Tõendusmaterjali kokkuvõte - EvSu

Kliiniline küsimus nr 14_II

Kas kroonilise neeruhaigusega patsientidel järgmiste ravimite kasutamise ja annustamise otsustamisel tuleb arvestada neerufunktsiooni (kreatiniin, eGFR) väärtusi vs mitte:
- digoksiin
- aminoglükosiidid
- allopurinol

Kriitilised tulemusnäitajad:
kroonilise neeruhaiguse ravi tulemuslikkus, põhihaiguse ravi tulemuslikkus, äge neerukahjustus, kroonilise neeruhaiguse progresseerumine, neeruasendusravi, hospitaliseerimine, patsiendi elukvaliteet, ravikulu, elulemus, üldsuremuse vähenemine

*vt ka KNH_EvSu_K12

Kliinilise küsimuse vastamiseks otsiti materjali eelnevalt sekretariaadi poolt Agree II meetodil hinnatud ravijuhenditest (**KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease; NICE** Clinical Guideline 182: **Chronic kidney disease (partial update). Early identification and management of chronic kidney disease in adults in primary and secondary care,** Academy of Medicine of Malaysia: **Management of Chronic Kidney Disease;** KHA-CARI Guideline: **Early chronic kidney disease: Detection, prevention and management;** Scottish Intercollegiate Guidelines Network**: Diagnosis and management of chronic kidney disease)**.

Lisaks teostati otsingud PubMed andmebaasis:
30.08.15. (((((digoxin) OR digitalis)) AND dosing)) OR ((((digoxin) OR digitalis)) AND (((((kidney function) OR renal function) OR renal insufficiency) OR creatinine) OR eGFR)) AND ("last 5 years"[PDat] AND Humans[Mesh] AND English[lang]) – leiti 135 vastet, millest valiti tõendusmaterjaliks 6 artiklit.
13.09.15. (((((dose[Text Word]) OR dosing[Text Word])) AND (((((aminoglycosides[MeSH Terms]) OR gentamicin[MeSH Terms]) OR gentamycin[MeSH Terms]) OR amikacin[MeSH Terms]) OR streptomycin[MeSH Terms])))) OR (((((((creatinine[MeSH Terms]) OR renal insufficiency[MeSH Terms]) OR kidney function[Text Word]) OR glomerular filtration rate[MeSH Terms]) OR GFR[Text Word]) OR renal function[Text Word])) AND (((((aminoglycosides[MeSH Terms]) OR gentamicin[MeSH Terms]) OR gentamycin[MeSH Terms]) OR amikacin[MeSH Terms]) OR streptomycin[MeSH Terms])) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp] OR systematic[sb]) AND "last 5 years"[PDat] AND Humans[Mesh]) – leiti 399 vastet, millest tõendusmaterjaliks valiti 4 artiklit
12.09.2015. (dosing[All Fields] AND ("allopurinol"[MeSH Terms] OR "allopurinol"[All Fields])) OR ((((((kidney function[Text Word] OR renal function[Text Word]) OR renal insufficiency[Text Word]) OR creatinine[Text Word]) OR GFR[Text Word]) OR glomerular filtration rate[Text Word]) AND ("allopurinol"[MeSH Terms] OR "allopurinol"[All Fields])) AND ("2010/09/14"[PDat] : "2015/09/12"[PDat] AND "humans"[MeSH Terms]) – leiti 172 vastet, millest tõendusmaterjaliks valiti 3 artiklit.

Ravijuhendid

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease *(Kidney inter., Suppl. 2013; 3: 1-150)*

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Ravijuhend annab soovitusi erinevate ravimite dooside korrigeerimiseks vastavalt neerufunktsioonile eesmärgiga vähendada ägeda neerukahjustuse ja KNH progresseerumise riski. Soovitused on koostatud pigem lähtuvalt farmakoloogia ja ravimite farmakokineetika alastest teadmistest kui randomiseeritud kontrollitud uuringutest.

Ravijuhendis soovitatakse arvestada ravimite manustamisel neerufunktsiooni, GFR-i täpsemaks määramiseks kaaluda tsüstatiin C-l põhinevaid meetodeid või otsest GFR-i mõõtmist. Samuti soovitatakse teatud potentsiaalslt nefrotoksliste ravimite manustamise ajutist katkestamist kaasuva ägeda haigusega KNH patsiendil, eriti võimaliku dehüdreerumise korral (oksendamine, kõhulahtisus).

Ravijuhendis on põgusalt mainitud digoksiini ja aminoglükosiidide kasutamist KNH patsientidel. Allopurinoli annustamist KNH patsientidel antud ravijuhend ei käsitle.

lk.102 – 103

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (1A)
4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (e.g., due to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (1C)
4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and **digoxin. (1C)**

4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes and drug levels regularly monitored. (1A)

Ravijuhendi soovitus **digoksiini** manustamise osas KNH patsientidel: **neerufunktsiooni langusega haigetel (GFR <60 ml/min/1.73m2) tuleks kaasuva ägeda haigestumise korral digoksiini manustamine ajutiselt katkestada. Digoksiini doosi on vajalik korrigeerida vastavalt plasmakontsentratsioonile.**

Aminoglükosiidide annustamise kohta on soovitused toodud ravijuhendi *tabelis 32*:
- **Reduce dose and/or increase dosage interval when GFR <60 ml/min/1.73 m2**
- **Monitor serum levels (trough and peak)**
- **Avoid concomitant ototoxic agents such as furosemide**

Süstemaatilised ülevaated

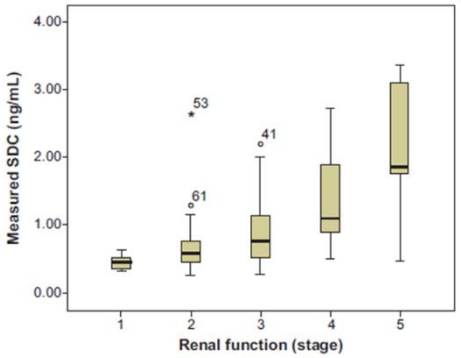
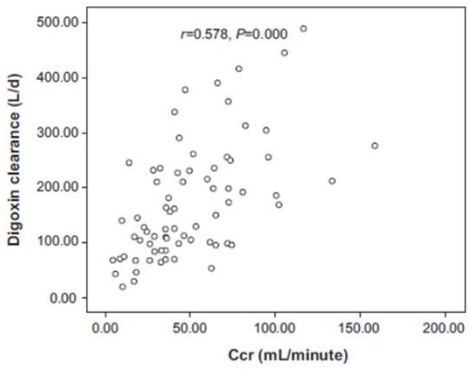
DIGOKSIIN

Digoksiini doseerimist vastavalt neerufunktsioonile on laiemalt käsitletud kuues leitud artiklis. Antud küsimuse tõenduspõhisus on võrdlemisi madal – leitud artilkitest ühe puhul on tegemist süstemaatilise kirjanduse ülevaatega, enamik ülejäänutest on väikese valimiga kohortuuringud digoksiini doseerimist hõlbustavate valemite kohta. Uuringute puuduseks on raske neerupuudulikkusega patsientide väljajätmine uuringugrupist. Suuri randomiseeritud uuringuid hindamaks digoksiini annustamist vastavalt neerufunktsioonile ei ole viimase viie aasta jooksul läbi viidud.

Leitud artiklitest selgub, et digoksiini kasutamist piiravad kitsas terapeutiline indeks ja keerukas farmakokineetika, sealjuures suur individuaalne varieeruvus. **Eelkõige on digoksiini toksiliste toimete risk suurem vanemaealistel, neerufunktsiooni langusega ja polüfarmakoteraapiat saavatel patsientidel. Toksiliste toimete vältimiseks on oluline regulaarne ravimi kontsentratsiooni määramine verest**, samas ei ole artiklites antud juhiseid digoksiini kontsentratsiooni monitoorimise sageduse kohta. **Digoksiini eesmärkväärtused soovitatakse hoida pigem madalad, erinevates uuringutes 0,4 – 1 ng/ml. Digoksiini annustamise hõlbustamiseks tavapopulatsioonil välja töötatud valemid ei sobi kohandamiseks neerupuudulikkusega patsientidele.**

Süstemaatiline kirjanduse ülevaade südamepuudulikkuse ravivõimalustest kroonilise neeruhaigusega patsientidel. - Kaasati 102 uuringut, otsitavate uuringute disaini osas kitsendusi ei olnud. - The use of digoxin has very limited indications and requires great prudence in patients with HF and CKD. The administration of this drug may be considered in selected cases with poorly controlled symptoms of HF or with high-ventricular rate atrial fibrillation, in the presence of optimal-dose therapy with diuretics, RAAS inhibitors, and beta-blockers. **Monitoring of serum digoxin concentration is required, with a target of 0.5 to 0.9 ng/mL; this is usually achieved by administering the drug at very low doses (e.g., 0.125mg every other day when GFR is 30 to 60 mL/min and less frequently in patients with more severe renal dysfunction).**	**Heart failure in patients with chronic kidney disease: a systematic integrative review.** Segall L, Nistor I, Covic A. Biomed Res Int. 2014;2014:937398.
Ülevaateartikkel, kus kolme randomiseeritud kontrollitud uuringu alusel (PROVED, RADIANCE, DIMT) käsitleti digoksiini kasutamist vähenenud EF-ga kroonilise südamepuudulikkusega haigetel, juhtides	**A perspective on re-evaluating digoxin's role in**

tähelepanu optimaalsele ohutule je efektiivsele seerumkontesntratsioonidele. - Experimental and clinical results suggest that optimizing therapeutic benefit and avoiding harm means dosing to **achieve low serum digoxin concentrations (0.5–0.9 ng/mL).** - Several groups have reported results that consistently show an association between low serum concentrations (generally 0.5–0.9 ng/mL) and reduced risk of all-cause mortality, cause-specific mortality, all-cause hospitalization, and cause-specific hospitalization when compared to placebo, whereas **safety concerns emerge at higher serum concentrations (above 1.0 or 1.2 ng/mL).** - Increasing digoxin concentration (above 1.0 ng/mL) produces a greater positive inotropic response, but the effective range is narrow and there is no convincing evidence of greater clinical benefit. - In patients with normal renal function, steady state would be expected to occur at approximately 7–10 days after initiation. **Because the elimination half-life of digoxin is prolonged in patients with impaired renal function, the time to reach steady state is delayed and may not occur until 3–4 weeks after initiation. Even with the low doses suggested, in such patients, it may be a conservative and reasonable approach to obtain both an early serum concentration (~7–10 days) and a concentration at presumed steady state (3–4 weeks).**	**the current management of patients with chronic systolic heart failure: targeting serum concentration to reduce hospitalization and improve safety profile** Adams KF Jr et al. Eur J Heart Fail. 2014 May;16(5):483-93.
Retrospektiivne kohortuuring, mis uurib korrelatsiooni ***Konichi valemi*** järgi ennustatava ja tegeliku mõõdetava digoksiini seerumkontsentratsiooni (SDC) vahel hiinlastel ning vaatleb neerufunktsiooni mõju digoksiini seerumokntsentratsioonile. - Soovituslik hoida südamepuudulikkusega patsientidel digoksiini kontsentratsioon **0.4–1.0** ng/mL ja tahhüarütmia korral **0.8–2.0** ng/mL. - Konishi formulated an equation to determine the daily dose of digoxin based only on creatinine clearance rate (Ccr) and SDC **L (ng/mL) = D (µg/day)/[2.22*Ccr + 25.7]** L - serum digoxin concentration D - the dose of digoxin - 72 patsienti südamepuudulikkuse või kodade tahhüarütmiga, keskmine vanus 71.5±13.0 aastat, kesmine eGFR 49.5±31.1 mL/min/1,73m2, vaatlusperiood 2 aastat - Uuritavad jaotati vastavalt KNH staadiumidele eGFR-i järgi viide gruppi. - **Kõigi uuritavate grupis esines ennustatava ja tegeliku digoksiini seerumkontsentratsiooni vahel tugev korrelatsioon (*r*=0.655, *P*<0.001), KNH erinevates staadiumides vastav korrelatsioon puudus (v.a. 3. staadium; eGFR 30 – 60 ml/min/1,73 m2).** - Digoksiini kontsentratsioon oli terapeutilises vahemikus 77.8% patsientidest, **toksilistes väärtustes kontsentratsioon esines raskema neerupuudulikkusega patsientidel.**	**Efficiency of individual dosage of digoxin with calculated concentration.** Zhao L. et al. Clin Interv Aging. 2014 Jul 22;9:1205-10.

 **Figure 1** Differences in SDC in patients with different levels of renal function. **Note:** *Represents a mild outlier and °an extreme outlier. **Abbreviation:** SDC, serum digoxin concentration.  **Figure 3** Correlation between clearance of digoxin and Ccr rate in all patients. **Abbreviations:** Ccr, creatinine clearance rate; d, day. - The 2013 American College of Cardiology Foundation/American Heart Association guidelines recommend using a lower digoxin dosage of 0.125 mg daily or 0.125 mg every other day in patients older than 70 years or with impaired renal function. **The results of this study indicate that clearance of digoxin and the creatinine clearance rate cannot be explained by renal function alone and that the validity of the Konishi equation for individualizing the digoxin dosage in Chinese patients is limited, being applicable only in stage 3 renal disease.**	
Retrospektiivne kohortuuring, populatsioonipõhine farmakokineetika analüüs. Uuriti digoksiini farmakokineetikat hiina vanuritel. - 142 uuritavat vanuses 65 – 82 a (keskmine vanus 75,5 a.), seerumi kreatiniin 105 ± 43.1 (41–287.8) mcmol/l. - Digoksiini manustati p.o. 0.0625 - 0.25 mg 1 - 2 korda päevas vähemalt 2 nädala jooksul ja saadud andmete põhjal konstrueeriti mudel digoksiini doseerimiseks. - Leiti, et digoksiini kliirens väheneb neerufunktsiooni languse, suurema kehakaalu, kaltsiumkanali blokaataorite või spironolaktooni koosmanustamise ning kongestiivse südamepuudulikkuse korral. - **Uuring näitab, et digoksiini intoksikatsiooni risk on suurim neerufunktsiooni langusega patsientide seas.** - **Autorid soovitavad neerufunktsiooni langusega patsientidel piirduda digoksiini manustamisel 0,125mg päevas, vajadusel vähendada annuseid veelgi.**	**Population pharmacokinetics of digoxin in elderly patients.** Chen R. et. al Eur J Drug Metab Pharmacokinet. 2013 Jun;38(2):115-21.
Retrospektiivne kohortuuring, populatsioonipõhine farmakonineetika analüüs. Uuriti digoksiini farmakokineerikat jaapani vanuritel. - 94 uuritavat, keskmine vanus 73.7 aastat, kreatiniini mediaan **76 (40,6 – 157,4) mcmol/l** - Digoksiini manustati 0,125 – 0,25mg üks kord päevas - Leiti, et dikoksiini kliirens sõltub kehakaalust, **seerumi kreatiniini väärtusest**, vanusest, südamepuudulikkuse olemasolust, kaltsiumkanalite blokaatorite manustamisest ja soost. - **Digoksiini manustamisel tuleb arvestada suure patsientidevahelise varieeruvusega:** näitena alltoodud graafik, kus esineb küll lineaarne seos digoksiini doosi ja seerumkontsentratsiooni vahel, kuid esineb võrdlemisi suur hajuvus.	**Determination of digoxin clearance in Japanese elderly patients for optimization of drug therapy: a population pharmacokinetics analysis using nonlinear mixed-effects modelling.** Yukawa M. et. al Drugs Aging.

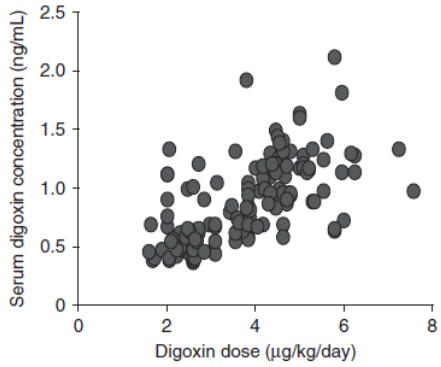


Fig. 1. Relationship between the daily dose of digoxin and serum concentration.

2011 Oct 1;28(10):831-41.

Prospektiivne multitsentriline uuring, mille eesmärgiks oli uurida Konishi poolt digoksiini doseerimiseks väljatöötatud valemi sobivust valgel rassil.

- 40 uuritavat, kreatiniin 116±38 mcmol/l, välja jäeti uuritavad, kelle eGFR oli alla 30 ml/min/1,73 m2.
- Doos kalkuleeriti vastavalt Konishi valemile:

$$\text{Daily dosage of digoxin (ug/day)} = \text{SDC (ng/ml)} \times [2.22 \times \text{Ccr (ml/min.)} + 25.7].$$

where SDC (*serum digoxin concentration*) is the target SDC and Ccr is the estimated clearance of creatinine as calculated with the Cockcroft–Gault equation.

- We found a reasonable correlation between predicted and measured SDC (r = 0.48; P<0.01) by the Konishi equation. Excluding patients with poor adherence and relevant worsening of renal function, the measured SDC (n = 54 measurements) was within the pre-defined therapeutic range in 95% of the cases. The mean, maximal and minimal measured SDC were 0.69±0.19, 1.00 and 0.32 ng/ml, respectively.
- **All patients with supratherapeutic SDC (n = 5) experienced a relevant worsening of the renal function during follow-up, defined as a reduction of the estimated creatinine clearance >20%.**

Individual dosage of digoxin in patients with heart failure. Muzzarelli S. et al QJM. 2011 Apr;104(4):309-17.

AMINOGLÜKOSIIDID

Aminoglükosiidide doseerimise kohta leiti 1 randomiseeritud kontrollitud uuring ja 3 ülevaateartiklit, milles on põgusalt käsitletud ka ravi neerufunktsiooni langusega haigetel. Uuringuid aminoglükosiidide manustamise kohta KNH patsientidel viimase 5 aasta jooksul avaldatud ei ole. Üldiselt on leitud uuringute kvaliteet madal.

Aminoglükosiidid on kitsa terapeutilise vahemiku ja potentsiaalselt nefrotoksilise toimega antibiootikumid. Aminoglükosiidide eliminatsioon toimub peaaegu täielikult neerude kaudu. Nende ravimite farmakokineetiline ja farmakodünaamiline varieeruvus inimeste vahel on suur. Ravimi annustamisel tuleks arvesse võtta patsiendi neerufunktsiooni, ravi paremaks juhtimiseks soovitatakse korrigeerida doose ravimi seerumkontsentratsiooni alusel. Spetsiaalsete ravimmonitoorimiseks mõeldud nomogammide või algoritmide kasutamine on kroonilise neeruhaigusega patsientidel piiratud, kuna enamik neist ei ole valideeritud neerufunktsiooni langusega patsientidel.

Ülevaateartikkel aminoglükosiidide terapeutilisest monitoorimisest ning soovitused aminoglükosiidide annustamise lihtsustamiseks ülekaalulisel

Aminoglycoside dosing in patients

patsiendil.

- Aminoglükosiidide annustamisel tuleb arvestada mikroobi ravimtundlikkust, patsiendi kehakaalu ja neerufunktsiooni. Suure varieeruvuse tõttu on vajalik lisaks jälgida ravimi seerumkontsentratsioone.
- **The reported correlation between CLcr and GFR with aminoglycoside CL has an R^2-value of 0.38–0.50. This implies that approximately 50% of the interindividual variability in the CL of aminoglycosides is not explained by CLcr or GFR.**
- Ajalooliselt kasutatakse ravimdooside korrigeerimiseks vastavalt neerufunktsioonile enim **Cockcroft-Gault'i valemit**. Valemi üheks sisendiks on kehamass (TBW, *total body weight)*, mis ülekaalulistel suureneb keharasva arvelt - nii ülehinnatakse ülekaaluliste neerufunktsiooni, mille tulemuseks on kõrgemad aminoglükosiidide doosid ja ravimtoksilisus.
- Ükski eGFR-i arvutamise valem ei ole ravimmonitooringuks valideeritud ja erinevad ravimtootjad kasutavad ravimuuringutes eri valemeid. **Seega peaks enne manustamist tootjainfost kontrollima, millise neerufunktsiooni määramismeetodi alusel soovitatakse ravmit doseerida.**
- **The risk of aminoglycoside-induced acute kidney injury follows a pattern of gentamicin > tobramycin ≥ amikacin**
- Aminoglükosiidide dooside arvutamise valemites eeldatakse, et aminoglükosiidi CL ≈ GFR. See ei kehti aga neerukahjustusega patsientide puhul, keda ei ole üldjuhul ravimuuringutesse kaasatud.

Table 3
Suggested bedside calculation approach of the initial and maintenance aminoglycoside dose.

Step	Initial dose calculation (every 24 hour administration)
1	Estimate CLcr (mL/min) $= \frac{140-\text{age (years)}}{72 \times \text{SCr(mg/dL)}} \times \text{TBW*(kg)} \times 0.85$(if female) *TBW should be replaced with ABW or LBW (do not multiply by 0.85 if female) in patients with a BMI ≥40 kg/m^2, CLcr values ≥150 mL/min should be capped at 150 mL/min, values <60 mL/min should trigger consideration of a traditional dosing approach
2	Aminoglycoside CL (L/h) = 0.054 × CLcr (mL/min)
3	Initial aminoglycoside single dose = AUC_{target} × CL (L/h)

Step	Maintenance dose (every 24 hour administration)
1	Measure 2 serum concentrations (C_1, C_2) at 3–4 hours (T_1) and 8–12 (T_2) hours after the initial dose
2	Calculate Ke = −Ln (C_2/C_1)/(T2 − T1)
3	Calculate $C_{max} = C_1/e^{-Ke(Tmax')}$, where Tmax' is the time between T_1 and end of infusion
4	Calculate $AUC_{0-\infty} = (C_{max} \cdot t' \cdot 0.5) + C_{max}/Ke$, where t' is the infusion time in hours
5	Maintenance aminoglycoside dose = (initial dose/$AUC_{0-\infty}$) • AUC_{target}

ABW = adjusted body weight (Bauer et al., 1983); LBW = lean body weight (Janmahasatian et al., 2005); AUC_{target} = target area under the concentration-time curve (mg•h/L); Ke = elimination rate constant; C_{max} = maximum concentration assumed to "occur" at the end of infusion.
Suggested initial AUC_{target} = 75 mg•h/L (gentamicin), 150 mg•h/L (tobramycin), 300 mg•h/L (amikacin).

by kidney function and area under the curve: the Sawchuk-Zaske dosing method revisited in the era of obesity.
Pai MP, Rodvold KA.
Diagn Microbiol Infect Dis.
2014
Feb;78(2):178-87.

Ülevaateartikkel aminoglükosiidide kasutamisest septilises šokis haigetel. - Nefrotoksilise toime vähendamiseks soovitatakse aminoglükosiidide manustamist **üks kord päevas** (*kõrgdoosis*), lühendades seejuures üldist ravikestust (*≤5 päeva*). Nii saavutatakse kiiremini efektiivne terapeutiline kontsentratsioon (C_{max}/MIC≥10) ning väheneb aminoglükosiidide akumulatsioon neerukoes. **Samas ei ole üks kord päevas annustamine näidanud olulist eelist varasema neerufunktsiooni langusega patsientidel. Kõrgdoosis manustamist pole varasema neeruhaigusega patsientidel uuritud.** - Cosgrove et al. and Radigan et al. initially proposed a **50 mL/min or 60 mL/min CR_{CL} threshold, respectively, for the aminoglycoside-associated nephrotoxicity risk to occur.** - **C_{min} is clearly related to nephrotoxicity**. - **Monitoring of C_{min} only for aminoglycoside treatment of more than 5 days or in the case of altered renal function has recently been recommended.** Cmin objectives vary from 0.5 – 2 mg/L *(erinevate uuringute eesmärkväärtused on erinevad!)* for gentamicin, tobramycin or netilmicin, and from 2.5 - 5 mg/L for amikacin. - **As soon as the MIC has been provided, aminoglycoside doses should be tapered.** - To date, no aminoglycoside TDM *(therapeutic drug monitoring)* has really proven its efficiency inside the ICU.	**Aminoglycosides in septic shock: an overview, with specific consideration given to their nephrotoxic risk.** Boyer A. et al. Drug Saf. 2013 Apr;36(4):217-30

Table 1 Risk factors for nephrotoxicity with aminoglycosides in patients with sepsis

Patient	Metabolic disturbances	Aminoglycoside treatment	Other nephrotoxic drugs [14, 54, 90]
Older age [38, 55]	*Hypercalcaemia* [93]	**Duration of therapy** [2, 14, 15, 24, 36, 37, 43, 44, 52, 54, 55, 168]	Furosemide[a] [14, 55, 169, 170]
Female sex[a] [37, 38, 168, 171]	*Metabolic acidosis* [22, 93]	**High daily AUC** [2, 23, 54, 56, 57]	Angiotensin inhibitor [172]
Diabetes [90, 172]	*Magnesium depletion* [93]	**High trough concentrations** [2, 23, 54, 56–58]	*NSAIDs* [22, 93]
Cirrhosis [55, 173]	*Potassium depletion* [93]	MDD[a] [2, 36, 44–47, 53, 125, 126]	*Cisplatin* [22, 93]
Ascitis [54, 174]	*Sodium depletion* [93]	**Circadian rhythm**[b] [35, 36]	*Ciclosporin (cyclosporine)* [22, 93]
Low albumin concentration [54, 175]		One class of aminoglycosides[a] in comparison with other classes [125, 168, 171]	Iodide contrast media [22, 90, 93]
Reduced renal function [22, 37, 38, 44, 73, 93, 173]			**Other antibacterials**
Reduced renal mass [22]			**Vancomycin** [22, 23, 54, 168]
Leukaemia [54]			Cephalosporins [22, 54]
			Piperacillin [168]
			Clindamycin [168]
			Amphotericin B [22, 54, 93]

Bold text indicates risk factors described by at least two authors with multivariate analysis
Normal text indicates risk factors described by only one author with multivariate analysis
Italicised text indicates risk factors cited by review articles without references
AUC area under the plasma concentration-time curve; *MDD* multiple daily dosing
[a] Although classified as a risk factor by at least two studies, other studies report contrasting results
[b] Night vs. diurnal administration

Ülevaateartikkel, mis käsitleb aminoglükosiidide farmakodünaamikat. - Kuna aminoglükosiidide bakteriotsiidne efekt on kontsentratsioonist sõltuv, soovitatakse üldpopulatsioonis parima raviefekti saavutamiseks suurema intervalliga annustamisskeemi, eesmärgiga saavuatada AUC 100mg·h/L 24 tunni jooksul ja C_{max}/MIC ≥ 8–10. Ravimi kogu päevadoos manustatakse ühekordse annusena. - Mitmetes prospektiivsetes randomiseeritud kontrollitud uuringutes ja metaanalüüsides on näidatud, et pikema intervalliga annustamisskeem võimaldab pikemat raviperioodi, enne kuid "nefrotoksilisuse lävi" ületatakse. Ototoksilisuse teke ei sõltu ravimi manustamisintervallist. - **Low trough serum concentrations are associated with a lower**	**Pharmacological considerations for the proper clinical use of aminoglycosides.** Pagkalis S. et al. Drugs. 2011 Dec ;71(17):2277-94.

potential risk of toxicity. In patients with reduced renal function, dosing intervals should be extended in order to reach low trough levels. - **Dosing intervals should be reduced in conditions associated with increased GFR.** - **Individualized pharmacodynamic monitoring has the potential of minimizing the toxicity and the clinical failures.**	
Randomiseeritud kontrollitud uuring hindamaks erinevate amikatsiini (AMK) raviskeemide efektiivsust ja ohutust võrreldes standardraviga. - Randomiseeriti 99 patsienti raske sepsis või septilise šokiga erinevatesse amikatsiini ravigruppidesse. Kõigis gruppides esines ka raske neerupuudulikkusega patsiente (kreatiniini kliirens < 30 ml/min). - Loading dose: Group 1, 25 mg/kg/day; Group 2, 30 mg/kg/day; Group 3, historical standard dose (15 mg/kg/day). **Results** - AMK C_{max} values were 57.4±9.8, 72.1±18.4 and 35.2±9.4 mcg/mL, respectively (P < 0.001 between Groups 1 and 2 versus Group 3, and P < 0.01 between Group 1 versus Group 2). - C_{max} > 60 mcg/mL was reached by 39%, 76% and 0% of patients in Groups 1, 2 and 3, respectively (P < 0.001) - Creatinine clearance at Day 28 was 95.6±47.4, 89.7±26.6 and 56.4±18.4 mL/min, respectively. Differences did not reach statistical significance. - Since AMK loading doses were not adjusted by renal function, there was in theory a risk of attaining higher C_{max} and potential toxicity. However, **we found an increase of C_{max} independent of renal function, and trough plasma concentration (C_{min}) values that stayed below the level of toxicity (5 mcg/mL) in the whole group as well as in patients with renal dysfunction when analysed separately**. **Thus, there was no further impact on renal function, and both renal function parameters (plasma creatinine levels and 24-h CLCr at Day 28) improved or returned to normal or baseline levels at Day 28. This suggests that in critical care patients with septic shock there is no indication for loading dose adjustment guided by renal function. Patients with renal dysfunction behaved similarly to those with normal function, and using lower doses for them would lead to a lower C_{max}. An independent decision is feasible, even in the presence of renal dysfunction, but must be associated with close monitoring of plasma levels.** In conclusion, a 30 mg/kg daily dose of AMK presents significantly higher C_{max} compared with the other groups, with 76% of patients reaching recommended peak plasma levels **with no association with higher nephrotoxicity.** Standard doses are insufficient in critically ill patients to reach the recommended C_{max}.	**Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity** Gálvez R. et. al Int J Antimicrob Agents. 2011 Aug;38(2):146-51
ALLOPURINOOL **vt ka KNH_EvSu_K12* Allopurinooli annustamist sõltuvalt neerufunktsioonist on käsitletud pikemalt kahes	

süstemaatilises kirjanduse ülevaates ja ühes kohortuuringus. Leitud uuringud soovitavad allopurinooli doseerimisel arvestada neerufunktsiooni. Põhjuseks on võimalik suurem ravimi raskete kõrveltoimete, eeskätt allopurinooli hüpersensitiivsusreaktsiooni risk neerukahjustusega patsientidel, mille üheks seletuseks võib olla allopurinooli metaboliidi oksüpurinooli ekskretsiooni vähenemine neerupuudulikkuse korral. Siiski ei ole kliinilised uuringud seoseid allopurinooli raskete kõrvaltoimete ja neerufunktsiooni languse vahel üheselt kinnitanud. Leitud artiklites tuuakse välja, et varasemalt laialdaselt kasutusel olnud neerufunktsioonile kohandatud allopurinooli doosid olid tegelikkuses tihti subterapeutilised ja ei andnud seega piisavat raviefekti. Käesolevates artiklites toodud soovituste alusel tuleks olenemata GFR-st allopurinooli doosi ülestiitrida, kuni saavutatakse kusihappe eesmärkväärtus (<360 mcmol/l). Küll aga tuleb ravi alustada madalate annustega, eriti oluline on see KNH-ga patsientidel.	
Süstemaatiline kirjanduse ülevaade hindamaks allopurinoli tõhusust kusihappe langetamisel ja selle ravimi kõrvaltoimete riski KNH patsientidel. - enamik võrdlemisi väikese valimiga retrospektiivsed kohortuuringud, KNH patsiendid olid enamikus uuringutes kogu kohordi üks alagruppidest - neerupuudulikkuse raskusastme võrdlemine eri uuringute vahel on keeruline, kuna klassifikatsioonid/KNH kriteeriumid on erinevad **Results** - Findings from Stamp et al in 2012, led to **a recommended starting dose of 1.5 mg of allopurinol per unit of eGFR, with monthly titrations. This aligns with guidelines to limit the starting dose of allopurinol in patients with renal insufficiency.** - In accordance with the clinical practice guidelines for patients with and without renal impairment, **allopurinol may be initiated with a dose no greater than 50 to 100 mg/d in CKD. Then, it can be titrated by 50 to 100 mg every 2 to 5 weeks with monitoring of the SUA level prior to the next dose increase. However, the titration schedule is not specific to renal function.** - **The risk of AHS** *(allopurinol hypersensitivity syndrome)* **does not seem to be related to maintenance dose, with no evidence that dose reductions decrease risk, and titration to doses exceeding 300 mg/d has been supported by the American College of Rheumatology. The optimal maintenance dose that a patient will require is based on achieving the goal SUA; therefore, a higher baseline plasma urate may require a higher maintenance dose of allopurinol.** - It is crucial to target a goal SUA of at least <6 mg/dL (357 mcmol/l) with ULT to minimize the risk of acute gouty attacks and subsequent complications. **Providers should be aware of the potential risk of allopurinol hypersensitivity syndrome as well as the need for reducing the initiation dose and gradual titration of allopurinol to safely achieve a target serum urate level in this population.** Therapy with allopurinol should be individualized for every patient with CKD treated for gout. Close monitoring of SUA levels and potential toxicity is warranted during dose titration to identify AHS early and withdraw allopurinol.	**Safety and efficacy of allopurinol in chronic kidney disease.** Thurston MM, Phillips BB, Bourg CA. Ann Pharmacother. 2013 Nov;47(11):1507-16

<table>
<tr><td>There is no evidence to suggest that restricting daily maintenance doses of allopurinol eliminates the risk of AHS, and maximum tolerable doses of allopurinol are not established relative to differing degrees of renal impairment. The most important concept when dosing allopurinol in CKD is the “start low and go slow” approach.</td><td></td></tr>
<tr><td>Kohortuuring selgitamaks välja plasma kusihappe taset mõjutavaid faktoreid allopurinoolravi ajal ja ennustada optimaalseid allopurinooli doose vastavalt kusihappe eesmärkväärtustele.
- 46 patsienti, neist 17-l eGFR <60 ml/min/1,73m2. Analüüsiti 112 proovi.
- Määrati plasma kusihappe ja kreatiniini tase enne allopurinoolravi
- Non-linear and multiple linear regression equations were used to examine the relationships between allopurinol dose (D), creatinine clearance (CLcr) and plasma concentrations of urate before (UP) and during treatment with allopurinol (UT).
RESULTS
- The dose of allopurinol required to lower plasma urate to recommended target concentrations is dependent only on the baseline, pre-treatment plasma concentration of urate. Surprisingly, CLcr is not influential with respect to the final maintenance dosage. This study confirms that higher doses of allopurinol than those indicated by creatinine clearance are required to reach recommended targets of plasma urate.
- However, CLcr should determine the starting dose of allopurinol.
<table><tr><th>Pre-treatment plasma urate (U_P, mmol l^{-1})</th><th>Predicted allopurinol dose (mg day^{-1}) to achieve EULAR target (U_T = 0.36 mmol l^{-1})</th><th>Predicted allopurinol dose (mg day^{-1}) to achieve BSR target (U_T = 0.30 mmol l^{-1})</th></tr><tr><td>0.65</td><td>405</td><td>775</td></tr><tr><td>0.6</td><td>335</td><td>665</td></tr><tr><td>0.55</td><td>265</td><td>554</td></tr><tr><td>0.5</td><td>195</td><td>443</td></tr><tr><td>0.45</td><td>126</td><td>332</td></tr></table>*Equation 3: $D = ID_{50} \times (U_P - U_T)/(U_T - U_R)$.
BSR, British Society of Rheumatology; EULAR, European League Against Rheumatism; ID_{50}, dose of allopurinol that has reduced the inhibitable urate ($U_P - U_R$) by 50%; U_R, apparent resistant plasma concentration of urate; U_T, plasma concentration of urate during treatment with allopurinol.
Optimized values for U_R and ID_{50} (from Table 1) are 0.20 mmol l^{-1} and 226 mg, respectively.
A high baseline plasma urate concentration requires a high dose of allopurinol to reduce plasma urate below recommended concentrations. This dose is dependent on only the pre-treatment plasma urate concentration and is not influenced by CLcr.</td><td>Understanding the dose-response relationship of allopurinol: predicting the optimal dosage. Graham GG et al. Br J Clin Pharmacol. 2013 Dec;76(6):932-8</td></tr>
<tr><td>Süstemaatiline kirjanduse ülevaade hindamaks podagra ravivõimalusi kroonilise neeruhaigusega patsientidel.
- Artikkel hõlmab vähe randomiseeritud kontrollitud uuringuid.
- Publications were deemed relevant if they reported results from clinical studies, case reports, or prescribing practices of the drug of interest in patients with gouty arthritis and CKD. Articles were not evaluated for risk of bias.</td><td>Challenges associated with the management of gouty arthritis in patients with chronic kidney disease: a systematic review.</td></tr>
</table>

- Allopurinol should be started at a low dose (eg, 100 mg daily) and increased by 100 mg every 2 to 4 weeks if required. **Allopurinol should be used with caution (and may be contraindicated) in patients with renal impairment.** - Allopurinooli soovituslik keskmine doos on 200-300 mg kerge artriidi korral, 400-600 mg in mõõduka kuni raske toofustega artriidi korral. - **In patients with CKD, allopurinol doses should be adjusted based on creatinine clearance.** - **Current allopurinol prescribing information states that if creatinine clearance is between 10 and 20 mL/min, allopurinol 200 mg/d is suitable. If creatinine clearance is <10 mL/min, the daily dose of allopurinol should not exceed 100 mg, and if creatinine clearance is <3 mL/min, the interval between doses may need to be lengthened (eg, 300 mg twice a week or less).** However, several studies have found that the lower recommended allopurinol doses used in patients with CKD do not lower serum uric acid to acceptable levels and that **doses higher than those recommended may be required to achieve serum uric acid levels below 6.0 mg/dl (360 mcmol/l).** - **EULAR guidelines state that patients with renal insufficiency are usually started at allopurinol doses of 50 to 100 mg/d, and dose is titrated upward until serum uric acid is below 6 mg/dl (360 mcmol/l).**	**Curiel RV, Guzman NJ.** Semin Arthritis Rheum. 2012 Oct;42(2):166-78.

Lisamaterjal

Töörühma soovil otsiti lisaks materjali allopurinooli annustamise kohta rahvusvahelistest podagra ravi käsitlevatest ravijuhenditest.

EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT).
(Zhang, W *et al*. Ann Rheum Dis, 2006. May; 65: 1312–1324. ; http://ard.bmj.com/content/65/10/1312.full.pdf+html)

Table 1 Level of evidence

Ia	Meta-analysis of randomised controlled trials
Ib	Randomised controlled trial
IIa	Controlled study without randomisation
IIb	Quasi-experimental study
III	Non-experimental descriptive studies, such as comparative, correlation, and case–control studies
IV	Expert committee reports or opinion or clinical experience of respected authorities, or both

lk.1318 – 1319

8. The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum uric acid below

the saturation point for monosodium urate ((360 mmol/l or (6 mg/dl).
Strength of recommendation: 91 (95% CI, 86 to 96) (VAS skaala 0 – 100)
/…/ the target of urate lowering treatment is best centred on an SUA level that is linked to the saturation point of monosodium urate rather than to a normal laboratory range. A level of SUA of ≤360 mcmol/l reflects a tissue level that is likely to be well below this saturation point. One cohort study has shown that maintaining the SUA below 6.2 mg/dl (370 mcmol/l) would significantly reduce tophi, whereas an SUA above 8.2 mg/dl (490 mcmol/l) did not reduce tophi. This was supported by other two cohort studies in which a linear relation was found between the level of SUA and reduction in tophi, and where depletion of urate crystals from knee synovial fluids could be achieved if the SUA was maintained below 6 mg/dl (360 mcmol/l) for at least 12 months.
In summary, the aim of urate lowering therapy is ''cure'' through prevention of urate crystal formation and enhancement of crystal dissolution. To achieve this aim there are clinical data to support the requirement to maintain the SUA at or below a level of 360 mcmol/l (6 mg/dl) (level III). This SUA level reflects a tissue level that is below the saturation point for monosodium urate.

9. Allopurinol is an appropriate long term urate lowering therapy. It should be started at a low dose (100 mg daily) and increased by 100 mg every two to four weeks if required. The dose must be adjusted in patients with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitisation (the latter only in cases of mild rash).
Strength of recommendation: 91 (95% CI, 88 to 95) (VAS skaala 0 – 100)
A reanalysis based on individual patient data from two studies showed a significant dose–response relation between allopurinol and SUA in which every 100 mg increment of allopurinol reduced SUA by approximately 1 mg/dl (60 mcmol/l). **There is general support for the ''go low, go slow'' strategy of starting allopurinol at 100 mg daily and increasing by 100 mg increments every few weeks until the therapeutic SUA target is achieved.** Compared with giving only a fixed dose of 300 mg (a very common practice throughout Europe), the possible benefits of slowly titrating up the doose include the following: reduced likelihood of provocation of acute attacks; reduced incidence of toxicity; tailoring of the dose to suit individual requirements; and emphasis on the importance of a sufficiently low target SUA.
One single blind, placebo controlled trial compared renal function (serum creatinine and creatinine clearance) in subjects with hyperuricaemia who received either allopurinol or placebo. After 2.5 years of treatment the trial overall found no significant increase of serum creatinine or decrease of creatinine clearance compared with placebo, but there was a reduction in creatinine clearance with allopurinol in hypertensive patients with glomerular filtration rates above 80 ml/min (p,0.02). Unfortunately the trial did not report details of allopurinol dosage and the optimal doses of allopurinol in patients with varying renal function remains unknown, though the principle of using lower (especially starting) doses of allopurinol in patients with impaired renal function is generally accepted.
One retrospective cohort study (n=120) compared the risk of adverse drug reactions between patients whose allopurinol maintenance dose matched the recommended dose according to their creatinine clearance rate (n=52) and patients whose maintenance dose exceeded the recommended doose (n=68). The risk of rash, AHS, fixed pigmented drug eruption, or leucocytoclastic vasculitis was similar between the two groups (RR=1.96 (95% CI, 0.34 to 11.92)).

Although not formally studied, the strategy of giving a starting dose of 100 mg daily (especially in those with renal impairment), with further 100 mg increments until the target level of SUA is achieved, is favoured over a fixed dose strategy (level IV).

2012 American College of Rheumatology Guidelines for Management of Gout Part I: Systematic Non-pharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia

(Khanna, D. et al. Arthritis Care Res (Hoboken). 2012 October ; 64(10): 1431–1446.; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683400/)

Core recommendations for pharmacologic ULT, including the serum urate target

The TFP (task faoce panel) recommended gout with CKD stage 2–5, or end stage renal disease (ESRD), as an appropriate indication, by itself, for pharmacologic ULT (Evidence C) in patients with prior gout attacks and current hyperuricemia.

The TFP recommended that **the goal of ULT is to achieve a serum urate target, at a minimum, of < 6 mg/dL in all gout case scenarios** (Evidence A).

Recommendations specific to allopurinol dosing and pharmacogenetics

TFP recommended that the starting dose of allopurinol be no greater than 100 mg per day (Evidence B), consistent with prior FDA and EULAR guidelines. The rationale of the TFP was partly that a low allopurinol starting dose could reduce early gout flares after ULT initiation, and partly as a component of risk management with respect to the potential for severe hypersensitivity reaction to allopurinol.

TFP recommended gradual upward titration of the allopurinol maintenance dose every 2–5 weeks to an appropriate maximum dose for gout, in order to treat to the serum urate target appropriate for the individual patient (Evidence C). The TFP weighed robust evidence that allopurinol monotherapy at doses of 300 mg daily or less failed to achieve the serum urate target of <6 mg/dL , or < 5 mg/dL in more than half of subjects with gout. The TFP reviewed small studies in which the allopurinol dose was titrated above 300 mg daily in gout with overall success in achieving the serum urate target. Importantly, in doing so, **the TFP also recommended that the maintenance dose of allopurinol can be raised above 300 mg per day, even in those with renal impairment**, provided there is adequate patient education and regular monitoring for drug hypersensitivity and other adverse events, such as pruritis, rash, and elevated hepatic transaminases, as well as attention to potential development of eosinophilia (Evidence B).

In their evaluation of the allopurinol starting dose as a component of risk management strategy, the TFP first weighed evidence that the highest risk of severe allopurinol hypersensitivity reaction is in the first few months of therapy. A recent case-controlled retrospective analysis of AHS and allopurinol starting dose further buttressed the aforementioned recommendation by the TFP of a **starting dose of allopurinol of no more than 100 mg daily, and the TFP recommendation of an even lower starting dose of allopurinol (50 mg daily) in stage 4 or worse CKD (Evidence B).**

Core recommendations in use of allopurinol and uricosuric ULT in gout

A. ALLOPURINOL:

- Starting dose should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD (Evidence B)
- Gradually titrate maintenance dose upwards every 2–5 weeks to appropriate maximum dose, in order to treat to chosen SUA target (Evidence C)
- Dose can be raised above 300 mg daily, even with renal impairment, as long as this is accompanied by adequate patient education and monitoring for drug toxicity (eg, pruritis, rash, elevated hepatic transaminases) (Evidence B)
- Prior to initiation, consider HLA-B*5801 in selected patients, specifically in higher risk sub-populations for severe allopurinol hypersensitivity reaction (eg, Koreans with stage 3 or worse CKD; Han Chinese and Thai irrespective of renal function) (Evidence A)