Richtlijn Anemie bij Chronische Nierinsufficiëntie, voor volwassen patiënten

gebaseerd op:

- Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal failure, 2004
- KDOQI Anemia in chronic kidney disease, 2006
KDOQI Anemia in chronic kidney disease, update 2007 on hemoglobin target

Deze richtlijn vervangt de NFN richtlijn Anemie uit 2004

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Geen belangenverstrengeling

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Geen belangenverstrengeling

De richtlijn bevat aanbevelingen van algemene aard. Het is mogelijk dat in een individueel geval deze aanbevelingen niet van toepassing zijn. Het is de verantwoordelijkheid van de behandelend arts te beoordelen of de richtlijn in de praktijk toepasbaar is. Er kunnen zich feiten of omstandigheden voordoen waardoor, in het belang van een goede zorg voor de patiënt, van een richtlijn moet worden afgeweken.

Achtergrond:

Dit document bevat de NfN richtlijn voor de diagnostiek en behandeling van anemie bij chronische nierinsufficientie bij volwassen patiënten en bestaat in de kern uit een samenvatting van de Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure uit 2004 (EBPG 2004), die waar nodig door de kwaliteitscommissie van de NfN van commentaar is voorzien teneinde aan te sluiten op de Nederlandse situatie.
Bij het vervaardigen van deze richtlijn zijn naast de EBPG 2004 de KDOQI Clinical Practice Guideline and Clinical Practice Recommendation for Anemia in Chronic Kidney Disease 2006 (KDOQI 2006) en de 2007 Update of Hemoglobin Target (KDOQI 2007) in beschouwing genomen.
De verantwoording voor de verschillende bron-guidelines is niet opgenomen in deze richtlijn. De originele uitgebreide guidelines zijn gepubliceerd in:
Nephrology Dialysis Transplantation 2004; vol 19, suppl 2
American Journal of Kidney Diseases 2006; vol 47, No 5 suppl 3
American Journal of Kidney Diseases 2007; vol 50, No 3 suppl 3

Elektronisch beschikbaar via
http://www.ndt-educational.org/guidelines.asp
http://www.kidney.org/professionals/KDOQI/guidelines.cfm

De EBPG 2004 en de KDOQI guidelines verschillen slechts op enkele punten van elkaar. Deze "key differences" zijn samengevat in Tabel 1.

Tabel 1. Vergelijking van de meest recente EBPG en KDOQI Anemie richtlijnen.

Onderwerp	EBPG 2004	KDOQI 2006	KDOQI 2007	Reden waarom nieuwe richtlijn afwijkt van voorgaande
Definitie van anemie: in g/dl (mmol/l)	Hb<12,0 g/dl (7,4) (mannen >70 jr), Hb< 13,5 g/dl (8,4) (jongere mannen); Hb<11,5 g/dl (7,1)(vrouwen)	Hb<13,5 g/dl (8,4) voor mannen Hb<12,0 g/dl (7,4) voor vrouwen		Gebruik van de nieuwere NHANES dataset, waarna anemie gedefinieerd als Hb onder 5^{e} percentiel.
Streefwaarde Hb: in g/dl (mmol/l)	>11,0 g/dl (6,8); >12,0 g/dl (7,4) wordt niet aanbevolen i.g.v. cardiovasculaire aandoeningen; >14,0 g/dl (8,6) is niet wenselijk voor HD pat'n	≥11,0 g/dl (6,8); Voorzichtigheid betrachten wanneer het Hb bewust >13 g/dl (8,0) wordt gehouden	11,0-12,0 g/dl (6,8-7,4); Niet hoger dan 13,0 g/dl (8,0)	De QoL is beter bij Hb >11,0 g/dl (6,8) dan bij een lager Hb; geen toename van QoL bij een streefHb >12,0 (7,4), terwijl risico's bij een hoger Hb wel toenemen
Streefwaarde ijzer	TSAT (%): Ondergrens: 20 Streef: 30-40 Ferritine (ng/ml): Ondergrens:100 Streef: 200-500	TSAT (%): Ondergrens: ≥20 Ferritine (ng/ml): Ondergrens: 200 (voor HD-pat'n), 100 (niet-HD-pat'n); >500 wordt niet algemeen aangeraden		KDOQI heeft geen bovengrens voor de TSAT gespecificeerd. KDOQI vindt onvoldoende bewijs om de voor-en nadelen van het handhaven van een ferritine > 500 vast te stellen. De EBPG geeft wel een bovengrens van de streefwaarde aan om het risico van ijzerstapeling bij het ver overschrijden te voorkomen.

Vanwege het feit dat de Europese richtlijn handzamer is in het gebruik, heeft de kwaliteitscommissie besloten de EBPG 2004 richtlijn als uitgangspunt te gebruiken. Verschillen tussen de EBPG en KDOQI guidelines zijn waar relevant toegevoegd aan het commentaar. Extra aandacht behoeft de KDOQI 2007 Update of Hemoglobin Target, die is verschenen naar aanleiding van het verschijnen van enkele nieuwe studies over de streefwaarde van het hemoglobine.

De indeling van evidence levels in deze richtlijn is volgens de EBPG richtlijn anemie 2004. In de diverse guidelines worden verschillende indelingen gebruikt voor evidence levels (tabel 2 en 3).

Tabel 2.

EBPG 2004 **Levels of evidence**	
A	Evidence from at least one good, randomized or quasi-randomized, controlled trial or meta-analysis of several such trials, or a Cochrane systematic review
B	Evidence from several uncontrolled, non-randomized open studies
C	Case studies or expert opinions (reviews)

Tabel 3.

KDOQI 2007 **Strength of guideline recommendations**	
Clinical Practice Guideline (Strong)	Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on health outcomes
Clinical Practice Guideline (Moderately strong)	The strength of the evidence is limited by the number, quality or consistency of the individual studies OR evidence is from a population other than the target population OR evidence is from studies with some problems in design and/or analysis OR evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and or safety in the target population
Clinical Practice Recommendation	Recommendations based on weak evidence (C) and/or consensus of expert opinion of the Work Group members

SECTION I. Anaemia evaluation

Guideline I.1: Which patients should be evaluated and when should work-up begin?

Recommendation

I. All patients with chronic anaemia associated with chronic kidney disease (CKD) should be investigated for possible treatment, irrespective of the stage of kidney disease and requirement for renal replacement therapy.

A work-up for a diagnosis of anaemia should be considered in patients with CKD when haemoglobin (Hb) concentration falls below the mean –2 SD (i.e.<95%) Hb level of the normal population, adjusted for age and sex:

- <11.5 g/dl in adult female patients
- <13.5 g/dl in adult male patients
- <12.0 g/dl in adult male patients aged >70 years.

(Evidence level B)

Commentaar:
KDOQI 2006 stelt de grens voor volwassen vrouwelijke patiënten op 12.0 g/dl.
De waarden voor het Hb in g/dl komen in mmol/l overeen met: (g/dl x 0,6206 = mmol/l)
11,5 g/dl = 7,1 mmol/l
13,5 g/dl = 8,4 mmol/l
12,0 g/dl = 7,4 mmol/l

Guideline I.2: What is the appropriate work-up to investigate anaemia in chronic kidney disease?

Recommendation

I. An initial clinical and laboratory evaluation should be completed prior to considering the commencement of treatment with an erythropoiesis-stimulating agent (ESA) in patients with chronic kidney disease (CKD), to evaluate possible causes of anaemia superimposed on relative erythropoietin deficiency.
(Evidence level C)

Assessment of anaemia should involve laboratory measurement of the following parameters:

- haemoglobin (Hb) concentration—to assess the degree of anaemia
- red blood cell indices [mean corpuscular volume (MCV) and mean corpuscular Hb (MCH)]—to assess the type of anaemia
- absolute reticulocyte count—to assess erythropoietic activity
- plasma/serum ferritin concentration—to assess iron stores
- functional iron available for erythropoiesis by the measurement of either:
  - – percentage of hypochromic red blood cells (HRC)
  - – plasma/serum transferrin saturation (TSAT)
  - – reticulocyte Hb content (CHr)
- plasma/serum C-reactive protein (CRP)—to assess inflammation.

(Evidence level B)

In patients on dialysis, the frequency and the received dose of dialysis should also be evaluated.
(Evidence level C)

Recommendation
II. A more extensive work-up may also include the following, as indicated by the initial clinical and laboratory evaluation:

- assessment of occult gastrointestinal blood loss
- serum B_{12} and red cell folate concentrations
- serum/plasma intact parathyroid hormone (iPTH) concentration
- differential white blood count and platelets
- tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test)
- plasma/serum and/or urine protein electrophoresis/ immunoblotting
- serum aluminium
- Hb electrophoresis and bone marrow examination in selected cases.

(Evidence level B)

Commentaar op recommendation II:
Verdere analyse van een onbegrepen anemie dient op de gebruikelijke wijze plaats te vinden.

Guideline I.3: Diagnosis of renal anaemia

Recommendation
I. A diagnosis of anaemia most likely to be due to erythropoietin deficiency should be considered if:

- there is significant impairment of renal function AND
- no cause for anaemia other than chronic kidney disease (CKD) is detected during work-up.

(Evidence level B)

SECTION II. Targets for anaemia treatment

Guideline II.1: What are the appropriate haemoglobin targets for anaemia treatment?

Recommendation

I. In general, patients with chronic kidney disease (CKD) should maintain a target haemoglobin (Hb) concentration of >11 g/dl [haematocrit (Hct) >33%]—or reach this target within 4 months of starting treatment—regardless of age, gender or ethnicity.

KDOQI 2007: In het algemeen, streefwaarde Hb tussen de 11 en 12 g/dl (6.8 –7.4 mmol/l, Evidence level C Opinion), echter niet hoger dan 13 g/dl (8,0 mmol/l, Evidence level B). Zie ook commentaar aan einde guideline II.1.

- Patients starting treatment with extremely low Hb concentrations should reach this target as soon as possible, with a monthly increase in Hb as specified in Recommendation V of Guideline III.1.
- For patients on haemodialysis (HD), Hb concentration should be determined from a sample taken prior to the dialysis session.

(Evidence level B)

Note: Please see Recommendations II and III of this guideline for target Hb values for various patient subgroups

Recommendation

II. Exact target Hb concentrations >11 g/dl should be defined for individual patients, taking gender, age, ethnicity, activity and co-morbid conditions into account. In HD patients, pre-dialysis Hb concentrations above 14 g/dl (8,7 mmol/l) are not desirable due to the risks associated with the effects arising from post-dialysis haemoconcentration.
(Evidence level C)

KDOQI 2007: In het algemeen, streefwaarde Hb tussen de 11 en 12 g/dl (6.8 –7.4 mmol/l, Evidence level C Opinion), echter streefwaarde niet hoger dan 13 g/dl (8,0 mmol/l, Evidence level B). Zie ook commentaar aan einde guideline II.1.

Recommendation

III. The optimal target Hb concentration may vary in patients with significant co-morbidity:

- Hb concentrations >12 g/dl (7,4 mmol/l) are not recommended for patients with severe cardiovascular disease [defined as class III and above of the New York Heart Association Classification of Congestive Heart Failure unless continuing severe symptoms (e.g.angina) dictate otherwise.

(Evidence level A)

- Until data become available, it seems prudent to recommend a cautious approach to raising Hb concentrations to levels >12 g/dl (7,4 mmol/l) in patients with diabetes, especially with concurrent peripheral vascular disease.

(Evidence level C)

- Patients with chronic hypoxaemic pulmonary disease may benefit from a higher Hb target.

(Evidence level C)

- In patients with CKD and sickle cell disease receiving ESAs, the aim should be to titrate the dose of ESAs to prevent the level of haemoglobin S (HbS) becoming much greater than 30%. Even with high-

dose ESA therapy, patients are unlikely to achieve an Hb greater than ~7–8 g/dl (4,3-5 mmol/l) due to ongoing red cell destruction from haemolysis.
(Evidence level C)

Recommendation
IV. The target Hb concentrations recommended in this guideline should not be used as targets for patients being treated with blood transfusions.
(Evidence level C)

Commentaar op Guideline II.1:
De KDOQI update of hemoglobin target 2007 bespreekt in extenso de nieuwe studies die verschenen zijn naar streefwaarden voor Hb. De belangrijkste uitkomsten zijn dat hogere Hb streefwaarden (> 13 g/dl = 8.0 mmol/l) geen voordeel bieden op gebied van mortaliteit en cardiovasculaire events; mogelijk is er zelfs sprake van toename. Vermeld dient te worden dat deze studies met name in predialysepatiënten zijn uitgevoerd. Er lopen op het ogenblik van schrijven nog enkele trials waaronder TREAT in 4000 predialysepatiënten.
De kwaliteitscommissie adviseert conform de KDOQI richtlijnen bij predialyse en dialysepatiënten die worden behandeld met ESA's in het algemeen te streven naar een Hb tussen 11 en 12 g/dl (6.8 –7.4 mmol/l, Evidence level C Opinion), waarbij de streefwaarde niet hoger moet liggen dan 13 g/dl (8,0 mmol/l, Evidence level B). Het advies betreft streefwaarden en niet bereikte Hb waarden. Benadrukt dient verder te worden dat de Hb waarden uitsluitend gelden voor patiënten die behandeld worden met ESA's.

Update 2010:
De TREAT studie is in november 2009 gepubliceerd (NEJM 361: 21 nov 2009), uitgevoerd bij > 4000 predialysepatiënten met diabetes mellitus, gerandomiseerd voor darbepoetinebehandeling met een streefwaarde van 13 g/dl (8,0 mmol/l) of geen darbepoetine tenzij het Hb < 9,0 g/dl (5,6 mmol/l) daalde. In de tweede groep werden vaker bloedtransfusies gegeven.
De belangrijkste uitkomst van de studie is dat in de eerste groep met het hogere Hb target geen verbetering in overleving of in cardiovasculaire eindpunten werd gevonden. Er was wel een verdubbeling van het aantal CVA's en een verhoogd tromboserisico. De studie bevestigt de bevinding van eerdere studies dat bij gebruik van ESA's een hoog Hb target van 8,0 mmol/l ongunstige effecten lijkt te hebben.
Het advies van de kwaliteitscommissie is conform de huidige KDOQI en EBPG richtlijnen te handelen en bij gebruik van ESA's terughoudend te zijn met een Hb target van 13 g/dl (8,0 mmol/l).

Guideline II.2: What are the appropriate iron targets for anaemia treatment?

Recommendation
I. Patients with chronic kidney disease (CKD) should be in iron balance, or have sufficient iron, to maintain (or reach) a haemoglobin (Hb) concentration of >11 g/dl [haematocrit (Hct) ≥33%].
(Evidence level B)

Recommendation
II. To reach and maintain target Hb concentration, sufficient iron should be administered to attain the following targets in all patients:
- serum ferritin >100 µg/l
- hypochromic red cells <10% [or transferrin saturation (TSAT) >20%, or reticulocyte Hb content (CHr) >29 pg/cell].

(Evidence level B)

In practice, to achieve these recommended minimum criteria, it will be necessary to aim for targets in the treatment population as a whole of:

- serum ferritin 200–500 µg/l
- hypochromic red cells <2.5% (or TSAT 30–40%, or CHr ~35 pg/cell).

(Evidence level C)

Commentaar:

De behoefte aan ijzersuppletie dient voor iedere patiënt individueel te worden beoordeeld in samenhang met de reactie op de ESA. Het beleid om voor de hele patiëntenpopulatie een hogere norm te stellen om zodoende iedereen op een acceptabele spiegel te laten uitkomen wordt door de KK niet aanbevolen.

De KK adviseert conform de KDOQI 2006 voor predialyse en PD patiënten een streefwaarde voor ferritine van 100 – 500 µg/l. Voor HD patiënten wordt conform de EBPG en KDOQI 2006 een hogere streefwaarde geadviseerd van 200 – 500 µg/l (Evidence level C Opinion). Daarnaast geldt voor iedere patiënt een streefwaarde voor transferrine saturatie van >20 of <10% hypochrome rode bloedcellen. Serumferritine kan niet gebruikt worden als maat voor de functionele ijzerstatus in geval van ontsteking / acute fase reactie.

SECTION III. Treatment of renal anaemia

Guideline III.1: Treatment of anaemia with erythropoiesis-stimulating agents

Recommendation

I. Erythropoiesis-stimulating agents (ESAs) should be given to all patients with chronic kidney disease (CKD) with haemoglobin (Hb) levels consistently (i.e. measured twice at least 2 weeks apart) below 11 g/dl [haematocrit (Hct) <33%], where all other causes of anaemia have been excluded (see Guideline I.2). This applies equally to:

- patients with CKD (stages 1–5) developing anaemia
- patients with CKD stage 5 treated with haemodialysis (HD) or peritoneal dialysis (PD)
- transplant patients with chronic renal insufficiency and anaemia.

(Evidence level A)

Recommendation

II. The recommended route of administration is dependent on the patient group being treated and the type of ESA used.

- For patients on HD, the intravenous (i.v.) route may be preferable for comfort and convenience, but the subcutaneous (s.c.) route can substantially reduce the dose requirements of ESA.

(Evidence level A)

- In CKD patients not undergoing dialysis and in transplant patients, epoetin beta should preferably be given s.c. for both economic and practical reasons.
- Patients on dialysis should preferably be given epoetin beta s.c., for economic reasons.

(Evidence level A)

Commentaar: De KK heeft geen voorkeur voor een bepaald product.

- Epoetin alfa (Eprex®, Erypo®) is not licensed for s.c. administration in all CKD patients in many European countries (including all member states of the European Union) due to the risk of pure red cell aplasia (PRCA).

(Evidence level B)

- Darbepoetin alfa can be given either i.v. or s.c. without dose adjustments in all CKD patients. In HD patients, darbepoetin alfa may be easier to administer i.v., but the s.c. route is preferable in all other CKD patients.

(Evidence level B)

- In patients treated with PD, the intraperitoneal (i.p.) route of administration is not currently recommended due to the poor bioavailability of ESAs when given by this route.

(Evidence level B)

Recommendation

III. The frequency of administration of ESA is influenced by several factors including dose, route, treatment phase, type of ESA used and patient group being treated.

- In HD patients receiving i.v. epoetin alfa or epoetin beta, the drug should be given three times per week during both correction and maintenance phases. Evidence does not support the use of i.v. epoetin alfa or epoetin beta once weekly. However, the dosing frequency of epoetin beta may be reduced to once or twice weekly when administered s.c. in some HD patients.

(Evidence level A)
- In CKD, PD and transplant patients, epoetin beta can be given s.c. three times per week during the correction phase and once per week during the maintenance phase of treatment.

(Evidence level C)
- During the correction phase, darbepoetin alfa should be given once per week either i.v. or s.c. in HD patients, and once per week s.c. in CKD, PD and transplant patients.

(Evidence level A)
- During the maintenance phase, darbepoetin alfa can also be given less often (e.g. every 2–4 weeks) either s.c. or i.v. in selected patients.

(Evidence level C)
- Darbepoetin alfa can be given once every 2 weeks either s.c. or i.v. to patients previously given s.c. epoetin alfa or beta once weekly.

(Evidence level B)

Recommendation
IV. The starting dose of ESA to correct renal anaemia may depend on several factors such as the degree and underlying cause of the anaemia.

- In the correction phase, the starting dose for ESA-naive patients should normally be 20–30% higher than the maintenance dose.

(Evidence level B)

Recommendation
V. ESA dose should be titrated in response to Hb level.
- During the correction phase, Hb levels should be monitored once every 2–4 weeks. Initially, the rate of increase in Hb levels should be 1–2 g/dl per month. A change of <1 g/dl in Hb level may indicate the need for a 25% stepwise (up or down) adjustment in the total weekly ESA dose. A rate of increase in Hb level >2 g/dl per month is undesirable and should be adjusted by temporarily withdrawing ESA therapy or by decreasing the total weekly ESA dose by 25–50%.

(Evidence level C)
- During the maintenance phase, when Hb levels are stabilized, Hb levels should be monitored every 1–2 months, and perhaps even less frequently in CKD patients not on dialysis. A change of >1 g/dl in Hb level may indicate the need for a 25% stepwise adjustment in the total weekly ESA dose (up or down) and/or dosing frequency according to the type of ESA.

(Evidence level C)
- Patients with normalized Hb targets with intercurrent diseases that might influence the Hb concentration, may require more frequent monitoring in both correction and maintenance phases.

(Evidence level C)

Recommendation
VI. Blood pressure should be monitored closely in all patients with CKD, particularly during initiation of ESA therapy until the target Hb is reached.

Target blood pressure should be the same as for CKD patients who are not receiving ESA therapy. One or more of the following strategies may be needed to control an increase in blood pressure related to ESA therapy:
- For patients undergoing dialysis, enhanced ultrafiltration can be used to reduce extracellular volume. However, care should be taken when using ultrafiltration in patients with pre-dialysis Hb concentrations in the normal range.
- Antihypertensive therapy may need to be initiated, or current antihypertensive medication increased, in all CKD patients.
- ESA dose may need to be reduced, especially if there is a rapid increase in Hb concentration.

(Evidence level B)

Recommendation
VII. The function of the vascular access should be monitored in all HD patients to prevent thrombosis. However, treatment with ESAs does not necessitate increased surveillance of the vascular access. Some evidence indicates that the risk of thrombosis in patients bearing polytetrafluoroethylene (PTFE) grafts is increased when Hb levels are normalized.
(Evidence level B)

Commentaar:
De richtlijn gaat nogal in detail in op dosering. In zijn algemeenheid is de meest belangrijke aanbeveling dat behandeling met erytropoetines gedaan moet worden door ervaringsdeskundigen en volgens de doseringsadviezen van de desbetreffende ESA producenten. Frequentie van toediening en controlefrequentie is deels afhankelijk van de patiënt. Belangrijk is dat het Hb niet te snel stijgt, waarbij met name voorzichtigheid betracht moet worden bij patiënten met preëxistente slechte regulatie van de bloeddruk en patiënten met ernstig vaatlijden.

Guideline III.2: Treatment of anaemia with iron

Recommendation
I. All chronic kidney disease (CKD) patients with renal anaemia undergoing treatment with an erythropoiesis-stimulating agent (ESA) should be given supplementary iron to maintain (or reach) the targets set in Guideline II.1, regardless of dialysis status. Patients undergoing haemodialysis (HD) usually have greater iron requirements than those not undergoing HD.
(Evidence level B)

Commentaar:
In het algemeen moeten de meeste patiënten die behandeld worden voor renale anemie met ESA's ijzersuppletie krijgen. Gevaar van de EBPG guideline zou kunnen zijn dat ook mensen met ijzerstapeling ijzer toegediend krijgen.

Recommendation
II. i.v. administration is the optimum route for the delivery of iron to patients with CKD, as oral iron is poorly absorbed in uraemic individuals.
(Evidence level A)

Commentaar:
Aan predialyse en PD patiënten kan ijzer oraal worden gegeven, tenzij de streefwaarden met orale toediening niet worden gehaald (KDOQI 2006).

Recommendation
III. No definitive recommendation can be made regarding the optimum frequency for the administration of iron therapy.
(Evidence level C)

Recommendation
IV. The optimal i.v. iron dose is 25–150 mg/week for the first 6 months of ESA therapy.
(Evidence level B)

Commentaar:
De optimale i.v. ijzerdosering is afhankelijk van de controlewaarden van ferritine en transferrinesaturatie. De EBPG geeft bij de rationale aan dat het probleem van oxidatieve stress/ijzerstapeling vooralsnog alleen theoretisch is en klinisch onbewezen. Men geeft wel een maximale ferritinespiegel aan van 800 microgr/l. Het snel bereiken van een target Hb bij een relatief lage ESA dosering lijkt te prevaleren bij de EBPG guidelines, boven het risico op ijzerstapeling. KDOQI 2006 stelt zich terughoudend op en zegt dat er onvoldoende bewijs is om routinematige toediening van i.v. ijzer te adviseren indien serum ferritine > 500 ug/l.
Als voorbeeld van praktische aanbeveling voor intraveneuze ijzersuppletie is hieronder de tabel weergegeven uit de vroegere NfN ijzerrichtlijn (Evidence level C, opinion).

Tabel 4. Intraveneus ijzer

	Ferritine <100 µg/l	**Ferritine 100-500 µg/l**	**Ferritine >500 µg/l**
TS <0.20; %HRBC>10%	10 weken regime 1	10 weken regime 1	10 weken regime 2 + onderzoek naar ontsteking
TS >0.20; %HRBC<10%	10 weken regime 1	10 weken regime 2	10 weken regime 3

Verklaring:		
Regime 1	IJzersaccharaat i.v.	1 x per week 100 mg óf 3 x per week 40 mg
Regime 2	IJzersaccharaat i.v.	1 x per maand 100 mg óf 1 á 2 x per week 20 mg
Regime 3		Geen ijzersuppletie

TS: transferrine saturatie
%HRBC: percentage hypochrome rode bloedcellen

Na drie maanden dosis herzien op basis van de nieuwe parameters.

Recommendation

V. Iron status should be assessed regularly in CKD patients.

- Ferritin levels should be used to measure iron stores.
- The percentage of hypochromic red blood cells (HRC) is the best measure of functional iron deficiency (FID). If HRC is unavailable, transferrin saturation (TSAT) may be used to detect FID. Reticulocyte Hb content (CHr) <29 pg is a third option for assessing FID.

(Evidence level B)

- Iron stores should be checked every 2–6 months in CKD patients with stable Hb levels who are not receiving ESAs. A sustained reduction in the Hb concentration and/or a decrease in the mean corpuscular volume indicate the need for further investigation.
- During initiation and titration of ESA therapy, iron status should be checked every 4–6 weeks in patients not receiving i.v. iron, and every 1–3 months in patients receiving i.v. iron, until the target Hb concentration is reached.
- After the target Hb concentration is reached, iron status should be checked every 1–3 months.

(Evidence level C)

- i.v. iron therapy (at doses >100 mg) should be stopped for at least 1 week before performing these measurements.

(Evidence level B)

Recommendation
VI. When selecting a source of supplementary iron, the tolerability profile of different sources of iron must be considered.
- Iron sucrose is generally considered to be the safest form of i.v. administered iron, followed by iron gluconate.
- Due to the risk of life-threatening/serious acute reactions associated with i.v. administration of iron dextran, this form of iron therapy is not generally recommended.
- If iron dextran is to be used, a test dose must be administered. In addition, special caution should be exercised in patients with multiple drug allergies/intolerance.

(Evidence level B)

Commentaar:
De voorkeur voor ijzersucrose uitgesproken boven ijzerdextran is gebaseerd op de ervaring van anafylactische reacties op vroegere dextranpreparaten.
Nieuwe preparaten zijn niet gecontra-indiceerd, mits ze een zelfde geringe bijwerkingenprofiel en risico hebben als ijzersucrose.

Guideline III.3: Optimization of dialysis for the treatment of anaemia

Recommendation
I. Dialysis should be optimized to ensure the effective treatment of renal anaemia. To maximize the effects of erythropoiesis-stimulating agent (ESA) therapy, the eKt/V should be >1.2 in a three times weekly haemodialysis (HD) programme and >1.8 in a weekly peritonealdialysis (PD) programme.
(Evidence level B)

Recommendation
II. The primary focus of treatment should be to optimize conventional dialysis before considering alternative forms of therapy such as enhanced convective treatment, or nocturnal or short daily dialysis.
(Evidence level B)

Guideline III.4: Treatment of anaemia with vitamins and adjuvant therapies other than iron

Definition
Adjuvant therapies are defined here as forms of therapy which may help to optimize a patient's response to treatment with erythropoiesis-stimulating agents (ESAs).

Recommendation
I.With the exceptions of iron and pharmacological doses of certain vitamins, the benefits of adjuvant therapies are not well established and are not widely recommended in routine clinical practice. However, some forms of adjuvant therapy may benefit individual patients.
(Evidence level B)

Recommendation
II. In patients with CKD, routine, low-level vitamin supplementation does not increase haemoglobin (Hb) levels. However, therapeutic doses of specific vitamins may improve control of anaemia, when combined with ESA therapy.

- Treatment with vitamin E may lessen oxidative stress, which is associated with resistance to treatment with ESAs. A single dose of oral vitamin E (1200 IU) given 6 h before an HD session, along with intensive i.v. iron, may protect against oxidative stress-related diseases in the long term.

(Evidence level B)

- Correction of impaired vitamin C status can reduce resistance to ESA therapy (hyporesponsiveness) and potentiate the effect of vitamin E. High-dose treatment with i.v. vitamin C requires monitoring.

(Evidence level B)

- Routine folic acid or vitamin B_{12} supplementation of HD patients receiving an adequate mixed diet is generally not necessary.

(Evidence level B)

Recommendation

III. A subpopulation of CKD patients (those on maintenance HD) may benefit from carnitine supplementation, but this form of adjuvant therapy is not recommended for general or routine use.
(Evidence level B)

Recommendation

IV. Androgen therapy may be used to stimulate erythropoiesis in some patients.

- In men aged >50 years on continuous ambulatory peritoneal dialysis (CAPD), intramuscular nandrolone decanoate 200 mg once weekly may alleviate symptoms of anaemia and is associated with beneficial effects on nutritional status.
- The risk of serious side effects may preclude the use of androgens in most other CKD patients.

(Evidence level B)

Recommendation

V. Reduced glutathione and other antioxidant treatments may reduce resistance to erythropoetic protein therapy through the reduction of oxidative stress.
(Evidence level B)

Commentaar op guideline III.4:
Voor de toevoeging van vitamines en voedingssupplementen verwijzen wij naar de NfN Richtlijn Voeding 2008.

Guideline III.5: Treatment of anaemia through improved nutrition

Note: Recommendations for treatment with vitamins and trace elements such as vitamins B, C and D, L-carnitine and iron are given in Guidelines III.2 and III.4.

Recommendation

I. Nutritional status should be monitored in patients with chronic kidney disease (CKD) who are at high risk of developing protein-energy malnutrition (PEM), which may contribute to anaemia. Adequate nutrition and
dialysis in patients on maintenance dialysis treatment is a key component in preventing and treating PEM in CKD patients.
(Evidence level C)

Guideline III.6: Treatment of anaemia by transfusion

Recommendation

I. Red blood cell transfusions should be avoided, if at all possible, in patients with chronic kidney disease (CKD), especially those awaiting kidney transplantation.
(Evidence level B)

Recommendation

II. Transfusions should not be given unless patients have one or more of the following:

- symptomatic anaemia (fatigue, angina, dyspnoea) and/or associated risk factors (diabetes, heart failure, coronary artery disease, arteriopathy, old age)
- acute worsening of anaemia due to blood loss (haemorrhage or surgery) or haemolysis
- severe resistance to, or hyporesponsiveness to, ESA therapy, e.g. due to the presence of a haematological disease or severe inflammatory systemic disease.

(Evidence level C)

SECTION IV. Failure to respond to treatment

Guideline IV.1: Failure to reach or maintain target haemoglobin levels

Recommendation
I. Resistance to erythropoiesis-stimulating agents (ESAs) should be suspected when a patient either fails to attain the target haemoglobin (Hb) concentration while receiving more than 300 IU/kg/week (~20 000 IU/week) of epoetin or 1.5 µg/kg of darbepoetin alfa (~100 µg/week), or has a continued need for such high dosages to maintain the target.
(Evidence level B)

Recommendation
II. The most common causes of incomplete response to ESAs are iron deficiency, either absolute or functional, and inflammatory disorders.
(Evidence level B)

Compliance should also be checked in patients selfadministering an ESA.
(Evidence level C)

The following conditions may cause apparent resistance to ESA therapy. They should be evaluated and, if reversible, treated:

- chronic blood loss
- hyperparathyroidism/osteitis fibrosa
- aluminium toxicity
- haemoglobinopathies (e.g. *a*- and b-thalassaemias, sickle cell anaemia)
- vitamin deficiencies (e.g. folate or vitamin B_{12} deficiency)
- multiple myeloma, myelofibrosis
- other malignancies
- malnutrition
- haemolysis
- inadequate dialysis
- adverse effects of certain drugs [e.g. cytotoxic and immunosuppressive agents, and angiotensin-converting enzyme (ACE) inhibitors].

(Evidence level B)

If the patient has none of these conditions, anaemia in ESA-resistant patients should be fully investigated (see Guideline I.2), including referral to a haematologist. If pure red cell aplasia is suspected, consult Guideline IV.2.
(Evidence level C)

Guideline IV.2: Antibody-mediated pure red cell aplasia
Due to the nature of the subject matter in Guideline IV.2: Antibody-mediated pure red cell aplasia (PRCA), this guideline was not subjected to evidence-based grading.

Recommendation
I. Pure red cell aplasia (PRCA) should be strongly suspected if a patient treated with an erythropoiesisstimulating agent (ESA) for ≥ 4 weeks has:

- a sudden, rapid decline in haemoglobin (Hb) concentration of ~0,5–1 g/dl/week despite ongoing ESA therapy, or requires transfusion of 1–2 units of red blood cells per week to maintain Hb level AND
- normal platelet and white cell counts AND
- a reticulocyte count <10 x 10^9/l.

Otherwise, look for other causes of resistance to ESA therapy.

Recommendation

II. A confirmed diagnosis of PRCA due to antierythropoietin antibodies requires the presence of the following:

- severe non-regenerative anaemia (as specified in Recommendation I)
- evidence of erythroid hypoplasia from bone marrow aspirate with:
    1. normal cellularity AND
    2. <5% erythroblasts AND
    3. evidence of a red cell precursor maturation block AND
- demonstration of anti-erythropoietin antibodies in patient serum.

Recommendation

III. If antibody-mediated PRCA is confirmed, all forms of ESA therapy should be stopped and immunosuppressive therapy considered. Blood transfusions should be given to patients with complications and/or severe anaemia.

Commentaar:

De incidentie van antilichaam gemedieerde PRCA ten gevolge van ESA's is na 2003 zeer laag (ongeveer 0.5 per 10000 patiëntjaren, KDOQI 2006).

Appendix A: Haematology methodology

When undertaking the measurement of the various parameters required for patient work-up, the following points of haematological methodology should be considered:

- Haemoglobin (Hb) concentration should be used in preference to the haematocrit (Hct) level. Hb concentration is a primary parameter that can be measured directly, for which there is an international standard, and which is not influenced by differences in technology. In contrast, the Hct value is not directly derived by automated blood count analysers, has no recognized international standard and may differ depending on the technology used.
- Throughout these guidelines, Hb concentrations are expressed in g/dl. To convert g/dl to g/l, multiply by 10. Other units, such as mmol/l, are used in some countries in Europe, including Denmark and The Netherlands. To convert g/dl to mmol/l, multiply by 0.62.
- All blood counts should be carried out on standardized, controlled and maintained automated counters in an accredited laboratory. In most European countries, accreditation is granted by an independent body such as Clinical Pathology Accreditation Ltd (CPA).
- Reticulocyte counts should be quantitative measures derived by automated flow cytometry, and the coefficient of variation should be <10%. Estimates based on visual assessment of stained blood films are only qualitative, with a coefficient of variation >50%. Results obtained in this manner cannot be compared with automated counts, and should not be used.

Appendix B: Assessment of iron stores and functional iron deficiency

Iron status should be regularly assessed for optimal management of anaemia of chronic kidney disease (CKD).

- Iron stores should be assessed by measuring serum ferritin.
- Iron availability should be assessed by measuring the percentage of hypochromic red blood cells (HRC), the percentage of transferrin saturated with iron (TSAT) or reticulocyte Hb content (CHr). HRC is the best currently available marker to identify functionally iron-deficient patients who are likely to increase their response to erythropoiesis-stimulating agents (ESAs) after supplementary iron therapy. Patients with HRC>6% are most likely to respond to intravenous (i.v.) iron. If HRC cannot be assessed, other tests to measure functional iron deficiency such as TSAT or CHr may be used.
- Blood sampling for iron parameters should be performed at least 1 week after the administration of a >100 mg/dose of any i.v. iron preparation.

Abbreviations used throughout the guidelines

AGE =advanced glycosylation end
CHr =reticulocyte Hb content
CKD =chronic kidney disease
CRP =C-reactive protein
CVD =cardiovascular disease
DST =donor-specific transfusion
ESA =erythropoiesis-stimulating agent
ESRD =end-stage renal disease
FID =functional iron deficiency
GFR =glomerular filtration rate
Hb =haemoglobin
Hct =haematocrit
HD=haemodialysis
HLA=histocompatibility leukocyte antigens

HRC =hypochromic red blood cells
iPTH =intact parathyroid hormone
KDQ =Kidney Disease Questionnaire
MCH=mean corpuscular haemoglobin
MCV =mean corpuscular volume
PD =peritoneal dialysis
PRCA =pure red cell aplasia
PTFE =polytetrafluoroethylene
QOL =quality of life
TBIC =total iron-binding capacity
sTfR =soluble transferrin receptor
TSAT =transferrin saturation
VO_2max =maximal rate of oxygen consumption
ZPP =zinc protoporphyrin