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Nephrology
Dialysis
Transplantation

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***)

Rationale and commentary

Treatment of renal anaemia using ESAs is a well established practice and has been shown to be effective in relieving symptoms and reducing complications of anaemia. The benefits of ESAs include an improved quality of life (QOL). Several randomized, controlled trials show that treatment with ESAs corrects anaemia and reduces the need for blood transfusion in pre-dialysis [1] and dialysis patients with anaemia [2,3]. Meta-analysis of randomized controlled trials or quasi-randomized controlled trials comparing ESAs with control (no ESA or placebo) in pre-dialysis patients with renal anaemia shows that ESA therapy significantly improves Hb levels [mean difference 2.3 g/dl; 95% confidence interval (CI) 1.37–3.23] and Hct (weighted mean difference 9.92%; 95% CI 8.78–11.05) and reduces the need for transfusion [odds rato (OR) 0.25; 95% CI 0.09–0.69] compared with control [1]. QOL and exercise capacity were also improved, although there was an increased need for antihypertensive treatment, which could have been attributed to the higher doses of ESA used in the early trials. The benefit of treatment with epoetin alfa was examined in a randomized, double-blind, placebo-controlled trial of PD patients. In the epoetin alfa group, Hct increased from 23.8% at baseline to 32% after 6 weeks of treatment, need for transfusion decreased during treatment and anaemia was ameliorated in 85% of patients by week 12. In contrast, in the placebo group, Hct did not change significantly from baseline (23.8%) and the need for transfusion was not reduced during the study [4].

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***)
- **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***)

Note: A table summarizing the information in this recommendation is provided at the end of this guideline.

Rationale and commentary

Treatment of anaemia with ESAs is associated with improved patient QOL and well-being and a significantly reduced need for blood transfusions. However, these benefits are achieved at a substantial

economic cost; therefore, analyses have been undertaken to determine the optimal use of ESA therapy.

In initial trials, epoetin was administered i.v. However, there is strong evidence from randomized trials in CKD patients receiving dialysis that s.c. epoetin is as effective as i.v. epoetin and may allow lower doses to be used, thereby reducing costs [5–10]. Dose requirements for s.c. epoetin (alfa or beta) are reported to be 22% lower than those of i.v. epoetin [11]. In a randomized trial, HD patients given s.c. epoetin alfa had a shorter correction phase and needed lower doses of s.c. epoetin during the correction phase compared with those given i.v. epoetin [5]. Similarly, in a randomized, unblinded trial of 208 patients receiving long-term HD, the average weekly dose of s.c. epoetin alfa needed during the maintenance phase was 32% lower than that of i.v. epoetin alfa [9]. In support of these data, pharmacokinetic studies suggest that epoetin alfa has lower bioavailability but a longer half-life after s.c. administration than after i.v. administration [12,13]. In contrast, some studies found no difference between the dose of s.c. and i.v. epoetin needed [14,15]. There was no significant difference in dose needed by patients who switched from s.c. to i.v. epoetin alfa, compared with those who continued s.c. epoetin alfa [14]. However, the later studies that showed no difference between the required dose of s.c. and i.v. epoetin examined fewer patients than those studies suggesting that s.c. epoetin is more effective than i.v. epoetin.

Darbepoetin alfa is a novel ESA, which, due to its increased sialic acid-containing carbohydrate content, has a three-fold longer terminal serum half-life than epoetin alfa. Evidence from randomized trials indicates that darbepoetin alfa can effectively treat anaemia in CKD patients when administered i.v. or s.c. In a multicentre, randomized, open-label study in HD and PD patients, doses of darbepoetin alfa needed were similar whether administered by the s.c. or i.v. route [11,16].

The i.p. route is rarely used for the administration of ESAs. Evidence suggests that i.p. administration is inferior to i.v. and s.c. administration, due to low bioavailability and an increased risk of peritonitis [6,17].

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***)

Note: A table summarizing the information in this recommendation is provided at the end of this guideline.

Rationale and commentary

ESA therapy typically follows a two-phase course: an initial correction phase followed by a maintenance phase. The optimal frequency of administration of ESA in these treatment phases is unclear. Epoetin alfa and epoetin beta have relatively short circulating half-lives, and are commonly given two or three times a week. Once weekly administration of these agents has been suggested. However, it has been proposed that the initial high peak level after a once weekly dose may be wasted because erythropoietin receptors on bone marrow progenitor cells become saturated and the level of serum epoetin will have fallen by the time the receptors are available again.

While there is a lack of evidence to support once weekly dosing of i.v. epoetin in HD patients, evidence from a number of trials suggests that s.c. epoetin is effective when dosed once weekly and may allow dose reduction [1,18]. A recent meta-analysis of randomized or quasi-randomized trials investigating various frequencies and routes of administration of epoetin, indicated that there was no significant difference in the effectiveness of epoetin in dialysis patients when administered s.c. once weekly compared with two to three times per week [1]. Results from one small study included in this meta-analysis suggested that once *vs* more than once per week dosing would require an additional 12 IU/kg/week of epoetin to achieve a similar Hb level in HD patients [19]. The results of a randomized, open-label trial of HD patients showed that s.c. epoetin beta given once weekly and three times weekly were statistically equivalent in terms of maintaining stable Hct and the dose of epoetin beta needed [20]. The dosing frequency of epoetin beta

may therefore be reduced to once or twice weekly when administered s.c. in HD patients. Epoetin alfa is not licensed for s.c. administration in many European countries because of the risk of PRCA (see Guideline IV.2).

It is convenient to administer epoetin by the s.c. route in CKD, PD and transplant patients [18]. However, the optimal frequency of epoetin administration is unclear. Data from one trial in continuous ambulatory PD patients showed no significant difference in the s.c. dose of epoetin needed to maintain Hct whether patients received their dose once, twice or three times a week [18]. It is possible that epoetin may effectively manage anaemia in CKD, PD and transplant patients when given s.c. three times per week during the correction phase and once per week during the maintenance phase. However, further evidence is required to elucidate fully the optimal s.c. dosing frequency in these patient populations.

Evidence from randomized trials shows that darbepoetin alfa administered once weekly or once every other week can effectively treat anaemia in CKD patients on dialysis. In a multicentre, randomized, open-label study of HD and PD patients, once weekly or once every other week darbepoetin alfa maintained Hb levels as effectively as once, twice or three times weekly epoetin alfa or beta [11]. These results were consistent irrespective of the ESA dose route (i.v. or s.c.); PD patients were always given s.c. darbepoetin alfa, epoetin alfa or epoetin beta. Similarly, a randomized, double-blind trial also supports once weekly dosing of darbepoetin alfa. Once weekly i.v. darbepoetin alfa was shown to maintain Hb concentrations as safely and effectively as i.v. epoetin alfa three times weekly in HD patients [3]. Furthermore, less frequent dosing of darbepoetin alfa was not associated with an increased risk of 'unstable Hb' (defined as Hb values necessitating a dose change). Results from the randomized trial reported by Vanrenterghem *et al.* [11] indicate that Hb levels can be maintained successfully in HD and PD patients switched from once weekly epoetin to darbepoetin alfa once every other week.

Evidence from a single randomized, open-label study indicates that administration of darbepoetin alfa in CKD patients not on dialysis also requires less frequent dosing compared with epoetin [21].

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-naïve patients should normally be 20–30% higher than the maintenance dose.**
  (***Evidence level B***)

Rationale and commentary

In a prospective, randomized study of PD patients, the median dose of s.c. epoetin beta needed to correct Hct (19.9 IU/kg/day at the end of the correction phase) was consistently higher than that needed to maintain a stable Hct (range 9.4–9.9 IU/kg/day) [22]. A multicentre dose titration study of patients on continuous PD shows that baseline Hb level affects the dose of epoetin beta needed; patients with low baseline Hb (<7.5 g/dl) need a higher maintenance dose of epoetin beta than those with a higher baseline Hb [23]. Patients with complicating factors such as haemorrhages and/or infection may also need a higher maintenance dose of epoetin beta than patients without complicating factors [23].

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

Rationale and commentary

Individual responses to ESAs may be assessed by checking Hb every 2–4 weeks following initiation of ESA therapy, or during alteration of ESA dose. In the maintenance phase, Hb should be monitored every 4–8 weeks. Patients with Hb targets in the normal range should be monitored every 2–4 weeks until stabilized. This reflects the general rule that patients with higher Hb targets need more frequent monitoring of Hb concentrations.

Evidence from randomized studies shows that stable Hct or Hb levels can be achieved [20] and maintained [2,11] by titrating the ESA dose in response to Hb. Consistent with this, a randomized, multicentre study shows that epoetin beta induces a dose-dependent increase in Hct level and reticulocyte count in anaemic dialysis patients [3].

In a randomized study of HD patients, stable Hct was achieved by adjusting the dose of once or three times weekly epoetin beta by 20% in response to changes in Hct of 3 vol% compared with baseline [20]. In another multicentre, randomized, open-label study, a stable Hb level was maintained successfully in $\geq 95\%$ of dialysis patients by adjusting the dose of ESA (darbepoetin alfa once weekly or once every other week, epoetin alfa or beta once, twice or three times weekly) by 25% in response to Hb changes of –1 g/dl to +1.5 g/dl from baseline [11]. Similarly, in a study of HD patients, Hb concentration was maintained effectively within −1 to +1.5 g/dl of baseline by increasing the dose of darbepoetin alfa once weekly or epoetin alfa i.v. three times weekly by 25% of the starting dose if Hb fell below target level for two consecutive weekly assessments [2].

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***)

Rationale and commentary

In early, controlled studies, the incidence of hypertensive episodes and/or increase in antihypertensive treatment was 4.9–21% higher in patients given ESAs than in control groups [24–30]. Normalization of Hb targets is linked to higher diastolic blood pressure in pre-dialysis patients with CKD than in similar patients with lower, conventional Hb targets [32]. However, no difference was seen between the blood pressure of dialysis patients with normalized Hb targets and those patients kept at lower target Hb levels [32,33].

In a review of the literature in the NKF-DOQI™ guidelines [34], 23% (785/3428) of CKD patients given ESAs either developed hypertension or required increased antihypertensive medication. There is no increased incidence in patients with normal renal function who are given ESAs [35]. Increased blood pressure in CKD patients is due primarily to a loss of hypoxic vasodilatation involving an increase in vasoconstrictor tone, the release of endothelin and vasoconstrictor prostanoids, increased sensitivity to noradrenaline and reduced expression of nitric oxide synthase. Continued high cardiac output may also play a role, particularly in HD patients who have high blood flow in their vascular access.

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***)

Rationale and commentary

Administration of ESAs appears to improve platelet function [36–39]. This may be due to increased Hb concentration, reflecting similar changes when Hb concentrations increase after red blood cell transfusion. Therefore, thrombosis of the vascular access may be a concern in dialysis patients receiving ESA therapy.

To assess the risk of thrombosis of the vascular access, the NKF-DOQI™ guidelines [34] reviewed data from >4000 HD patients given ESAs to raise Hb concentrations to 10–12 g/dl. These data showed an overall thrombosis rate of 7.5% for all types of vascular access during treatment, but adequate control data were lacking. In three controlled studies, the incidence of clotting of the vascular access was significantly lower in the control group [26,28,30,32]. However, data from the Canadian Erythropoetin Study [26,28] and a single controlled study [24] showed no difference in the rate of thromboembolic adverse events between patients treated with ESAs and untreated patients for those with native arteriovenous fistulae. Overall, there are no conclusive data indicating that the risk of thrombosis of the vascular access increases when Hb concentrations are between 10 and 12 g/dl.

Data are also inconclusive on the risks of vascular access thrombosis at higher Hb concentrations. It appears that patients with prosthetic, PTFE grafts may be prone to excess thrombosis at higher Hb concentrations, while those with native arteriovenous fistulae have no increased incidence [40,41]. In a USA-based prospective, randomized study of patients with

Table 1. Recommended route and frequency of administration

Recommendation	Patient type			
	CKD stages 1–5 not on dialysis	HD	PD	Transplant
Recommended **route** of administration	s.c.	s.c. or i.v.	s.c.	s.c.
Recommended **frequency** of administration				
Correction	EA: N/A EB: 1–3×/week DA: 1×/week	EA: 3×/week (i.v. **only**) EB: 3×/week (i.v. or s.c.) DA: 1×/week (i.v. or s.c.)	EA: N/A EB: 3×/week DA: 1×/week	EA: N/A EB: 1–3×/week DA: 1×/week
Maintenance	EA: N/A EB: 1–3×/week DA: 1×/week to 1×/2 weeks	EA: 3×/week (i.v. **only**) EB: 1–3×/week (s.c.) EB: 2–3×/week (i.v.) DA: 1×/week to 1×/2 weeks (i.v. or s.c.)	EA: N/A EB: 1–3×/week DA: 1×/week to 1×/2 weeks	EA: N/A EB: 1–3×/week DA: 1×/week to 1×/2 weeks

EA = epoetin alfa; EB = epoetin beta; DA = darbepoetin alfa; N/A = not applicable because not licensed for use by this route. Supporting evidence levels can be found in Recommendations II and III.

congestive heart failure or ischaemic heart disease, the incidence of access thrombosis was significantly higher during 14 months follow-up among patients randomized to a normal Hct group (42%; Hb concentration 13 g/dl), both in PTFE grafts (48 *vs* 37%) and in native vascular fistulae (26 *vs* 11%) [33]. These rates are high by European standards. In a Scandinavian study, there was no significant difference in the incidence of thrombosis between patients randomized to normalized Hb targets, and those with Hb targets of 9.0–12.0 g/dl [32].

Prevention of clotting of the vascular access using anti-thrombotic agents has yet to be fully evaluated. A single small but randomized, controlled trial suggested that dipyridamole reduced thrombosis rates in PTFE grafts in patients with an Hb concentration of 10–12 g/dl. In an observational study, calcium channel blockers and aspirin use were associated with better graft patency, and angiotensin-converting enzyme (ACE) inhibitor use was associated with better secondary fistula patency [42].

The recommended aspirin dose in ischaemic heart disease is 162–325 mg, according to a recent review [43]. However, as stated above, there are very few published data supporting a preventive effect of aspirin on clotting of the vascular access in HD patients, and there are absolutely no published data indicating that low doses are better than high. A recent randomized study [44] found no positive effect of a combination of clopidrogel and aspirin on the incidence of HD access graft thrombosis, and bleeding complications were increased in the treatment group. In fact, aspirin has been reported to increase thrombosis rates [45].

Recommendation

VIII. The dialysis schedule should not be altered during ESA therapy as the incidence of potential adverse events such as seizures and headache, loss of dialyser clearance and hyperkalaemia does not significantly increase. There is also no increased need for heparin anticoagulation during HD in patients receiving ESA therapy. (***Evidence level B***)

Rationale and commentary

Most CKD patients receiving ESAs will experience a certain level of adverse events. Despite the findings of the early ESA studies, it now appears that the incidence of the potential adverse effects, such as seizures and headache, increased need for heparin anticoagulation during HD, and loss of dialyser clearance and hyperkalaemia [46], is not increased during treatment with ESAs. The incidence of adverse events in both the experimental and control groups of large clinical trials examining ESA therapy has been high, but this reflects the high background rate of medical complications associated with CKD. Safety profiles and adverse event rates are similar for all available ESAs, except in the case of PRCA.

In early studies of ESAs, most of which were open-label and non-randomized, increased incidences of seizures and headache [24–26,29–31], increased need for heparin anticoagulation during HD, loss of dialyser clearance [47–52] and hyperkalaemia [47,48,50,52–54] were observed. However, in more recent studies of ESA-treated CKD patients [34], the incidence of these potential adverse events was found to be no higher in experimental groups when compared with control groups.

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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***)

Rationale and commentary

Regardless of dialysis status, patients with CKD are at increased risk of being in negative iron balance compared with non-uraemic individuals. Normal subjects will absorb up to 1 mg per day of iron from their diet, adequately balancing daily iron losses from the gut. Uraemic individuals are at risk of increased gastrointestinal iron losses and have an increased tendency to bleed due to platelet dysfunction. In addition, it has been suggested that uraemic individuals absorb iron from the gut less effectively than non-uraemic individuals [1,2]. Drugs such as calcium carbonate and aluminium salt phosphate binders used by uraemic patients as prophylaxis against renal osteodystrophy may further compromise iron absorption.

Patients receiving HD also have additional sources of blood loss. Annual blood loss from dialysis has been calculated to be ~2.5 l. This represents an annual loss of ~750 mg of iron (or 2 mg/day) in addition to the normal gastrointestinal losses of 1 mg/day. In some dialysis patients, further blood losses as high as 700 ml (200 mg of iron per year, or 0.54 mg/day) have been recorded.

Demand for iron is also increased by treatment with ESAs. During the first 3 months of ESA therapy, HD patients will require ~1000 mg of supplementary iron (up to 30 mg every 24 h), of which 400 mg will replace ongoing losses in the dialyser and from blood sampling. There is also evidence that setting higher target haemoglobin (Hb) concentrations leads to an increased demand for iron [3]. The need for and use of supplementary iron to maximize the benefits of ESA therapy amounts to synergy between these two forms of treatment. However, the administration of intravenous (i.v.) iron in the absence of ESA therapy may improve anaemia in some renal patients, in particular CKD patients not yet requiring dialysis [4].

In conclusion, the majority of, if not all, CKD patients will benefit from iron supplementation. Patients undergoing regular HD are especially vulnerable to iron deficiency, and virtually all patients receiving this modality of renal replacement therapy will require iron supplementation. The appropriate markers of iron status may provide more specific guidance as to which patients should receive iron supplementation, but any patient showing clinical or laboratory evidence of absolute or functional iron deficiency should be treated with iron.

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***)

Rationale and commentary

There is strong evidence from randomized, controlled trials that treatment with i.v. iron is more effective than oral iron in renal failure patients. In two such studies [5,6], no differences were seen when oral iron was compared with placebo or no iron in HD patients receiving ESA therapy. These data support the results of other studies, which suggest that oral iron is poorly absorbed in uraemic patients. In three randomized, controlled studies, i.v. iron was superior to oral iron in terms of efficacy [5,7,8]. In addition, there is considerable evidence from other studies to suggest that i.v. iron is more efficacious than oral iron in treating iron insufficiency in CKD patients (e.g. a prospective crossover trial) [9]. There is however, one randomized, controlled study that observed no difference between i.v. (iron sucrose 300 mg/month) and oral iron supplementation (ferrous sulfate 200 mg, three times daily) in patients with progressive renal insufficiency [10]. One small, single-armed trial has also reported that uraemic patients maintain sufficient intestinal iron absorption to cover daily gastrointestinal and sampling iron losses [11], although it was not sufficient to cover the degree of blood loss associated with HD.

Taken as a whole, the evidence strongly supports the use of i.v. iron supplementation in CKD patients, particularly those on dialysis and those receiving ESA therapy. However, for practical reasons, oral iron can be considered for CKD patients not yet on HD.

Recommendation

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

Rationale and commentary

Oral iron is usually administered three times per day (e.g. ferrous sulfate 200 mg tablets); but, as discussed in the next section, this dosing regimen may not be sufficient to meet the iron requirements of patients receiving ESAs [12]. I.v. iron may be administered at a dose of 20–60 mg per HD session; many dialysis units choose, however, to administer 100 or 200 mg i.v. iron at weekly or even monthly intervals. Pre-dialysis and peritoneal dialysis patients may require weekly to monthly administration of i.v. iron. During the maintenance phase of ESA therapy, iron supplementation may only be required every 3 months. However, no definitive recommendation can be made regarding the optimum frequency for the administration of iron therapy. This reflects the lack of randomized, controlled trials comparing the efficacy and safety of different iron treatment regimens.

Recommendation

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

Rationale and commentary

In terms of efficacy, the optimal iron dose is in the region of 25–150 mg/week for the first 6 months of ESA therapy. Evidence from a randomized, controlled study showed that 25–150 mg/week of iron, following a loading dose of 400–600 mg administered over 2 weeks, yielded better results than the same regimen given without the loading dose [13]. Another study has examined the efficacy of 200 mg of iron administered once weekly for 5 weeks in pre-dialysis patients [14]. Most studies conclude that higher doses of i.v. iron yield better results in terms of efficacy. However, there are some safety concerns regarding the administration of very high doses of i.v. iron, specifically that this dosing strategy may lead to organ damage from iron deposition, exacerbate oxidative stress-related disease and predispose patients to infections. Although the association between these potential problems and iron overload has been reported in published *in vitro* studies [15–18], studies examining this issue in a clinical setting are lacking and these problems therefore remain theoretical and unproven (see Guideline II.2). In the meantime, it seems prudent to monitor serum ferritin levels in patients receiving i.v. iron, and to discontinue treatment if ferritin levels exceed 800 μg/l.

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***)

Rationale and commentary

Titration of iron supplementation should be performed by measuring the serum ferritin level, along with HRC, TSAT or CHr, depending on the methodology available. These tests, and the rationale for their use, are described in detail in Appendix B.

There is little evidence on the optimal frequency for monitoring of iron status, but most studies aiming to optimize anaemia management describe monthly tests of iron indices [19–21]. It is important to note that serum ferritin levels may not accurately reflect iron stores for a period of up to 1 week after i.v. iron therapy, especially if large intermittent doses are used.

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*)

Rationale and commentary

There are a number of points that should be taken into consideration when selecting a source of supplemental iron. Oral iron frequently is associated with gastrointestinal intolerance including nausea, vomiting, abdominal pain, constipation and diarrhoea [22], and this may in turn result in poor compliance with therapy. All i.v. iron therapies may be followed by a vasoactive reaction and hypotension, especially when larger doses are administered rapidly [23–25]. In addition, severe upper loin and abdominal pain is a rare adverse event associated with ferric sodium gluconate [26]. Administration of i.v. iron dextran may result in the delayed onset of arthralgia and myalgia, particularly following high doses. However, these adverse events rarely occur with doses of 100 mg or less [27]. Conversely, arthralgia and myalgia associated with the use of iron gluconate are acute, rather than delayed.

The incidence of life-threatening/serious acute reactions to i.v. iron dextran has been reported as 0.65% (three of 471 general patients) [27] and 0.7% (four of 573 dialysis patients) [28]. In addition, pre-existing anti-dextran antibodies have been reported in some patients [29]. It is therefore imperative that a test dose be administered to patients prior to iron supplementation with iron dextran, although this may not always predict a subsequent reaction; anaphylaxis to iron dextran has been reported in patients having had a previously negative test dose. In addition, special caution should be exercised in patients with multiple drug allergies/intolerance.

A test dose is, however, not required for other i.v. iron preparations. Patients with a previous sensitivity reaction to iron dextran have a low risk of sensitivity to other preparations (e.g. iron gluconate and iron sucrose) and may be treated safely with these preparations [30].

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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 peritoneal dialysis (PD) programme.
(***Evidence level B***)

Rationale and commentary

Optimal dialysis is of paramount importance in the treatment of renal anaemia [1–5]. The two main types of dialysis are HD and PD. HD includes haemofiltration (HF), haemodiafiltration (HDF) and acetate-free biofiltration; PD includes continuous ambulatory PD and automated PD. Optimal conventional dialysis techniques have clear benefits [1–5] and should be considered the cornerstone in the management of patients with chronic kidney disease (CKD) and anaemia on dialysis.

PD has some advantages over HD in the treatment of renal anaemia since PD patients need lower doses of ESAs to reach target haemoglobin (Hb) concentrations compared with HD patients.

Although HD has been shown to have a significant, positive impact on Hb levels [2,3], there is also clear evidence that patients on PD need fewer red blood cell transfusions [6] and lower doses of ESAs to reach target Hb concentrations [6] compared with patients on HD. There are several reasons why this may be so: (i) PD is associated with less blood loss (i.e. gastric bleeding and extracorporeal losses which occur during HD sessions); (ii) PD is performed at home, so blood sampling occurs less frequently (monthly to quarterly) than with HD; and (iii) PD provides better preservation of residual kidney function than conventional HD [7,8]. Interestingly, the annual iron requirement for PD patients is about one-third of that needed by HD patients (~1000 mg in PD patients *vs* 3000 mg in HD patients), emphasizing the significance of blood losses in HD patients. However, there is no clear evidence to explain this; the benefits of PD do not appear to be related to patient characteristics or, seemingly, to the PD technique itself. Currently, the blood-sparing nature of PD and the lack of repeated heparin administration may be possible explanations for this phenomenon.

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***)

Rationale and commentary

Alternative dialysis therapies and anaemia correction

There is some evidence that alternative dialysis treatments such as enhanced convective treatments (HDF and HF) with on-line production of substitution fluid may improve the correction of anaemia with reduced doses of ESA therapy. Treatments such as high-flux HDF, HF and acetate-free biofiltration may improve correction of anaemia and reduce the dose of ESA therapy compared with conventional dialysis techniques [9–12]. Preliminary findings also suggest that short daily or nocturnal dialysis can improve correction of anaemia [13–17]. It is difficult, however, to discriminate whether these effects are due to the type of dialysis modality used, the improved haemocompatibility or a result of increased dialysis dose or removal of larger molecular weight toxins [18–20].

Alternative dialysis treatments and uraemic toxins

Uraemic toxins are believed to downregulate the production of erythropoietin and inhibit erythropoiesis in patients with CKD. Dialysis with conventional, cellulose membranes only removes small and medium sized molecules, so any toxins of high molecular weight would remain. It has been suggested that high-flux dialysis and enhanced convective therapies (HDF and HF), using highly permeable and biocompatible membranes with increased permeability, might remove more high molecular weight toxins than dialysis with conventional cellulose membranes [21]. If this were the case, then dialysis with highly porous membranes should improve erythropoietin production and anaemia, compared with conventional membranes. When this hypothesis was tested in a multicentre, randomized, controlled trial, no difference was found in Hb level increase in patients dialysed using each type of membrane [22]. However, it is possible that the limited follow-up (12 weeks) might have influenced these findings.

Albumin toxin-bound substances may also play a role in the inhibition of erythropoiesis. Preliminary studies performed with albumin-leaking membranes show an improvement in erythropoiesis in patients after several weeks of use [23–26].

Ultrapure dialysate

The quality of water used for dialysis has been shown to impact a patient's response to ESA therapy. In a randomized, controlled trial, the use of ultrapure dialysate was found to reduce the dose requirement for ESAs [27].

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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***)

Rationale and commentary

Supplementary intravenous (i.v.) iron is now commonly used in haemodialysis (HD) patients receiving treatment with ESAs. Other forms of adjuvant therapy may also be appropriate in some chronic kidney disease (CKD) patients, especially those who are unresponsive to or require large doses of ESAs [1]. As well as clinical benefits, some adjuvant therapies, particularly androgens, have also been associated with economic benefits in countries with limited resources. However, solid evidence in favour of adjuvant therapies is scarce, and routine use of non-pharmacological doses of vitamins, nutritional supplements and androgens is not widely recommended in CKD patients.

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***)

Rationale and commentary

Vitamin E and oxidative stress

Giving i.v. iron to anaemic patients on chronic HD leads to 'oversaturation' of the transport protein transferrin [2]. High levels of saturated transferrin are linked to non-transferrin-bound, potentially redox-active iron—a potent pro-oxidant and trigger for iron-induced lipid peroxidation in the presence of hydrogen peroxide or lipid hydroperoxides. As with other oxygen free radicals, these compounds can start the chain reaction of lipid peroxidation and disturb tissue and organ function. Vitamin E deficiency has been linked to increased osmotic fragility, and some scarce data show that vitamin E supplementation benefits CKD patients with anaemia [3,4]. In HD patients, vitamin E-coated dialysis membranes have been associated with improved control of anaemia [5,6]. Vitamin E is known to be a strong antioxidant that inhibits lipid peroxidation and may protect against oxidative stress-related degenerative diseases in the long term [7,8]. Data demonstrate that a single oral dose of vitamin E taken 6 h before an HD session lessens lipid peroxidation in patients given i.v. iron [2]. Correction of low plasma vitamin C levels may also potentiate the effect of vitamin E.

Use of vitamins as adjuvants

There are no large controlled trials of the effect of pharmacological doses of vitamins on anaemia in CKD patients. However, there is evidence that large doses of vitamin C mobilize otherwise inaccessible iron stores and enhance the response to ESA treatment in CKD patients with functional iron deficiency [9,10]. However, the risk of oxalate deposition from such large doses precludes a recommendation for routine clinical use.

Deficiencies of water-soluble, dialysable vitamins such as folic acid and vitamin B_{12} are well-defined causes of deficiency anaemias associated with macrocytosis [11,12]. These deficiencies may occur in CKD patients and need assessment and correction if responsiveness to ESA therapy decreases. In one study, pyridoxine (vitamin B_6) supplementation was linked to higher Hb levels in HD patients with microcytic anaemia [13]. However, the evidence is inconclusive on folate supplementation in HD patients receiving ESA therapy and an adequate mixed diet [14].

A review of the general evidence revealed that routine, low-level vitamin supplementation has no ESA-sparing effect in CKD patients [15] but multivitamin preparations may be used to ensure that patients receive recommended dietary intakes of vitamins B and C.

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***)

Rationale and commentary

Carnitine loss or deficiency observed in maintenance dialysis patients may be due to reduced food intake and/or an increased rate of carnitine loss during dialysis. A systematic review of the effects of L-carnitine supplementation in dialysis patients has shown that it may have a positive effect on anaemia in patients on maintenance HD [16]. One study found that, in addition to iron supplementation, L-carnitine reduced the need for ESA therapy in a subgroup of HD patients resistant to ESA therapy and may affect red blood cell survival [17]. Another small study showed that patients over 65 years old given L-carnitine needed a lower ESA dose to maintain stable Hb than patients not given the supplement [18].

High morbidity and mortality is common among chronic HD patients with impaired cellular immune defence systems. Abnormal carnitine metabolism may contribute to this impairment, but clinical trial data have shown that L-carnitine given to patients on maintenance dialysis has no beneficial effect on phagocytic function and viability of blood leukoctytes [19].

A lack of carnitine may also contribute to reduced exercise and functional capacity in patients with end-stage renal disease (ESRD). An increased plasma carnitine concentration in patients with ESRD is linked to improved patient-assessed fatigue [measured by the Kidney Disease Questionnaire (KDQ)] and may contribute to a decline in exercise capacity [assessed by maximal rate of oxygen consumption (VO_{2max})] [20]. However, in chronic HD patients, L-carnitine therapy had no overall effect on quality of life as assessed by the KDQ [21]. Restoration of tissue or plasma carnitine may not be sufficient to correct all patient symptoms, and rigorous clinical trials are needed to assess the efficacy, optimal dose and best route of administration of L-carnitine therapy [16].

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***)

Rationale and commentary

Prior to the introduction of ESA therapy, androgens were widely used in the treatment of renal anaemia. There is evidence that androgens may potentiate the effect of exogenous erythropoietic protein and also stimulate erythropoiesis by enhancing erythrocyte stem cell differentiation. In HD patients, injectable nandrolone decanoate (in men and women) and testosterone enanthate (in men) have been linked to a 5% rise in haematocrit (Hct) [22]. Oral formulations are less effective and are only recommended for needle-phobic patients. Improved haematological status with androgen therapy has also been reported in CAPD maintenance patients. Trial data show that men over 50 years of age on CAPD treated with either recombinant human erythropoietin or nandrolone decanoate had a mean rate of rise of >2.5 g/dl in Hb and >8% in Hct [23]. Nandrolone decanoate has also been linked to improved nutritional status in this subpopulation of CAPD patients.

In chronic HD patients responding adequately to low doses of ESA therapy, androgen therapy was found to have no beneficial effect on their anaemia [24].

Therefore, the scope for androgen therapy with these patients is limited.

Androgens may be an effective alternative therapy in countries where ESAs are not available, but they are generally poorly tolerated and long-term use should be limited to patients who have had symptomatic and haematological improvement after 6 months of treatment [22]. The risk of liver disease and malignancy, virilization and hirsutism in women, priapism in men and disfiguring acne in patients of both sexes may outweigh the benefits of androgen therapy in most anaemic patients.

Recommendation

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

Rationale and commentary

Reduced glutathione is known to have antioxidant properties. Some preliminary reports have shown positive effects on the anaemic status of CKD patients given parenteral reduced glutathione 1200 mg at the end of each dialysis session [25]. However, the optimal dose and the best route of administration for glutathione and other forms of antioxidant adjuvant therapy still require further investigation.

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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***)

Rationale and commentary

Patients with CKD are at high risk of developing PEM, and their nutritional status should therefore be monitored regularly [1,2]. In different cohorts of dialysis patients, the prevalence of malnutrition has been reported to vary between 10 and 65% [3,4], inflammation between 30 and 55% [5–7], and cardiovascular disease between 36 and 55% [8,9]. Therefore, CKD patients with anaemia, and/or a poor response to erythropoiesis-stimulating agent (ESA) therapy, should also be investigated for these commonly co-existing conditions that constitute the malnutrition–inflammation–atherosclerosis (MIA) syndrome [10], which is commonly associated with anaemia [11].

Patients with a low body mass index (BMI) are more likely to suffer from severe anaemia [12,13]. Obese CKD patients with a high BMI have high leptin levels and, in two observational studies, higher haemoglobin levels and/or reduced ESA needs (per kg body weight) compared with non-obese patients [13,14].

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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***)

Rationale and commentary

Erythropoiesis-stimulating agents (ESAs) can greatly reduce the need for red blood cell transfusions in patients with anaemia of CKD [1] when target haemoglobin (Hb) concentrations are reached and maintained [2].

With the advent of new immunosuppressive regimens in the period after 1995, the benefits of pre-transplantation transfusion have largely been rendered obsolete. There is some evidence that donor-specific transfusion (DST) with living donor transplantation improves survival, but the decision to perform DST must still be made on a case by case basis. Blood transfusions can induce histocompatibility leukocyte antigens (HLAs) that can reduce the success of kidney transplantation, so transfusions should generally be avoided in patients awaiting a renal transplant [3]. If deemed essential, red blood cell transfusions in this patient group should be conducted in line with the recommendations in the European Best Practice Guidelines for Renal Transplantation [4].

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***)

Rationale and commentary

If ESA therapy is started at the Hb concentration recommended in Guideline I.1 and Hb levels are maintained at the recommended target concentration, blood transfusions should only be given to patients with acute bleeding (usually gastrointestinal), acute haemolysis or severe inflammation, or blood loss through surgery, and then only in an emergency or if the patient exhibits a rapid decline in condition. International guidelines provide criteria for deciding when transfusion is necessary [5–7].

CKD patients on haemodialysis (HD) are more likely to need blood transfusions than those on peritoneal dialysis, due to the HD procedure itself. Patients on HD lose blood from frequent blood tests, trapped blood in the dialyser and tubing [8] and increased risk of gastrointestinal bleeding from anti-coagulants. The Hb targets given in Guideline II.1 are not suitable for patients receiving red blood cell transfusions.

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