Kliiniline küsimus nr 16

Kas kõikidel kroonilise neeruhaigusega patsientidel tuleb aneemia diagnoosimiseks teostada kindlad laboratoorsed uuringud (hemogramm, transferriini saturatsioon, ferritiin) ja samasuguse sagedusega vs mitte?

Tulemusnäitajad: kroonilise neeruhaiguse progresseerumine, kroonilise neeruhaiguse ravi tulemuslikkus, südame-veresoonkonna tüsistused, kukkumine, hospitaliseerimine, patsiendi elukvaliteet, ravikulu, elulemus, üldsuremuse vähenemine

Kliinilise küsimuse vastamiseks otsiti materjali eelnevalt sekretariaadi poolt Agree II meetodil hinnatud ravijuhenditest

- 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; http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf) **(KDIGO)**

- National Clinical Guideline Centre; National Institute for Health and Care Excellence. **Chronic kidney disease (artial update). Early identification and management of chronic kidney disease in adults in primary and secondary care**. Clinical Guideline 182. 2014 (http://www.nice.org.uk/guidance/cg182/evidence/cg182-chronic-kidney-disease-update-full-guideline3) **(NICE)**

- Academy of Medicine of Malaysia: **Management of Chronic Kidney Disease**, 2011 (http://www.acadmed.org.my/index.cfm?&menuid=67) **(Mal)**

- KHA-CARI Guideline: **Early chronic kidney disease: Detection, prevention and management**.2013 (http://www.cari.org.au/CKD/CKD%20early/ckd_early_ckd.html) **(CARI)**

- Scottish Intercollegiate Guidelines Network**: Diagnosis and management of chronic kidney disease**. A national clinical guideline 103. 2008. (http://www.sign.ac.uk/pdf/sign103.pdf) **(SIGN)**

Täiendava tõenduspõhise materjali leidmiseks kasutasime infosüsteeme PubMed, SumSearch2; kitsenduseks viimased 5 aastatm saada olevad täistekstd - otsinudsõnad olid järgmised: Anemia and chronic kidney disease; Anemia and CKD stage; Anemia and chronic kidney disease and stage; Prevalence of anemia and chronic kidney disease; Anemia and albuminuria and CKD; Anemia and CKD and prognosis; Anemia diagnosis and chronic kidney disease; Anemia management and chronic kidney disease; Iron deficiency and chronic kidney disease; Iron status and chronic kidney disease

Süstemaatilised ülevaated ja muud uuringud

Süstemaatilisi ülevaateid ega meta-analüüse antud teemal pole leitud. Kõik leitud uuringud on suhteliselt vanad. Allpooltoodud uuringutele on viidatud ka rahvusvahelistes ravijuhendites (sh. NICE Anemia CKD Guideline 2015).
Hemoglobiini taseme määramise vajalikkuse ja sageduse kohta andmed põhinevad suure Ameerika Ühendriikide kohortuuringu andmetel (NHANES III riiklik tervise ja toitumuse

uuring), mille raames oli läbi viidud mitu läbilõikeuuringut, et hinnata aneemia levimust KNH puhul ning aneemia seost neerufunktsiooni alanemisega (Melissa E. Stauffer et al. 2014, Brad C. Astor et al. 2002, Inker LA et al. 2011). Samuti NHANES raames hinnati ka rauadefitsiidi esinemissagedust KNHga patsentidel (TSAT ja ferritiini tase) (Fishbane 2009, Hsu 2002).
Simona Stancu et al. uuringus hinnati rauaravi efektiivsust ja raua perifeersete indeksite tundlikkust erütropoeesi hindamisel. Uuringule on viidatud NICE ja KHA-CARI ravijuhistes. Uuringu puuduseks on väike osalejate arv.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Melissa E. Stauffer, Tao Fan. Prevalence of Anemia in Chronic Kidney Disease in the United States 2014 (NHANES) Abstract Anemia is one of the many complications of chronic kidney disease (CKD). However, the current prevalence of anemia in CKD patients in the United States is not known. Data from the National Health and Nutrition Examination Survey (NHANES) in 2007–2008 and 2009–2010 were used to determine the prevalence of anemia in subjects with CKD. The analysis was limited to adults aged >18 who participated in both the interview and exam components of the survey. Three outcomes were assessed: the prevalence of CKD, the prevalence of anemia in subjects with CKD, and the self-reported treatment of anemia. CKD was classified into 5 stages based on the glomerular filtration rate and evidence of kidney damage, in accordance with the guidelines of the National Kidney Foundation. Anemia was defined as serum hemoglobin levels =<12 g/ dL in women and =<13 g/dL in men. We found that an estimated 14.0% of the US adult population had CKD in 2007–2010. Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. A total of 22.8% of CKD patients with anemia reported being treated for anemia within the previous 3 months–14.6% of patients at CKD stages 1–2 and 26.4% of patients at stages 3–4. These results update our knowledge of the prevalence and treatment of anemia in CKD in the United States. **NHANES III on Amerika Ühendriikide riikliku tervise ja toitumuse uuring, mille raames oli läbi viidud mitu uuringut, et hinnata aneemia levimust KNH puhul ning aneemia seost neerufunktsiooniga. 2014 aastal viidi läbi läbilõikeuuring, mille käigus hinnati aneemia esinemissagedust KNHga inimestel ning korrelatsiooni KNH staadiumi ja aneemia esinemise vahel. Tulemustest selgus, et aneemia esinemissagedus oli 2 korda suurem KNH rühmas võrreldes üldpopulatsiooniga. Samuti oli leitud, et aneemia esinemissagedus korreleerub KNH ataadiumiga: 1 staadiumis aneemia protsent on 8,4%, 5 staadiumis 53,4%.** (Brad C. Astor et al. Association of Kidney Function With AnemiaThe Third National Health and Nutrition Examination Survey (1988-1994)) 2002 aastal läbiviidud läbilõikeuuring, et hinnata korrelatsiooni olemasolu neerufunktsiooni ja hemoglobiini taseme vahel. Hinnati 15419 inimeste	http://www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0084943&representation=PDF (2014) http://archinte.jamanetwork.com/article.aspx?articleid=211681 (2002)

andmeid ning selgus, et madalam neerufunktsioon (< 60ml/min/1,73m2) on statistiliselt oluliselt kõrgema aneemia esinemissagedusega.)	
Inker LA, Coresh J, Levey AS et al. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol 2011 Higher levels of albuminuria associate with increased risk for adverse outcomes independent of estimated GFR (eGFR), but whether albuminuria also associates with concurrent complications specific to chronic kidney disease (CKD) is unknown. Here, we assessed the association of spot albumin-to-creatinine ratio with anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism, and hypertension among 30,528 adult participants in NHANES 1988 –1994 and 1999 –2006. After multivariable adjustment including eGFR, higher albumin-to-creatinine ratios associated with anemia, acidosis, hypoalbuminemia, hyperparathyroidism, and hypertension but only weakly associated with acidosis and anemia. Furthermore, the associations between albumin-to-creatinine ratio and both anemia and acidosis were not consistent across eGFR strata. Higher albumin-to-creatinine ratio levels did not associate with hyperphosphatemia. Lower eGFR associated with higher prevalence ratios for all complications, and these associations were stronger than those observed for the albumin-to-creatinine ratio; after multivariable adjustment, however, the associations between eGFR and both hypoalbuminemia and hypertension were NS. In conclusion, albuminuria and eGFR differentially associate with complications of CKD. **Selles uuringus samuti kasutatud NHANES andmed, uuriti seoseid albuminuria (albumiini/kretiniini suhe), arvutusliku filtratsioonikiiruse (eGFR) ja KNH tüsistuste vahel (aneemia, atsidoos, hüpoalbumineemia, hüperfosfateemia, hüperparatüreoidism, hüpertensioon).** **Kõrgem albumiini/kreatiniini suhe oli seotud aneemiaga sõltumata eGFRst. Samuti oli näidatud seost madalama eGFRi ja aneemia esinemissageduse tõusu vahel. Seos eGFR ja aneemia vahel oli statistiliselt tugevam kui albuminuria ja aneemia vaheline seos.**	http://jasn.asnjournals.org/content/22/12/2322.full.pdf+html
Steven Fishbane et al. Iron Indices in Chronic Kidney Disease in the National Health and Nutritional Examination Survey 1988 –2004 (2009) *Background and objectives:* Anemia is a common and early complication of nondialysis chronic kidney disease (CKD). One contributing factor is iron deficiency, which may be particularly problematic during erythropoietin replacement therapy. The aim of this study was to examine the prevalence of iron deficiency in nondialysis CKD. Design, setting, participants, & measurements: The National Health and Nutritional Examination Survey (NHANES) data for NHANES III (1988 to 1994) and subsequent NHANES 2-yr datasets, 1999 to 2000, 2001 to 2002, and 2003 to 2004 were analyzed for individuals >18 yr old. *Results:* It was found that low levels of iron tests [either serum ferritin < 100 ng/ml or transferrin saturation (TSAT) < 20%] were present in most patients with reduced creatinine clearance (CrCl). The percentage of low iron tests was higher among women than men, present in 57.8 to 58.8% of men and 69.9 to 72.8% of women (P < 0.001). With declining levels of CrCl, in women, TSAT levels decreased, whereas, surprisingly, serum ferritin tended to progressively increase. The percentage of anemic subjects increased progressively with declining quartiles of TSAT but	http://cjasn.asnjournals.org/content/4/1/57.full.pdf+html

was unrelated to serum ferritin quartiles. *Conclusions:* It was found that low levels of iron tests, following National Kidney Foundation/Kidney Disease Outcomes Quality Initiative guidelines (either serum ferritin < 100 ng/ml or TSAT < 20%) were present in most patients with reduced CrCl. **2009 aastal läbiviidud uuring (NHANES andmebaasi põhine) näitas, et rauafunktsiooni näitajad (TSAT või seerumi ferritin) olid madalamad enamikel alanenud CCr haigetest. Madalate rauanäitajate protsent oli kõrgem naistel. CCr alanemisel naistel alanes ka TSAT tase, kuid ferritiitini tase oli tõusutendentsiga**.	
CHI-YUAN HSU et al. Iron Status and Hemoglobin Level in Chronic Renal Insufficiency (2002) *Abstract.* Much has been written on the important contribution of iron deficiency toward anemia and epoetin resistance among end-stage renal disease (ESRD) patients, but there are few studies of iron status among chronic renal insufficiency (CRI) subjects not yet requiring dialysis. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Practice Guidelines recommend maintaining ferritin >100 ng/ml and transferrin saturation (TSAT) >20% to ensure adequate iron supply for erythropoiesis among patients with chronic kidney disease, whether or not they are dialysis-dependent. Analysis of the nationally representative data from the Third National Health and Nutrition Examination Survey (NHANES III 1988–1994) revealed that only a minority of anemic CRI subjects in the United States met these K/DOQI targets. For example, in the range of creatinine clearance (CrCl) 30 to 50 ml/min, less than one third of men with hemoglobin <12 g/dl and women with hemoglobin <11 g/dl had ferritin >100 ng/ml and TSAT >20%. In addition, TSAT levels above 20% were independently associated with higher hemoglobin levels. Such data raise the question whether the K/DOQI targets should be reevaluated. It is concluded that ferritin and TSAT targets derived from ESRD studies may not be applicable to subjects with CRI. Further studies are needed to guide optimization of iron status and hemoglobin level in the much larger CRI population. **Uuringus samuti kasutatud NHANES andmebaasi, et selgitada välja kuidas rauafunktsiooni näitajad on seotud KNH staadiumiga.** **Vähem kui 1/3 KNHga uuritavatest (CrCl 30-50ml/min) TSAT tase oli > 20% ja feriitiini tase >100mkg/l.**	http://jasn.asnjournals.org/content/13/11/2783.full.pdf+html
Simona Stancu et al. Can the Response to Iron Therapy Be Predicted in Anemic Nondialysis Patients with Chronic Kidney Disease? (2010) *Background and objectives:* Anemia is iron responsive in 30 to 50% of nondialysis patients with chronic kidney disease (CKD), but the utility of bone marrow iron stores and peripheral iron indices to predict the erythropoietic response is not settled. We investigated the accuracy of peripheral and central iron indices to predict the response to intravenous iron in nondialysis patients with CKD and anemia. *Design, setting, participants, & measurements:* A diagnostic study was conducted on 100 nondialysis patients who had CKD and anemia and were erythropoiesis-stimulating agent and iron naive. Bone marrow iron stores were evaluated by aspiration. Hemoglobin, transferrin saturation index (TSAT), and ferritin were measured at baseline and 1 month	http://cjasn.asnjournals.org/content/5/3/409.full.pdf+html

after 1000 mg of intravenous iron sucrose. Posttest predictive values for the erythropoietic response (≥1-g/dl increase in hemoglobin) of peripheral and central iron indices were calculated. *Results:* The erythropoietic response was noted in a higher proportion in bone marrow iron-deplete than in iron-replete patients (63 *versus* 30%). Peripheral iron indices had a moderate accuracy in predicting response. The positive (PPV) and negative predictive values (NPV) were 76 and 72% for a TSAT of 15% and 74 and 70% for a ferritin of 75 ng/ml, respectively. In the final logistic regression model, including TSAT and ferritin, the chances of a positive response increased by 7% for each 1% decrease in TSAT. *Conclusions:* Because an erythropoietic response is seen in half of patients and even one third of those with iron-replete stores responded whereas peripheral indices had only a moderate utility in predicting response, the therapeutic trial to intravenous iron seems to be a useful tool in the management of anemia in nondialysis patients with CKD. **Sellele uuringule on viidatud NICE ja KHA-CARI ravijuhendites. Puuduseks on väike osalejate arv (100 inimest). Hinnati luuüdi vastust suures doosis IV rauaravile 1 kuu peale rauapreparaasi manustamist. Patsiendid olid KNHga mittedialüüsravil, enne pole saanud ei rauda ega ESA. Tulemuseks oli positiivne erütropoeesi vastus suurel protsendil, kuid raua perifeersete indeksite (TSAT ja ferritiin) määramine oli ainult mõõduka tundlikkusega.**	

Ravijuhendid

KDIGO CKD management (lk. 81-82)
Info aneemia definitsiooni ja esinemissageduse kohta. Aneemia definitsioon põhineb WHO andmetel 2008).
Andmed KNH aneemia esinemissageduse ja Hgb määramise sageduse kohta võetud 2011 aasta artiklist (Inker LA, Coresh J, Levey AS et al. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol 2011; 22: 2322–2331.**)** – antud uuringus on kasutatud NHANES III (National Health and Nutrition Examination Survey 2002) raames kirjeldatud kohorti.

Definition and identification of anemia in CKD

- **3.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/ dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (Not Graded)**

- **Diagnoosi aneemiat KNHga täiskasvanutel ja lastel vanuses >15 aastat kui Hgb kontsentratsioon on <130 g/l meestel ja <120 g/l naistel.**

Soovitus põhineb WHO andmetel (World Health Organization. Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia. de Benoist B, McLean E, Egli I, and Cogswell M (eds), 2008)

- **3.2.3: To identify anemia in people with CKD measure Hb concentration (Not**

Graded):

-when clinically indicated in people with GFR >= 60 ml/min/1.73 m^2 (GFR categories G1-G2);

-at least annually in people with GFR 30-59ml/min/1.73 m^2 (GFR categories G3a-G3b);

-at least twice per year in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5).

- **Selleks, et diagnoosida aneemiat KNHga inimestel, määra Hgb kontsentratsiooni:**

  -Kui selleks on kliiniline näidustus inimestel GFRga >=60ml/min/1,73m2 (G1-G2);

  -Vähemalt 1 kord aastas inimestel GFRga 30-59 ml/min/1,73m2 (G3a-G3b);

  -Vähemalt 2 korda aastas inimestel GFRga <30ml/min/1,73m2 (G4-G5)

Tabel 27 Inker LA, Coresh J, Levey AS et al. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol 2011; 22: 2322–2331.

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease (2012)

Ravijuhendis on infot:

-aneemia esinemissageduse kohta – NHANES III

-Hgb määramise sageduse kohta ilma aneemiata KNH haigetel

-Hgb määramise kohta aneemia ja KNHga patsientidel

-Vajalikke analüüside kohta aneemia diagnoosimiseks (Uuringute andmed aastast 1974-2001)
-Rauaravi kohta

Er. massi ülekanded

(ESA ravi)

Paljud soovitused on põhinevad vanade ja väiksemate uuringute andmetel ja on "Not Graded".

TESTING FOR ANEMIA

Frequency of testing for anemia

	GFR >90	GFR 60-89	GFR 45-59	GFR 30-44	GFR <30
Aneemia esinemissagedus	4,0%	4,7%	12,3%	22,7%	51,5%

1.1.1: For CKD patients without anemia (as defined below in Recommendation 1.2.1 for adults and Recommendation 1.2.2 for children), measure Hb concentration when clinically indicated and (Not Graded):
- at least annually in patients with CKD 3
-at least twice per year in patients with CKD 4–5ND
-at least every 3 months in patients with CKD 5HD and CKD 5PD

1.1.1. Määra Hgb kontsentratsiooni KNHga patsientidel ilma aneemiata kui see on kliiniliselt näidustatud ja:

-Vähemalt 1 kord aastas CKD 3

-Vähemalt 2 korda aastas CKD 4-5ND

-Vähemalt iga 3 kuu tagant CKD 5HD ja CKD 5PD

1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (Not Graded):
-at least every 3 months in patients with CKD 3–5ND and CKD 5PD
-at least monthly in patients with CKD 5HD [See Recommendations 3.12.1–3.12.3 for measurement of Hb concentration in patients being treated with ESA.]

1.1.2: Määra Hgb kontsentratsiooni aneemiaga KNH-tel kui selleks on kliiniline näidustus ja:
-Vähemalt igal 3 kuul patsientidel CKD 3-5ND ja CKD 5PD
-Vähemalt 1 kord kuus CKD 5HD

NHANES III Astor BC, Muntner P, Levin A et al. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002; 162: 1401–1408

Diagnosis of anemia

1.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (Not Graded)

- **1.2.1: Diagnoosi aneemiat KNHga täiskasvanutel ja lastel vanuses > 15 aastat kui Hgb kontsentratsioon on <130g/l meestel ja <120 g/l naistel.**

WHO andmed

Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (Not Graded):
-Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count
-Absolute reticulocyte count

-Serum ferritin level
-Serum transferrin saturation (TSAT)
-Serum vitamin B12 and folate levels

1.3: KNH ja aneemiaga patsientidel (sõltumata KNH staadiumist) aneemia diagnoosimine sisaldab (Not Graded):
-Täisvere analüüsi, mis sisaldab Hgb, erü., leuk. + valem, tromb.
-Retikulotsüütide absoluutarvu
-Seerumi ferritiini taset
-Seerumi transferriini saturatsiooni (TSAT)
-Vit. B12 ja foolhappe taset

Uuringute andmed aastast 1974-2001

- **2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (Not Graded)**

  2.1.1: Rauaravi määramisel peab hoidma potentsiaalset kasu (vereülekannete arvu vähendamine, ESA ravi, aneemiast põhjustatud sümptoomid) ja kahju riski (anafülaktiline reaktsioon, mud ägedad reaktsioonid, teadmata likajalised risked) tasakaalus (Not Graded)

- **2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):**

an increase in Hb concentration without starting ESA treatment is desired* and

TSAT is <=30% and ferritin is <=500ng/ml (<=500 mkg/l)

2.1.2: Täiskasvanud KNH ja aneemiaga patsientidel, kes ei saa ei raua ega ESA ravi, me soovitame IV rauaravi (voi KNH ND patsientidel 1-3 muu tsüklina suukaudne rauaravi) kui (2C):

on vajalik tõsta Hb taset ilma ESA ravita ja

TSAT on <=30%ja ferritiini tase <=500ng/ml (<=500 mkg/l)

- **2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (Not Graded)**

2.1.4: KNHga mittedialüüsravil patsiendi jaoks, kes vajab rauaasendusravi, vali raua manustamise viisi sõltuvalt raua defitsiidist, veenitee olemasolust, suukaudse rauaravi efektsiivsusest, suukaudse ja intravenoosse rauaravi kõrvaltoimetest, hinnast (Not graded).

• 2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (Not Graded)

2.1.5: Korralda edaspidi rauaasendisravi sõltuvalt Hgb vastusest ravile, verekaotusest, rauanäitajate kontsentratsioonidest (TSAT ja ferritin), Hgb taseme muutusest, patsiendi seisundist (Not Graded).

- *2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (Not Graded)*

- *2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (Not Graded)*

• 2.3: When the initial dose of IV iron dextran is administered, we recommend (1B) and when the initial dose of IV nondextran iron is administered, we suggest (2C) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

2.3: Kui esimene IV rauadekstraani annus on manustatud soovitame (1B) ning kui esimene IV dekstraani mittesisaldav raua preparaat on manustatud soovitame (2C) jälgida patsienti 60 minutit peale infusiooni ning et elustamiseks vajalikud vahendid ja väljaõpetatud personal oleksid raskete kõrvaltoimete raviks saadaval.

• 2.4: Avoid administering IV iron to patients with active systemic infections. (Not Graded)

2.4: Väldi IV raua manustamist ägeda (aktiivse) süsteemse infektsiooniga patsientidel (Not Graded).

• When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (1B)

Kroonilise aneemia ravis soovitame vältida erütrotsüütide massi ülekandeid põhiriskide vähendamiseks (1B).

• 4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (1C)

4.1.2: Patsintidel, kes on sobilikud organi siirdamiseks me eriti sovitame vältida erütrotsüütide massi ülekandied, selleks et vähendada allosensibilisatsiooni riski (1C)

- *4.1.3: When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (2C):*

-ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)

-The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)

4.1.3: Kroonilise aneemia ravi korraldamisel me arvame, et erütrotsüütide massi ülekande kasu või ületada kahju patsientidel (2C):

-kellel ESA ravi ei ole efektiivne (nt. hemoglobinopaatiad, luuüdi puudulikus, ESA resistsensus)

-ESA ravi riskid võivad ületada kasu (nt. pahaloomuline kasvaja anamneesis või aktiivne, eelnev insult)

- **4.1.4: We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (2C)**

4.1.4: Me aravame, et otsus teha vereülekannet KNHga patsiendil mitte-ägeda aneemiaga ei peaks põhinema suvalisel Hgb tasemel, vaid aneemia sümptomide esinemisel (2C)

4.2: In certain acute clinical situations, we suggest patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (2C):

-When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)

-When rapid preoperative Hb correction is required

4.2: Me arvame, et võib teha vereülekannet patsiendile kliinilises olukorras kui vereülekande kasu ületab riski (2C):

-kui äge aneemia korrektsioon on vajalik, et stabiliseerida patsiendi seisundit (nt. äge verejooks, ebastabiilne koronaarhaigus)

-kui kiire preoperatiivne Hgb korrigeerimine on vajalik

NICE CKD guideline (lk. 392)

<u>13.1 Anaemia identification in people with CKD</u>

- **NHANES III** US (*Coresh J, Astor BC, Greene T et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. American Journal of Kidney Diseases 2003; 41(1):1-12.)*

- **NEOERICA project UK, anaemia identification in CKD: prevalence of Hb <11 g/dl in the general population** *(Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney International 2007; 72(1):92– 99).)*

In the UK we know that from primary care data 85% of patients who have had a serum creatinine measurement have also had their haemoglobin level measured. This study demonstrated that the prevalence of anaemia rises sharply from CKD stage 3b onwards (Table 130), suggesting the importance of testing for anaemia at levels of GFR <45 ml/min/1.73 m^2.

NICE clinical guideline 114 ('Anaemia management in people with CKD')[273] recommended that investigation and management of anaemia should be considered in people with anaemia of CKD when their haemoglobin (Hb) level falls to 11g.dl or less or they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpatations). The guideline was written for people with a GFR <60ml/min/1.73 m^2 already known to have a haemoglobin level less than 11 g/dl but gave no recommendations about testing for anaemia.

- **13.1.2 Recommendation**

If not already measured, check the haemoglobin level in people with a GFR of less than 45 ml/min/1.73 m^2 (GFR category G3b, G4 or G5) to identify anaemia (haemoglobin less than 110 g/litre (11.0 g/dl), see Anaemia management in people with chronic kidney disease [NICE clinical guideline 114]). Determine the subsequent frequency of testing by the measured value and the clinical circumstances. [2008]

Kontrolli Hgb taset inimestel GFRga < 45ml/min/1,73m2 (G3b, G4, G5), et diagnoosida aneemiat (Hgb tase < 110g/l) kui seda pole veel määratud.

NICE (NG8): Anaemia Management in Chronic Kidney Disease (Partial update 2015)

2015 aastal uuendatud ravijuhis aneemia ohta KNHtel.

Käsitleb:

-Aneemia diagnoosimine ja edasine uurimine

-Testid rauadefitsiidi kindaks tegemiseks ja ravi efktiivsuse hindamiseks (soovitatud kasutada uuemaid markereid) info uute markerite kohta dialüüsihaigetel

-rauaravi

-erütropoetiini määramise vajadus

-C vitamin, foolhape, karnitiin aneemia ravis

-vereülekanded

(-ESA ravi)

3.2 Complete list of recommendations

1. Consider investigating and managing anaemia in people with CKD if:

□□their Hb level falls to 110 g/litre or less (or 105 g/litre or less if younger than 2 years) or

□□they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations). [2011]

1. Uuri ja tegele aneemiaga KNHga patsientidel kui:

- Hgb tase on =< 110 g/l või

- esinevad aneemiaga seotud sümptomid (väsimus, õhupuudus, tahhükardia jt.)

Quality of evidence: There was **low to moderate quality evidence** from **prospective and retrospective cohort studies.** The majority of the studies were adjusted for confounding factors but the GDG considered that confounding (for example the more severe the chronic kidney disease, the lower the Hb is likely to be) remained an important issue in deciding at which level of Hb to initiate management.

The 2011 update to the guidance on anaemia in CKD (CG114) indicated that the blood count should be monitored in CKD, without specifying the interval. The GDG for the 2015 update felt that blood count monitoring has to be tailored to the patient, and usually coincides with eGFR testing (to avoid unnecessary needlesticks).

Health economic evidence statements [2011] Evidence statement:

There is moderate quality evidence[189] that is partially applicable to the guideline to show that in untreated patients:

- low Hb [<11 g/dL] compared to higher Hb [>11 g/dL] is associated with increased costs.
- an decrement in Hb level of 1 g/dL is associated with increased cost.

Lefebvre and colleagues[189] reported that, in CKD patients untreated for anaemia, a haemoglobin level <11 g/dL was associated with an additional monthly cost of £320 (CI: £223, £408) compared to a haemoglobin level >11 g/dL. Every 1g/dL decrease in haemoglobin was associated with a £52 increase in cost (CI: £32-£71).

2. An estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m^2 should trigger investigation into whether anaemia is due to CKD. When the eGFR is greater than or equal to 60 ml/min/1.73m^2 the anaemia is more likely to be related to other causes. [2006]

2. Kui eGFR on madalam kui 60ml/min/1,73m2 siis peaks uurima kas aneemia põhjuseks on KNH. Kui eGFR on võrdne või kõrgem kui 60ml/min/1,73m2, siis on suurem tõenäosus, et aneemial on mud põhjused.

Clinical introduction: Data from population studies such as **NHANES III** in the USA and the **NEOERICA** study in the UK suggest an increasing prevalence of anaemia with decreasing GFR level. A similar relationship between glomerular filtration rate (GFR) and anaemia has also been demonstrated in population cohorts of people with diabetes[354]. Although anaemia is common in people with diabetes it is also commonly unrecognised and undetected[335]. The prevalence of anaemia in people with diabetes is increased at all levels of renal function in those with increased proteinuria/albuminuria[355], and it has been suggested that in people with diabetes, anaemia associated with CKD may occur earlier in the evolution of CKD when compared with people without diabetes. In investigating the evidence base, this section seeks to describe the relationship between GFR and haemoglobin levels and provide guidance for clinicians about the threshold level of GFR below which they should suspect that anaemia is associated with CKD.

A literature search identified five studies investigating the association between GFR or creatinine clearance (CCr) with Hb/Hct levels in non-diabetic patients[25,113,146,170,216] and four studies in diabetic patients 85,100,353,354. **(Level 2+, level 3)**

3. Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months (every 1–3 months for people receiving haemodialysis).

Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.

If using percentage of hypochromic red blood cells is not possible, use reticulocyte Hb content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte Hb equivalent.

If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015]

Vii läbi teste raua defitsiidi diagnoosimiseks ja määra potentsiaalset rauaravi tundlikkus iga 3 kuu tagant (iga 1-3 kuu tagant HD patsintidel)

- **Kasuta hüpokroomsete erütrotsüütide protsenti (HRC >6%) ainult siis kui vereproovi on võimalik töödelda 6 tunni jooksul**
- **Kui hüpokroomsete erütrotsüütide protsenti pole võimalik määrata, kasuta**

retikulotsüütide Hgb sisalduse määramise (vähem kui 29 pg) või muu testi nt. retikulotsüütide Hgb ekvivalenti

- **Kui neid teste pole võimalik teostada või tegemist on talasseemia diagnoosiga patsiendiga, siis määra transferrini saturatsiooni (vähem kui 20%) ja ferritiini (vähem kui 100mkg/l) kombinatsiooni.**

4. Do not request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anaemia of CKD. [new 2015]

4. Ära määra ainult transferriini saturatsiooni või seerumi ferritiini rauadefitsiitse aneemia hindamiseks KNH ja aneemiaga patsientidel

Summary: Based on the evidence (**ranging from low to very low quality**) which showed that %HRC had high sensitivity and specificity, followed by CHr, and the results of the health economic model, the GDG recommended %HRC (>6%) as the first-line test to diagnose iron deficiency followed by CHr or equivalent test (<29 pg). TSAT (<20%) and SF (<100 micrograms/litre) in combination were only recommended for the diagnosis of iron deficiency when any of the other tests were not available; the GDG agreed that as the sensitivity for each test was very low, neither TSAT nor SF could be used for diagnosis of iron deficiency and recommended against their use in isolation. However, it was acknowledged that SF still has a place in the diagnosis of iron overload (SF >800 micrograms/litre) and should be used (link to CG114 recs and algorithm).

• Üks uuring predialüüsihaugete kohta: Stancu S, Barsan L, Stanciu A, Mircescu G. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? Clinical Journal of The American Society of Nephrology. 2010; 5(3):409-416 (http://cjasn.asnjournals.org/content/5/3/409.long)

Evidence statements

CHr

• Two studies were identified looking at the performance of CHr to predict response to iron therapy based on average dose of ESA used to maintain target haematocrit. Moderate quality evidence from one RCT[111] (n=138) favoured using CHr at a threshold of less than 29 pg compared with using TSAT or SF. Low quality evidence from another RCT[166] (n=183) favoured the use of TSAT alone compared with using CHr at a higher threshold of less than 32.5 pg.

• Low quality evidence based on raw data scores in three cohort studies[51,93,350] (n=178) using a less than 29-30 pg threshold showed highly variable and mediocre sensitivity (point estimates of 33%, 47% and 57% with a range of 10-73%) and high but variable specificity (point estimates of 100%, 83% and 93% with a range of 36-100%). Two of these studies reported fair AUC[51,350] (75.2 and 79.8). One very low quality paper[54] (n=69) also reported a fair AUC of 74. One very low quality paper[109] (n=32) using a lower threshold (less than 26%) reported higher sensitivity (100%) and similar specificity (80%).

- %HRC

- Very low quality evidence based on raw data scores in two cohort studies[51,350] (n=157) using a more than 6% threshold showed reasonably high and variable sensitivity (point estimates of 82% and 92% with a range from 62-100%) and reasonably high and variable specificity (point estimates of 75% and 95% with a range of 51-99%). These studies also reported excellent AUC (93.7 and 92.9). One very low quality paper[54] (n=69) also reported a fair AUC of 72. One very low quality paper[109] (n=32) using a higher threshold (more than 10%) reported lower sensitivity (43%) and similar specificity (80%).

- TSAT

- Very low quality evidence from a diagnostic meta-analysis of six studies[51,93,109,110,332,350] (n=357) using a less than 20% threshold showed variable and mediocre sensitivity 61% (34-84%) and mediocre specificity 78% (63-91%). AUC from three of the six studies[51,332,350] (n=257) and one additional very low quality study[54] (n=69) not included in the meta-analysis ranged from very poor/equal to chance to good (40-90).

- SF

- Very low quality evidence from a diagnostic meta-analysis of six studies[51,93,109,110,332,350] (n=357) using a less than 100 micrograms/litre threshold showed low senility 39% (20-60%) and reasonably high specificity 81% (65-92%). AUC from two of the six studies[332,350] (n=225) and one additional very low quality study[54] (n=69) not included in the meta-analysis ranged from very poor/equal to chance to poor (38-69).

- TSAT/SF combinations

    - Very low quality evidence from one study[63] (n=100) investigating the use of TSAT and SF alone or in combination (and/or) showed very low sensitivity 27% and high specificity 92%. Moderate quality evidence from a second paper[332] (n=100) investigating TSAT and SF in combination showed similarly low sensitivity 33% and high specificity 98%.

- sTfR

    - Very low quality evidence from one cohort study[12] (n=17) showed reasonably high but highly variable sensitivity 82% (47-100) and specificity 78% (40-97). Very low quality evidence from two other studies[51,350] reported fair to excellent AUC (78.3 and 98.9).

Economic evidence

Results

The results of the base case analysis are presented in Table 47. For haemodialysis patients, %HRC more than 6 dominated all other strategies (it led both to more QALYs and lower cost). For the other patients, TSAT less than 20% and SF less than 100 micrograms/litre was the lowest cost strategy, but %HRC was the most cost-effective, costing £11,300 per additional QALY gained. The results were subjected to a number of sensitivity analyses. %HRC was ranked 1st in all but the following scenarios:

- When we used the accuracy data from Bovy2007 instead of Tessitore2001 for %HRC (optimal strategy = CHr less than 29 pg – both subgroups).

- When we assumed 1.4% of SAEs were fatal (based on EMA data) and no survival benefit from achieving target Hb (optimal strategy = TSAT less than 20% and SF less than 100 micrograms/litre for both subgroups).

- When we used the cost of a day case from the NHS reference costs for each iron infusion for non- haemodialysis patients (optimal strategy = TSAT less than 20% and SF less than 100 micrograms/litre)

5. Do not routinely consider measurement of erythropoietin levels for the diagnosis or management of anaemia in people with anaemia of CKD. [2006] (lk. 115)

5. Ära määra rutiinselt erütropoetiini taset aneemia diagnoosimiseks ja ohjamiseks KNHga patsientidel.

Evidence statements:

Adults with diabetes

In people with Type 2 diabetes without nephropathy (n=62) a significant negative correlation between serum EPO and Hb levels was found (r2=0.612, p=0.01)[76]. **(Level 3)**

In contrast to the above finding, a study in people with Type 1 diabetes with diabetic nephropathy (in the absence of advanced renal failure) (n=27), found no significant EPO response to lower Hb levels[50]. **(Level 3)**

A cross-sectional study conducted in people with diabetes[352] found no significant EPO response in anaemic patients (defined as Hb <12 g/dl for women and Hb <13 g/dl for men) with GFR >60 ml/min/1.73m2 or >90 ml/min/1.73m2. **(Level 3)**

In a subgroup of iron replete diabetic patients (transferrin saturation level >16%), from the above study[352], serum EPO levels did not change significantly with Hb level as shown below.

Adults with chronic renal failure on conservative therapy

In patients with CKD of varying renal function (CCr 2 to 90 ml/min/1.73m2 (n=117)),

mean serum EPO levels were significantly elevated in all patients when compared with healthy controls (n=59) ($p<0.01$). In a subgroup analysis of patients with CCr 2–40 ml/min/1.73m2 (n=88), CCr and serum EPO showed a positive correlation ($r=0.27$, $p<0.015$)[292]. **(Level 2+)**

Unselected population of adults

In a random sample of patients investigated by coronary angiography (n=395) stratified by renal function, a significant inverse relationship was found between serum EPO and Hb levels in participants with CCr >40 ml/min ($r=-0.35$, $p<0.0001$). No significant correlation was found, however, in participants with CCr <40 ml/min[104]. **(Level 3)**

From evidence to recommendations

Anaemia is associated with increased EPO levels in individuals without evidence of CKD but the anaemia associated with CKD is characterised by a relative lack of EPO response. However, in the clinical situation routine measurement of EPO levels is of limited value in assessing anaemia.

The GDG reached consensus on a threshold GFR of 40 ml/min, below which anaemia is most likely to be of renal aetiology and measurement of erythropoietin levels will not be required except in exceptional circumstances. At GFR levels between 40 and 60 ml/min, the utility of testing is uncertain from the existing evidence, and a research recommendation is given.

7. In people treated with iron, serum ferritin levels should not rise above 800 micrograms/litre. In order to prevent this, review the dose of iron when serum ferritin levels reach 500 micrograms/litre. [2006]

7. Rauaravil patsientidel seerumi ferritiini tase ei peaks tõusma üle 800mkg/l. Selle vältimiseks vaata üle raua doosi kui seerumi ferritiini tase jõuab 500 mkg/l.

5.2.1 Clinical introduction: Iron is crucial for survival and is necessary for erythropoiesis and the production of usable energy through oxidative phosphorylation. However, iron-overload states are harmful and the potent oxidising ability of non-transferrin bound iron makes it potentially toxic. The majority of iron not actively circulating as haemoglobin is safely sequestered in the form of ferritin and hemosiderin in macrophages of the reticuloendothelial system. Molecules that hold iron tend to be very large, containing a central core of iron with a proteinaceous envelope that insulates the body from the iron atom. We know that in iron-overload states, such as haemochromatosis, in which serum ferritin levels can increase to more than 10,000 µg/l, the body is presented with unmanageable levels of free iron leading to iron-related toxicity. The focus of debate about potential iron toxicity in patients with anaemia associated with CKD revolves around the possible increased susceptibility to infectious complications and increased cardiovascular morbidity and mortality engendered by iron administration. In vitro, iron preparations enhance bacterial growth, induce leukocyte dysfunction, inhibit phagocytosis, produce reactive oxygen species, increase oxidative stress, consume antioxidants and, at very high doses, promote lipid peroxidation and cell death. These observations have led to concern that too much iron might

translate these in vitro phenomena into adverse infectious and cardiovascular in vivo effects.

5.2.2 Methodological introduction: A comprehensive literature search did not identify any studies that were suitable to address the clinical or economic aspects of this section, therefore no evidence statements are given.

5.2.3 From evidence to recommendations: Because of the lack of evidence, it was agreed that an upper limit of 800 µg/l of ferritin should be used in line with the current European Best Practice Guidelines. This level is drawn from data on iron toxicity studies performed in the pre-ESA era that demonstrated that high ferritin levels >1,000 µg/l led to the deposition of iron in tissues. However, in practice, in order to prevent serum ferritin from rising above 800 µg/l a patient's iron dose should be reviewed if their serum ferritin levels exceed 500 µg/l. It was noted that it was not known whether there are any long-term consequences related to the administration of intravenous iron as this route bypassed normal absorption routes and homeostatic mechanisms.

13. Supplements of vitamin C, folic acid or carnitine should not be prescribed as adjuvants specifically for the treatment of anaemia of CKD. [2006]

13. Vit. C, foolhape või karnitiin ei tohiks olla määratud kui adjuvantravi aneemia raviks KNH puhul.

Vitamin C: Haemodialysis patients A non-randomised trial (n=52)[343] where 100 mg ascorbic acid was administered i.v. three times weekly in one group (n=23) and as an adjunct to ESA and i.v. iron in another, found no significant change in Hb levels from baseline in either group after 6 months. In addition, no changes were identified in either group in any of the eight domains of quality of life assessed using the Short-Form 36 (SF 36) scale. **(Level 2+)**

In a randomised controlled trial (RCT) of cross-over design (n=27)[134], where ascorbic acid 1,500 mg/week was administered i.v. for 3 months, Hb increased ($p<0.01$ in group I and $p<0.005$ in group II) and TSAT increased (both group I and group II $p<0.001$), whereas ferritin decreased ($p<0.004$ in group I and $p<0.001$ in group II) when compared with baseline levels. Epoetin doses, however, remained unchanged in both groups. **(Level 1+)**

Folic acid: Reticulocyte counts (both $p<0.05$) and Hct levels (both $p<0.01$) increased from baseline levels in both sets of patients receiving folic acid 5 mg three times a week over 12 months (n=10) and patients whose folic acid supplementation had been stopped over this time period (n=10). Hct levels increased further (both $p<0.01$) in the 6-month follow-up period after folic acid supplementation had been stopped in both groups of patients. There were no differences, however, in response to epoetin between the two groups[261]. **(Level 1+)**

Carnitine: No differences were observed in any of the five domains of quality of life as assessed by the Kidney Disease Questionnaire or in overall quality of life, in a RCT of cross-over design (n=16) in which placebo or 20 mg/kg L-carnitine were administered i.v. over a 12-week period. Similarly, no differences were observed in epoetin dose or Hb levels[311]. **(Level 1+)**

No differences were observed in epoetin dose requirement or Hct and reticulocyte counts in a

6-month study investigating the effects of supplementation with 1 g L-carnitine three times a week in elderly patients (n=28), after which patients were followed up for 3 months[56]. **(Level 1+)**

No differences were found when patients treated with epoetin were supplemented with 1 g carnitine three times a week or placebo (n=24) for 6 months and compared in terms of epoetin dose, endogenous epoetin levels or Hct and iron levels[180]. **(Level 1+)**

No significant changes in epoetin dose requirement were observed between patients supplemented with either 5 mg/kg (n=15) or 25 mg/kg (n=5) L-carnitine vs placebo (n=20) over 8 months. However, a greater reduction in change in epoetin dose was observed in the carnitine treated group ($p<0.05$) and a higher epoetin resistance index (epoetin dose:Hb ratio) ($p<0.02$). Additionally, after 4 months, there were significant negative correlations between plasma free carnitine, plasma total carnitine and plasma free carnitine:plasma total carnitine to EPO dose and ERI in both treatment groups[174]. **(Level 1+)**

It was concluded that there was no evidence to support the adjunctive use of vitamin C, folic acid or carnitine supplements in the treatment of anaemia of CKD. **There was very little evidence available for the CKD population and no evidence in the predialysis population.** It was considered acceptable to extrapolate the conclusions to the predialysis population.

23. Avoid blood transfusions where possible in people with anaemia of CKD in whom kidney transplant is a treatment option. [2006]

23. Väldi vereülekanideid KNH ja aneemiaga patsientidel, kellel neerusiirdamine on üks ravi võimalustest.

24. In people with anaemia of CKD, there may be situations where a transfusion is indicated clinically. In these cases, follow the relevant national guidance. [2006, amended 2015]

24. KNH ja aneemiaga patsientidel võivad olla olukorrad kui vereülekanded on näidustatud.

Hemodialüüsi patsientide rühmas Level 3, peritoneaaldialüüsi rühma Level 2+.

33. The correction to normal levels of Hb with ESAs is not usually recommended in people with anaemia of CKD.

- **Typically maintain the aspirational Hb range between 100 and 120 g/litre for adults, young people and children aged 2 years and older, and between 95 and 115 g/litre for children younger than 2 years of age, reflecting the lower normal range in that age group.**

- **To keep the Hb level within the aspirational range, do not wait until Hb levels are outside the aspirational range before adjusting treatment (for example, take action when Hb levels are within 5 g/litre of the range's limits). [2011, amended 2015]**

33. KNH ja aneemiaga patsientidel pole soovitav ESA raviga korrigeerida Hgb taset normi tasemeni:

- **Tavaliselt säilitatakse Hgb tase vahemikus 100-120 g/l täiskasvanutel**

- **Selleks, et hoida Hgb tase antud vahemikus ära oota kui Hgb tase on allpool vahemiku alumist piiri enne kui alustada ravi**

40. Offer iron therapy to people with anaemia of CKD who are iron deficient and who are not receiving ESA therapy, before discussing ESA therapy.

Discuss the risks and benefits of treatment options. Take into account the person's choice.

For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 33), offer intravenous iron therapy.

40. Pakku rauaravi KNH, aneemia ja rauadefitsiidiga patsientidele kes ei saa ESA ravi, enne kui arutada ESA ravi.

- **Aruta erinevate ravi võimaluste riski ja kasu. Võtta arvesse patsiendi valikut.**

- **Mitte hemodialüüsravil patsientidel alusta suukaudse rauaasendusraviga enne IV ravi. Kui patsient ei talu suukaudest rauaprepatraati või Hgb sihtväärtus pole saavutatud 3 kuu jooksul, määra IV rauaravi.**

44. When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose low-frequency intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion. Take into account all of the following:

preferences of the person with anaemia of CKD or, where appropriate, their family or carers

nursing and administration costs

cost of local drug supply

provision of resuscitation facilities. Intravenous iron administered at a low dose and high frequency may be more appropriate for all children and for adults who are receiving in-centre haemodialysis. [new 2015]

44. Kui määrata IV rauaravi mitte HD ravil patsiendile vali valikmeetodiks suures doosis madala sagedusega IV rauaravi, et täita rauavarusid. Arvesse tuleb võtta:

- **patsiendi eelistusi, kui on vajalik, siis patsiendi pereliikmete ja hooldajate eelistusi**

- **protseduuri läbiviimise maksumust (med. õe töö…)**
- **preparaadi hind**
- **elustamisvahendite olemasolu**

Evidence statements

Clinical

High-dose/low-frequency IV iron compared to low-dose/high-frequency IV iron

When comparing high-dose/low-frequency IV iron with low-dose/high-frequency IV iron, there appeared to be a clinically important benefit for high-dose/low-frequency IV iron compared with oral iron in relation to achieving a predefined Hb increase of more than or equal to 1 g/dl (two studies[209,260], n=2363). However, this was **very low quality evidence**.

High quality evidence from one study [209] (n=305) showed a clinically important benefit for high-dose/low-frequency IV iron over oral iron in respect to time to target Hb.

Two studies[209,260] (n=2363) showed a clinically unimportant benefit of high-dose/low-frequency IV iron over low-dose/high-frequency IV iron for people's change in Hb. This was **low quality evidence**.

With regard to other important iron parameters, such as measures of SF and TSAT. **Moderate to Low quality evidence** from one study[209] (n=305) suggested that while there was not a clinically important difference with regards to TSAT, a **clinically important benefit was observed with high-dose/low- frequency IV iron over low-dose/high-frequency IV iron for SF change from baseline.**

Low quality evidence from one study[209] (n=305) suggested that low-dose/high-frequency IV iron was preferable when considering numbers of people requiring blood transfusion(s) and numbers of people needing to initiate ESA therapy.

46. People with anaemia of CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The length of time to monitoring of iron status is dependant on the product used and the amount of iron given. [2006] (Level 2, 2+)

46. KNH ja aneemiaga patsiendil ei tohiks kontrollida raua taset (näitajaid?) varem kui 1 nädal peale IV raua manustamist. Aeg raua näitajate kontrollika sõltub raua preparaadist ja manustatud raua kogusest (Level 2, 2+)

47. Routine monitoring of iron stores to prevent iron overload using serum

ferritin should be at intervals of 1–3 months [2006, amended 2015] (Level 2, 2+)

47. Raua üledoseerimise vältimiseks peaks rauavarusid rutiinselt kontrollima vahemikus 1-3 kuud (Level 2, 2+)

- 1 kohort uuring **(**Besarab A, Kaiser JW, Frinak S. A study of parenteral iron regimens in hemodialysis patients. American Journal of Kidney Diseases. 1999; 34(1):21-28)

KHA-CARI Guideline: Use of iron in chronic kidney disease patients (2013)

We recommend:
a. That therapeutic iron be used to correct diagnosed iron deficiency (1D).

b. Parenteral iron (intravenous) is administered in preference to oral iron to correct iron deficiency. As it is more likely to:

- **achieve target haemoglobin (Hb) levels (1B),**
- **maintain ferritin and transferrin saturation (%TSAT) at target ranges (1C),**
- **reduce erythropoiesis stimulating agent (ESA) dose requirements (1C) and**
- **have fewer adverse reactions (1C).**

Me soovitame:

a. **et rauaravi oleks kasutatud diagnoositud rauadefitsiiti korrigeerimiseks (1D)**
b. **Parenteraalne rauaravi on eelistatum kui suukaudne, et korrigeerida rauapuudust. Kuna suurema tõenäosusega:**
    - **Saab saavutada vajalikku Hgb taset (1B)**
    - **Tõstab ferritiini ja transferriini saturatsiooni vajaliku tasemeni (1C)**
    - **Vähendab ESA manustmist (1C)**
    - **Rauaravil on vähem kõrvaltoimeid (1C).**

We suggest:

c. **That to achieve target haemoglobin levels in patients with CKD (2C), HD (2B) and PD (2D) the following iron indices should be targeted by increasing or decreasing iron therapy (Prior to ESA):**

    Serum ferritin >100 µg/L

    Transferrin saturation (TSAT %) >20%

d. That when ferritin levels are >500 µg/L, that iron dosage be reduced (2C), although, ferritin levels ≤1200 µg/L have shown no sign of toxicity in short term studies (<6 months) (2C).

e. Delivery of iron can be given intravenously as a smaller weekly bolus (50 mg to 100 mg) or large bolus (1000 mg) as both achieve responses in iron indices and haemoglobin targets (2C).

Soovitame (arvame):

c. Selleks, et saavutada Hgb taseme eesmärki KNHga (2C), HD (2B), PD (2D) järgmised raua indeksid peaksid olema saavutatud suurendades või vähendades rauaravi (enne ESA ravi):

-seerumi ferritin > 100 mkg/l

- transferriini saturatsioon >20%

d. Vähendada raua annust kui ferritiini tase on > 500mkg/l, kuigi ferritiini tase <= 1200mkg/l ei näidanud toksilisust (uuringutes kestvusega < 6 kuud) (2C).

e. Raud võib olla manustatud IV väiksema boolusena (50-100mg) või suurema boolusena (1000mg) kuna mõlemal viisil saavutatakse raua indeksite ja Hgb tõusu (2C).

Ungraded:

• Regular monitoring helps to predict iron overload and the overshoot of target Hb: CKD stage 1-2 as clinically indicated, CKD stage 3-5 not on dialysis 3 monthly

• For CKD (Stages 3–5; not on dialysis) patients with anaemia, there is benefit from IV iron in achieving target iron indices and less ESA use but no benefit in the maintenance of target Hb levels.

•Mortality data would suggest that not exceeding 1000 mg every 6 months as total maximum dose per patient per period is desirable.

• IV iron can usually be given as a bolus rapid infusion (<1 h) with minimal toxicity.

•Vitamin C administration has been shown to be associated with mild improvement in iron indices in the short term when given in conjunction with standard care for supplementary iron but not in the achievement of target Hb levels in HD patients.

Ungraded:

- **Regulaarne monitoring aitab ennustada raua ülekoormust või liiga kõrget Hgb väärtust: KNH 1-2 staadium – kui on kliinniliselt vajalik, KNH 3-5 staadium (mitte dialüüsravil) - 3 kuu tagant**

- **3-5 staadiumi KNH (mitte dialüüsravil) on kasu IV rauaravist, selleks, et saavutada raua indeksite eesmärki, vähendada ESA kasutamist, kuid ei ole kasu Hgb vajaliku taseme saavutamisel**

- **Andmed suremuse kohta soovitavad, et 6-kuu maksimaalne raua kogus (1000mg) ei oleks ületatud**

- **IV raud tavaliselt võib manustada boolusena (< 1 tund), sellega kaasneb minimaalne toksilisus**

- **On leitud seost C vitamiini manustamise ja raua indeksite vähese paranemisega kui seda manustada koos standartse raviga, Hgb taseme eesmärk ei olnud saavutatud HD haigetel**

SIGN Guideline: infot ei ole
Malaysia CKD management: infot ei ole