin
• Metabolic acidosis		• Cephalosporin

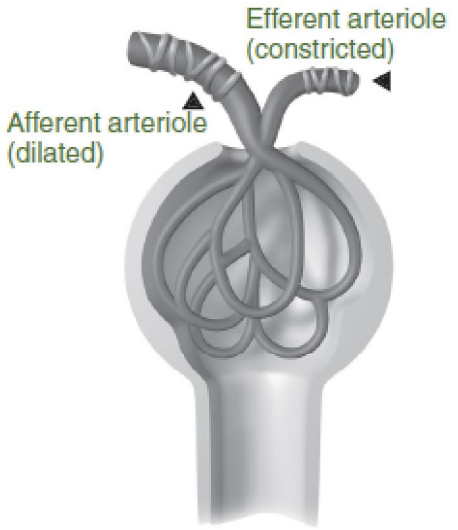
Clinical Queries: Nephrology 0101 (2012) 29–33

Preporuke za prevenciju aminoglikozidne nefrotoksičnosti

3.8.1:	**We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available. (*2A*)**
3.8.3:	**We recommend monitoring aminoglycoside drug levels when treatment with multiple daily dosing is used for more than 24 hours. (*1A*)**

Oštećenje bubrega izazvano NSAIL

- Interstitial nephritis
- Retencija natrijuma i vode
- Hiperkalijemija
- Papilarna nekroza
- Hipertenzija
- Nefrotski sindrom



1.proteinuria (> 3.0g/d)
2.Tubulointersticijska infiltracija
3.Nonoliguric course
4.Eosinophilia/eosinophiluria
5.Različito vreme za razvoj oštećenja
6.Uloga steroida u rezoluciji nejasna

ACEi i ARBi

- Obustaviti primenu u slučaju razvoja ABI, posebno kod starijih
- Ponovo uključivanje leka – manja doza, postepeno povećanje

Monitoring Recommendations[6]

Medication	Interaction with NSAIDs	Recommendation
ACE inhibitors	↓Antihypertensive effect ↑Risk of renal impairment Hyperkalaemia	Monitor blood pressure, weight and renal function. Monitor serum potassium
Diuretics	↓Diuretic effect ↑Risk of renal failure Heart failure may be exacerbated	Monitor blood pressure, weight and renal function
ACE inhibitors + diuretics	↑Risk of renal failure	**AVOID** combination with NSAIDs if possible

THE TRIPLE WHAMMY **- SAFE PRESCRIBING - A DANGEROUS TRIO**	
1.	ACE inhibitor or angiotensin II receptor antagonist ['sartan']
2.	Diuretic
3.	Non-steroidal anti-inflammatory drug [NSAID] or **COX-2 inhibitor** ['coxib']

IMUNOSUPRESIVI i CITOSTATICI

- ciklosporin, tacrolimus, metotreksat, cisplatin
- akutna, dozno-zavisna redukcija renalnog protoka i patomorfofolološke bubrežne promene
- Adekvatna hidratacija i doziranje lekova, kontrola elektrolita, monitoring koncentracije

STATINI

- retko rabdomioliza, oprez kod Tx pacijenata
- akutna tubularna nekroza
- mialgia, hematuria, elektrolitni dizbalans i ABI

CHAPTER 74

Herbal and Over-the-Counter Medicines and the Kidney

Kidney Syndromes Induced by Herbal Medicines

Hypertension	• *Glycyrrhiza* species (Chinese herbal teas, gancao, boui-ougi-tou) • *Ephedra* species (ma huang)
Acute tubular necrosis	• Traditional African medicine: toxic plants (*Securidaca longepedunculata, Euphoria matabelensis, Callilepsis laureola,* Cape aloes, or adulteration by dichromate) • Chinese medicine: *Taxus celebica* • Morocco: Takaout roumia (paraphenylenediamine)
Acute interstitial nephritis	• Peruvian medicine (*Uno degatta*) • Tung Shueh pills (adulterated by mefenamic acid)
Fanconi syndrome	• Chinese herbs containing AAs (*Akebia* species, Boui, Mokutsu) • Chinese herbs adulterated by cadmium
Papillary necrosis	• Chinese herbs adulterated by phenylbutazone
Chronic interstitial renal fibrosis	• Chinese herbs or Kampo containing AAs (*Aristolochia* species, *Akebia* species, Mutong, Boui, Mokutsu)
Urinary retention	• *Datura* species, *Rhododendron molle* (atropine, scopolamine)
Kidney stones	• Ma huang (ephedrine) • Cranberry juice (oxalate)
Urinary tract carcinoma	• Chinese herbs containing AAs

Springer Link

Central European Journal of Medicine

February 2011, Volume 6, Issue 1, pp 113–116

Acute renal failure after licorice ingestion: A case report

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West Indian Medical Journal

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Joint Influence of Protein Supplements, Soft Drinks and Extreme Physical Activity on the Development of Acute Renal Failure and Hypokalemia

Authors: S Djordjevic, D Kitic, M Kostic, B Apostolovic, S Brankovic, IM Ciric, R Velickovic-Radovanovic

DOI: 10.7727/wimj.2014.360

ABSTRACT

We present a case of a 33-year old man who complained of weakness, fever and decreased urinating. A personal history revealed a consumption of creatine, protein supplements, soft drinks containing caffeine and stevia, and extreme physical activity which included lifting of heavy weights. The patient developed anuria, uraemia, fatigue, rhabdomyolysis and paradoxical hypokalaemia. After the patient had seven successive dialysis treatments, normal kidney function was restored. The report presents the first case of acute renal failure followed by hypokalaemia due to the combined action of the excessive consumption of supplements, soft drinks with stevia and caffeine, and extreme physical activity.

Prevencija nefrotoksičnosti
(nivo dokaza C)

- Doziranje lekova prema Cockcroft-Gaultovoj formuli
- Procena renalne funkcije na osnovu MDRD
- Izbegavati nefrotoksične kombinacije
- Korigovati faktore rizike pre/tokom primene lekova
- Monitoring bubrežne funkcije i vitalnih parametara
- Prednost dati lekovima koji su ekvivalentni po efikasnosti bez nefrotoksičnog potencijala
- Poseban oprez- starije osobe sa komorbiditetima i pacijenti sa GFR< 60ml/min

Am Fam Physician. 2008

Farmakoterapija kod starijih osoba sa smanjenom funkcijom bubrega

Neadekvatno propisivanje lekova

- ***Beers' criteria*** – *lista lekova koji predstavljaju rizik za starije*
  (alprazolam, barbiturati, dugodelujući benzodiazepini, H2blokatori, NSAI, teofilin)

- ***STOPP criteria*** *(„Screening Tool of Older Persons Potentionally Inappropriate Prescriptions") – lekovi koje treba izbegavati kod starih (80)*

- ***START criteria*** *(„Screening Toll to Alert doctors to the right Treatment") – lekovi koje treba koristiti kod starijih na osnovu dokaza (34)*

Franklin BD. Potentially inappropriate medication in elderly patients with chronic renal disease--is it a problem? Postgrad Med J. 2013
Gallieni M, et al. Drugs in the elderly with chronic kidney disease NDT. 2015.

Drug or Drug Class	Potentially inappropriate use in elderly (i.e., 65 years and older) per STOPP[8]	Clinical concern[8]	Therapeutic alternative
Look for therapeutic duplication (e.g., two NSAIDs, two SSRIs, two ACEI). Optimize monotherapy, then add drug from different class.			
NSAIDs	• With history of ulcer or GI bleed, not receiving PPI, H2-blocker, or misoprostol • With blood pressure 160/100 mmHg or higher • With heart failure • Use over three months for mild osteoarthritis pain • With GFR<50 mL/min • Long-term use for gout • With warfarin	• Risk of ulcer or GI bleed • Worsening hypertension • Worsening heart failure • Safer, effective alternatives available • Worsening renal function • Not preferred treatment • GI bleed	• With peptic ulcer disease history: add gastroprotective agent[8] • For gout: allopurinol with short-term colchicine or NSAID during initiation[8] • With cardiac, renal issues; osteoarthritis: acetaminophen, topicals[6] • With warfarin: acetaminophen, topicals[6]
Opioids	• With tricyclic antidepressant • Codeine for diarrhea of unknown etiology • Codeine for severe gastroenteritis (e.g., bloody diarrhea, fever) • Long-term in patients with recurrent falls • Long-term use of strong opioids (e.g., morphine) first line for mild to moderate pain • Use for more than two weeks with chronic constipation without laxative • With dementia unless needed for palliative care or moderate-severe pain	• Constipation • Delayed diagnosis, delayed recovery from gastroenteritis, constipation with overflow diarrhea, toxic megacolon in inflammatory bowel disease • Worsening infection or delayed recovery • Falls • Not indicated • Worsening constipation • Worsening cognitive impairment	• For mild/moderate pain: APAP, short-acting NSAID (e.g., ibuprofen); Topicals (neuropathic pain, arthritis): lidocaine (*Lidoderm* [U.S.]), capsaicin[6] • For diarrhea: aluminum hydroxide, cholestyramine, diet change[6]

O'Mahony D, et all. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015

STOPP: Screening Tool of Older People's Potentially Inappropriate Prescriptions

The following drug prescriptions are potentially inappropriate in persons aged ≥ 65 years of age

Drugs that adversely affect fallers.

1. Benzodiazepines
2. Neuroleptic drugs
3. First generation antihistamines
4. Vasodilator drugs with persistent postural hypotension i.e. recurrent > 20mmHg drop in systolic blood pressure
5. Long-term opiates in those with recurrent falls

Analgesic Drugs

1. Use of long-term powerful opiates e.g. morphine or fentanyl as first line therapy for mild-moderate pain
2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives
3. Long-term opiates in those with dementia unless indicted for palliative care or management of moderate/severe chronic pain syndrome

Duplicate Drug Classes

Any duplicate drug class prescription e.g. two concurrent opiates, NSAID's, SSRI's, loop diuretics, ACE inhibitors

Knol W, et all. Detecting inappropriate medication in older people: the revised STOPP/START criteria]. 2015

Zaključak

- Brojni lekovi imaju nefrotoksični potencijal
- Starost, bubrežna oboljenja, komorbiditeti, politerapija povećavaju rizik za akutno oštećenje bubrega uzrokovano lekovima
- Obratiti pažnju na potencijalne faktore rizika
- Poznavanje mehanizama nefrotoksičnosti
- Monitoring bubrežne funkcije i vitalnih parametara u toku primene nefrotoksičnih lekova