

Guideline 9: Route of administration of epoetin

A. Epoetin should normally be administered subcutaneously in pre-dialysis and peritoneal dialysis patients since this is almost always more convenient, especially if self-administration is practised.

(Evidence level C)

B. According to patient characteristics and preference, epoetin can be administered either subcutaneously or intravenously in patients on regular haemodialysis, but the subcutaneous route will usually lead to lower doses of epoetin being required, and, in general, this route is preferable.

(Evidence level A)

C. When epoetin is given subcutaneously, the site of injection should be rotated with each administration.

(Evidence level C)

D. Patients using the subcutaneous route should be encouraged to self-administer epoetin whenever possible.

(Evidence level C)

E. In a few peritoneal dialysis patients in whom both subcutaneous and intravenous administration of epoetin is not feasible, e.g. in some paediatric patients, intraperitoneal administration may be considered.

F. Intraperitoneal administration must be given into a dry abdomen, which should remain dry for at least 6–8 h. Intraperitoneal epoetin dose requirements may be higher than those associated with intravenous and subcutaneous administration.

(Evidence level B)

Commentary on Guideline 9: Route of administration of epoetin

When epoetin initially became available, it was always given intravenously. However, in 1988, Bommer and colleagues showed that epoetin could be effective when given subcutaneously [272] and it has now become apparent that, despite incomplete availability (ca. 20%) and low plasma concentrations, this route has more favourable pharmacokinetics than intravenous injection [273–279]. There are about 50 published papers and abstracts comparing subcutaneous and intraven-

ous administration of epoetin [119,203,235,273–320], but patient numbers in the majority of these studies (including several randomized trials) are small, methodological problems are present, and, on aggregate, it has been difficult to make firm recommendations.

However, the data tend to show that, using the subcutaneous route, equivalent Hb concentrations can be attained using lower doses than are necessary using the intravenous route: an (unpublished) meta-analysis of the data from the 11 available randomized studies [203,286,290,292,295,297,301,304,307,310,311] shows a weighted median reduction in dosage of 21% (range

Guideline 10: Initial epoetin administration

A. The starting dose of epoetin should be 50–150 IU/kg/week (typically 4000–8000 IU/week), depending on body weight, the total epoetin requirement and the need to utilize the whole vial with some preparations.

B. When epoetin is administered subcutaneously (see Guideline 9), doses in the lower part of this range should be used, 2–3 times per week. For intravenous administration, the starting dose should be in the upper range (typically 6000 IU/week) 3 times per week.

(Evidence level B)

C. Higher initial doses of epoetin may be used if the patient has either complicating disorders leading to anaemia, or severe anaemia (Hb concentration < 8 g/dl).

D. Titration of dosage: epoetin doses in the upper range can be reached progressively as the individual patient's maintenance dose is established, usually by decreasing the interval between subcutaneous injections. Intravenous injection should be continued thrice weekly with a dosage increase. If the patient requires less than the starting dose to maintain the target Hb concentration (see Guideline 5), either the intervals between each subcutaneous dosage can be extended, or thrice weekly intravenous dosage decreased.

(Evidence level C)

E. Paediatric patients younger than 5 years of age may require greater doses of epoetin on a body weight basis (up to 300 IU/kg/week) than older paediatric patients and adults.

(Evidence level B)

Commentary on Guideline 10: Initial epoetin administration

When selecting an initial dose of epoetin, the aim is to reach the target Hb concentration in 2–4 months from initiation of treatment; using the doses recommended here an increment in Hb concentration of 0.2–0.5 g/dl/week can be expected [42,119,235,324–330]. However, the individual response will need to be measured, and the dose adjusted accordingly. The tendency has been to use lower starting doses, especially when the subcu-

taneous route is being employed (see Guideline 9). Obese patients tend to need a lower dosage/kg than lean individuals, which may arise from not only body composition, but also their increased serum leptin concentrations [331]. In patients with vascular disease and diabetes mellitus, in whom a slow increase in Hb concentration is desirable, an initial dose in the lower range may be chosen. For reasons which have not been established, children younger than 5 years of age have a greater requirement for epoetin per unit body weight than older children or adults [235, 326].

1–33%, 160.2 vs 127.1 IU/kg/week) when the subcutaneous route is compared with the intravenous route, a smaller difference than was claimed in some earlier reports (in two studies included in this meta-analysis [293,295], the doses used (>200 IU/kg/week) were greater than those used in current practice, and greater than those used in the other randomized studies). The largest prospective controlled study [311], comprising 208 patients, showed a difference of 32% (140 vs 95 IU/kg/week), although a substantial minority (23%) of patients who were switched from intravenous to subcutaneous administration needed *more* epoetin.

Thus, while the subcutaneous route generally appears to be preferable, a choice is available for patients on haemodialysis and their physicians as to which route should be employed. Factors that both

parties will need to take into account include convenience, pain at the site of subcutaneous injection, the presence of dermatological disease or obesity (which may impair absorption) and cost. For patients not yet on dialysis and for those on CAPD, the usual preferred route will be subcutaneous. The frequency of dosing will also need to be considered. Thrice weekly subcutaneous injections appear to be more efficient than once weekly injections [318], but are less convenient, unless self-administered by patients who attend hospital only every few weeks. Daily injections confer no advantage and carry obvious inconveniences [40,120].

Intraperitoneal administration of epoetin is little used, except in some children on CAPD who will not tolerate subcutaneous injections and in whom intravenous injections are not practicable [274,320–323].

Guideline 11: Monitoring of haemoglobin concentration during epoetin treatment

A. The Hb concentration should be measured every 1–2 weeks following initiation of treatment or following a dose increase or decrease, until a stable Hb concentration and epoetin dose have been reached. The target should be to increase the Hb concentration by 1–2 g/dl per month.

B. Once a stable target Hb concentration and epoetin dose have been reached, the Hb concentration should be monitored every 4–6 weeks in both haemodialysis and CAPD patients and less often in pre-dialysis patients, unless intercurrent diseases occur that may influence the Hb concentration.

(Evidence level C)

Commentary on Guideline 11: Monitoring haemoglobin concentration during epoetin therapy

With the doses recommended above and optimal iron stores, the increase in Hb concentration can be expected to be about 0.2–0.5 g/dl/week, although the variation from patient to patient is large.

Guideline 12: Titration of epoetin dosage

- A.** If the increase in Hb concentration after initiation of epoetin therapy or after a dose increase has been < 0.7 g/dl (haematocrit $< 2\%$) over a 2–4 week period, the dose of epoetin should be increased by 50%.
- B.** If the absolute rate of increase of Hb concentration after initiation of epoetin therapy or after a dose increase is > 2.5 g/dl (haematocrit $> 8\%$) per month, or if the Hb concentration exceeds the target Hb concentration, the weekly dose of epoetin should be reduced by 25–50%.
- C.** When the weekly epoetin dose is being increased or decreased, a change may be made in the amount administered in a given dose and/or in the frequency of dosing (if given subcutaneously). It is preferable to round off the dose to the nearest whole vial to prevent wastage.

(Evidence level C)

- D.** The median maintenance dose of epoetin in a non-selected population of patients given subcutaneous epoetin will usually be < 125 IU/kg/week. The lowest effective doses are likely to be about 50 IU/kg/week, with $> 90\%$ of patients receiving < 300 IU/kg/week.

(Evidence level B)

Commentary on Guideline 12: Titration of epoetin dosage

Dose adjustment remains empirical, and there are no data comparing different approaches. While it is good not to take too long to attain the target Hb concentration, it is equally important that the increase in Hb

concentration not be too rapid, since severe hypertension and seizures are more common in these circumstances (see Guideline 18). The titration recommended here is based on a number of reports which record safe and effective use of epoetin to attain Hb concentrations of > 10 g/dl [133,324,327,329].

Guideline 13: Epoetin dosage perioperatively, during intercurrent illness and after transplantation

A. Epoetin should not normally be discontinued in patients who undergo surgery, who develop significant acute intercurrent illness or who require transfusion of red blood cells for acute blood loss. In some patients, the dose may need to be increased.

(Evidence level C)

B. Immediately following transplantation, no evidence is yet available to make a recommendation as to whether epoetin should be stopped immediately, continued for a specified period of time (e.g. for 4 weeks), or continued until the allografted kidney demonstrates excretory function. If acute allograft rejection results in irreversible graft failure, epoetin should be restarted as for any other patients with CRF (see Guidelines 1–5, 9–12).

(Evidence level C)

C. Patients with a slowly failing transplant (e.g. from chronic rejection) should be treated exactly as other patients with chronic renal insufficiency, and epoetin should be (re)started before graft failure and return to dialysis. The dosage required will often be greater than usual in the presence of a rejecting graft for the same degree of renal insufficiency and anaemia.

(Evidence level B)

Commentary on Guideline 13: Epoetin dosage perioperatively, during intercurrent illness and after transplantation

There is a general impression that the response to epoetin is reduced during intercurrent illness and in those patients who undergo surgery [332–335], in agreement with the findings in chronic illness and infection discussed in Guideline 14. Although there are few useful data in this area, we have included this guideline here to highlight the need for controlled studies in these areas. Severe anaemia, which takes some time to reverse, may arise if epoetin is stopped during intercurrent illness, with an increase in epoetin requirements; in this case, there may be no cost savings

by following this strategy—although controlled data are lacking.

In particular, in the early stages after transplantation, during which epoetin secretion by the allograft has not begun, the relative roles of epoetin and transfusion have not been established [336–341]. Only one study in a small number of patients [342] has addressed the epoetin requirement immediately after transplantation; in this study, transfusion requirements declined, and there was no difference in graft function.

During chronic graft failure, the use of epoetin has been examined in a number of open studies and found to be effective [339–340,343–349]. The effective dose of epoetin required, however, is usually greater than in other types of uraemia [340,350].

Guideline 14: Causes of an inadequate response to epoetin treatment

A. An arbitrary (but data-based) definition of ‘resistance’ to epoetin is either failure to attain the target Hb concentration while receiving more than 300 IU/kg/week (ca. 20 000 IU/week) of epoetin subcutaneously, or a continued need for such dosage to maintain the target. ‘Resistance’ (or hyporesponsiveness) to epoetin treatment is usually relative, and an ‘adequate’ response depends on a number of patient variables as well as on the initial dosage of epoetin chosen.

(Evidence level B)

B. The most common cause of an incomplete response to epoetin is *absolute or functional iron deficiency*. In the iron-replete patient who has an inadequate response to epoetin, one should first consider whether the dose is adequate and (in those self-administering) whether the injections are actually being given and, if so, whether they are being sited properly under the skin.

C. Then the following conditions should be evaluated and, if reversible, treated:

- Chronic blood loss (gut, uterus)
- Infection/inflammation (access infections, surgical inflammation, tuberculosis, systemic lupus erythematosus, chronically rejecting allografts, AIDS)
- Hyperparathyroidism/osteitis fibrosa
- Aluminium toxicity
- Haemoglobinopathies (e.g. alpha and beta thalassaemias, sickle cell anaemia)
- Folate or vitamin B₁₂ deficiency
- Multiple myeloma, myelofibrosis
- Other malignancy
- Malnutrition
- Haemolysis
- Drug intake (e.g. high dose ACE inhibitor or AT₁ receptor antagonist therapy)
- Inadequate dialysis

(Evidence level B)

In the absence of abnormalities or deficiencies in one of the above conditions, a marrow examination is indicated.

Commentary on Guideline 14: Causes of an inadequate response to epoetin treatment

There is no agreed definition of 'resistance' to epoetin, which is usually relative rather than absolute, i.e. *hyporesponsiveness*, in that a greater dose than usual is required to produce an expected increase in Hb concentration. An arbitrary definition used in this document is a *continued* requirement for >20 000 IU/week (300 IU/kg/week); 90% of iron-replete patients receiving subcutaneous epoetin would be expected to respond to a lower dose than this, which is 2.5 times the usual mean/median dose [324]. A somewhat higher threshold (400 IU/kg/week) needs to be used if epoetin is administered intravenously (see Guideline 9).

Apart from *absolute or functional iron deficiency* (see Guidelines 6–8), the list given in this guideline shows the many different possible causes of inadequate response to epoetin. The frequency of these causes differs in various series, so an algorithm for the investigation of inadequate response has not been included. Most causes of hyporesponsiveness listed here are well established [39,178,332–335,350–396], but others remain controversial.

Blood loss should always be suspected in patients who require an increasing dose of epoetin to maintain a stable Hb concentration, in patients whose Hb concentration is declining, and in patients who fail to augment iron stores even after intravenous iron administration.

The diagnosis of *inflammation and infection* [335,351,353–356,389,391–393,395,397,398] is broad. A number of cytokines can influence early maturation of red cell precursors [399,400], including a negative effect of several inflammation-associated cytokines such as IL-6 and TNF alpha. Thus, in chronic inflammatory states, which can be assessed clinically using the plasma concentration of C-reactive protein, inhibition of erythropoiesis can lead to anaemia and blunt the response to epoetin. In many such patients, an effect of epoetin can be obtained but at a higher dosage, perhaps because epoetin itself may reduce plasma concentrations of TNF alpha, and increase IL-10 [401].

There is good evidence that *high plasma iPTH* concentrations [357,358,361,381–385,396,402], especially in the presence of histological osteitis fibrosa [357], are associated with resistance to the action of epoetin; this may be counteracted either by treatment with active forms of vitamin D [396,402] or by parathyroidectomy [381–384].

Aluminium intoxication [358–363] leads to a relative resistance to epoetin. It is well known that *haemoglobinopathies (sickle cell disease, alpha and beta thalassaemias)* [364–368] are associated with resistance to epoetin treatment.

Myeloma patients will respond to epoetin, but usually at greater than usual doses [374–377]. Some investigators [403–405], but not all [406], have reported an increase in light chain excretion during

epoetin treatment, which could be a result of engagement of epoetin receptors on myeloma and non-erythroid cells, but the significance of this is not clear.

Haemolysis, either mechanical, immunological or from disorders of the red cell envelope, has been recorded as a cause of epoetin resistance [380].

Patients with various forms of *solid tissue malignancy* may show chronic anaemia relatively resistant to epoetin treatment [335,352]. The effect of this added to the anaemia of CRF is not clear, but is likely to be significant.

Whether or not an *inadequate amount of dialysis* or the use of *bioincompatible dialysis membranes* leads to relative resistance to epoetin, and whether this can be corrected by increasing dialysis delivery, remains uncertain [387,398,407,408], although long slow dialysis is known to improve anaemia [409]. Nevertheless, attention to dialysis and *malnutrition* [378,379] should underpin the treatment of anaemia with epoetin in uraemic patients as part of their integrated care. Low serum albumin and low Hb concentrations are associated in dialysis populations, and acute inflammation can lead to a reduction in the serum albumin concentration.

The influence of *ACE inhibitors* on both absolute Hb concentrations and the response to epoetin has been controversial, with almost equal numbers of reports suggesting or denying an effect [410–424]. Nearly all of these studies, however, are retrospective comparative analyses; of two prospective (but unrandomized) studies, one [421] showed a clear effect of enalapril in a dose of 10–20 mg in increasing the dose of epoetin required in comparison with nifedipine-treated controls, but the other [419] (reported only in abstract form so that details of the agents used and their dosages are not yet available) showed no difference. Thus, in the case of a patient not fully responding to epoetin who is being treated with an ACE inhibitor, especially in high dosage, our recommendation is to consider the possibility of stopping administration of the ACE inhibitor and evaluating the epoetin response in its absence. Few data are available on *AT₁ receptor antagonists* in patients on dialysis [425,426] and these do not agree that an effect is present, although data from transplanted patients with erythrocytosis suggest that these agents are capable of lowering the Hb concentration [427,428]. In general, however, *AT₁ receptor antagonists* do not induce anaemia in patients with hypertension.

A need for adequate *carnitine* to achieve full erythropoiesis has been suggested [429–434] but not established; however, in cases for which no other cause of anaemia can be found and the plasma carnitine concentration is low, supplementation with L-carnitine should be considered.

There is some evidence that *vitamin C* may act as a synergist to epoetin [435,436], but risks of oxalate deposition from the large doses required do not permit its routine recommendation. It may be worth exploring in some resistant cases with high ferritin concentrations, since there is evidence that vitamin C, in a poorly

understood fashion, can mobilize otherwise inaccessible stored iron [435].

Folic acid and vitamin B₁₂ deficiencies, which are both water soluble and therefore dialysable vitamins, are well-defined causes of deficiency anaemias associated with macrocytosis, and require assessment when epoetin responsiveness decreases [369–372]. Although 2 mg/week of folate is probably necessary to maintain balance in patients receiving dialysis, the evidence that it affects epoetin response in patients without obvious folate deficiency is inconclusive [372,373,437].

Vitamin E has been suggested as an anti-oxidant supplement for epoetin [438], but more data are required.

In some circumstances, e.g. *haemoglobinopathies* or *chronic inflammatory disease*, it may not be possible to remove the cause of hyporesponsiveness. Some such patients *can* be treated with doses of epoetin greater than those usually recommended, and many will respond to, for example, >40 000 IU/week, but the cost of such treatment will often preclude its use.

Guideline 15: Management of patients resistant to epoetin

Anaemia in epoetin-resistant patients (arbitrarily defined here as a continued failure to respond to 20 000 IU/week) should be fully investigated as outlined in Guidelines 2 and 14, including referral to a haematologist.

Thereafter, if no other cause is identified and there is failure to respond to dosages of epoetin in the range of 40 000 IU/week, patients may be treated in a manner similar to that in which dialysis patients were treated before epoetin was available, including optimal dialysis and nutrition, except with androgens which are not currently recommended because of lack of effect and toxicity.

(Evidence level C)

Commentary on Guideline 15: Management of patients resistant to epoetin

For a discussion of resistance, see Commentary on Guideline 14. The use of L-carnitine has also been reviewed in the Commentary on Guideline 14.

In the period before the introduction of epoetin, androgens were tried extensively as a treatment for the

anaemia of CRF, with minor success and evident toxicity, especially in females. More recently, androgen therapy has been suggested either to reduce the dose of epoetin necessary to achieve a response or, again, as an alternative to epoetin, although the data are conflicting [439–445]. It is our view that androgens should not be used outside of clinical trials until further data have defined their role, if any, more clearly.

Guideline 16: Red blood cell transfusions in patients with chronic renal failure

Red blood cell transfusions are indicated in:

A. The severely anaemic patient with recognized symptoms or signs of anaemia, e.g. the patient with acute blood loss associated with haemodynamic instability, the patient with severe angina.

(Evidence level C)

B. The epoetin-resistant patient with blood loss whose Hb concentration decreases to critical levels.

(Evidence level C)

Commentary on Guideline 16: Red blood cell transfusions in patients with chronic renal failure

Red blood cell transfusions should always be limited to circumstances in which the anaemia is not otherwise reversible. Careful prior assessment of any symptoms or clinical signs which are likely to be reversed by transfusion is obligatory [446].

The main reasons for avoiding red blood cell transfusion in patients on dialysis are to avoid sensitization

against major histocompatibility complex (MHC) antigens, the possibility of transfusion reactions, the risk of transmission of viral or parasitic diseases, the risks associated with iron overload and transfusion haemosiderosis, and finally the fact that the effect on anaemia is short-lived.

If transfusions have to be given to patients likely to have a transplant in the future, or actually on a transplant waiting list, then steps to minimize MHC sensitization, such as leukocyte filtration, should be taken.

Guideline 17: Possible adverse effects of epoetin treatment: hypertension

A. Blood pressure should be monitored closely in all patients with CRF, particularly during initiation of epoetin therapy until the target haemoglobin has been reached. In pre-dialysis patients, the target blood pressure should be within the low normal range.

(Evidence level B)

B. Convective strategies, such as increased ultrafiltration during dialysis, initiation of anti-hypertensive therapy or an increase in anti-hypertensive medication, and reduction in epoetin dose if there has been a rapid increase in Hb concentration, may be required to control an increase in blood pressure related to epoetin therapy. Ultrafiltration will have to be used with caution in patients whose pre-dialysis Hb concentration is already within the normal range.

(Evidence level B)

Commentary on Guideline 17. Possible adverse effects of epoetin treatment: hypertension

In a review of the literature [34,41,118,122,297,307,324,328,376,447–483] in the NKF-DOQI® guidelines, 785 of 3428 patients receiving epoetin who also had CRF either developed hypertension or required an increase in anti-hypertensive medication during treatment (23%); this is not seen in patients with normal renal function given epoetin [352]. The causes of this increase in blood pressure are complex [484–493], involving an increase in vasoconstrictor

tone, perhaps involving release of endothelin and vasoconstrictor prostanoids [490,493], increased sensitivity to noradrenaline [488], and reduced expression of NO synthase [489]. A continued high cardiac output probably also plays a role. Surprisingly, rheological changes [158,485,494] do not seem to play a major role.

A persistent worry that epoetin therapy might worsen risk for cardiovascular disease (strokes and cerebrovascular disease, myocardial infarcts) in uraemic patients [158,168,495–499] has not been borne out by the available data, although complications of severe acute hypertension may be seen [500].

Guideline 18: Possible adverse effects of epoetin treatment: access thrombosis

- A. The optimum strategy for surveillance of fistulas/grafts for possible thrombosis has not yet been determined.**
- B. Whatever method is used, there is no need for increased surveillance for the prevention of access thrombosis in haemodialysis patients with either native fistulae or synthetic grafts when patients are treated with epoetin.**
- C. Patients bearing PTFE grafts seem to be at no extra risk of thrombosis if the Hb concentration is increased to 10–12 g/dl; however, at Hb concentrations within the normal range, these patients have an excess of thrombosis. Patients with arteriovenous fistulae have a similar pattern of risk for thrombosis, but the risk level is lower for any given Hb concentration.**

(Evidence level B)

- D. In patients with fistulae made from artificial materials (e.g. PTFE), anti-platelet therapy with agents other than aspirin can be considered.**

Commentary on Guideline 18: Possible adverse effects of epoetin treatment: access thrombosis

Haemostasis is disturbed in uraemia in a complex fashion [501,502], and the effect of epoetin on circulating pro- and anticoagulant proteins [503] and on disturbed endothelial and platelet function is also complex and still under investigation. The main effect of epoetin appears to be in improving platelet function [504–507], which may be due to effects of the increased Hb concentration, since similar changes are observed when the Hb concentration is increased by transfusion in both normal and uraemic individuals [508]. Endothelial function is also improved [509–511] by epoetin.

Data from more than 4000 patients on haemodialysis treated with epoetin to obtain an Hb concentration of 10–12 g/dl reviewed in the NKF-DOQI[®] guidelines [34,41,43,69,137,291,307,324,450,475,476,480,512–525] show an overall thrombosis rate of access of all types of 7.5% during treatment, but adequate control data for these figures are lacking: a single controlled study in patients with native arteriovenous fistulae showed no difference between epoetin and untreated patients [518]. There are, therefore, no data suggesting an excess of thrombosis in patients with native arterio-

venous fistulae at these Hb concentrations. However, data for higher Hb concentrations remain scanty and contentious. It seems that patients bearing prosthetic PTFE grafts may be prone to an increased rate of access thrombosis at greater Hb concentrations [526,527], while those bearing native arteriovenous fistulae again show no difference. In one prospective randomized study in patients with clinical evidence of congestive heart failure or ischaemic heart disease [153], the access thrombosis rate was significantly greater during a mean of 14 months follow-up in those patients randomized to a 'normal-haematocrit' group (42%; Hb concentration 13 g/dl), both in PTFE grafts (48% vs 37%), and in native vessel fistulas (26% vs 11%) [D. Goodkin, personal communication]. These rates are high by European standards, however. A single small randomized controlled trial suggested that administration of dipyridamole reduced thrombosis rates in PTFE grafts in patients with an Hb concentration of 10–12 g/dl; in contrast, aspirin increased thrombosis rates [528]. Other anti-platelet agents have not been evaluated fully, nor has prophylaxis in patients with normal Hb concentrations (12–14 g/dl) been studied. Until more data are available, aspirin should be avoided, since other data on the complex coagulopathy of uraemia suggest that this agent can have paradoxical results in the uraemic state.

Commentary: Other possible adverse effects of epoetin treatment

Seizures

Three per cent (59/2203) of adult patients treated with epoetin reviewed in the NKF-DOQI[®] guidelines [34,450,457,470,476,480,513,529–531] suffered seizures. The seizures occurred most frequently during the correction of the anaemia, and were associated with a rapid increase in Hb concentration and poor control of hypertension. These data may be compared with a single study of ESRD patients not on epoetin, 5% of whom experienced seizures [530]. Seizures are more common in children on dialysis than in adults.

Patients with a previous history of seizures need not be denied epoetin, and seizures are probably no more common in patients given epoetin, provided that the dosage is titrated and hypertension managed as outlined in Guidelines 12 and 17.

Heparin dosage during epoetin therapy

There is no evidence from two large American and Canadian multicentre studies [133,324] that heparin requirements increase during epoetin treatment, although a single European study showed a 40% increase [522].

Loss of dialyser clearance and hyperkalaemia

Although in the past hyperkalaemia was thought to be a problem [42], it now appears that this was the result of a voluntary reduction in quantity of dialysis by some patients in early studies. More recently accumulated data have not supported the suggestion that hyperkalaemia is any more common in patients on epoetin than in those not treated with epoetin: there were only 12 instances of hyperkalaemia in 1167 patients [42,450,457,518,524] included in the NKF-DOQI[®] review of the subject. When patients receiving and not receiving epoetin were compared [518,524], the incidence of hyperkalaemia in the epoetin-treated patients was equal to or less than in the non-epoetin-treated patients.

An increase in Hb concentration would be expected to lead to lower clearances of solutes not capable of diffusing into red cells [532], but this has not been a clinical problem [521]. Moreover, an increased Hb concentration has not led to faster fall-off in clearances during dialyser re-use [533].

Antibodies directed against epoetin

Antibodies directed against epoetin are rarely detectable and almost never of clinical significance, although they have been noted in a few patients, including one in whom pure red cell aplasia was attributed to the effects of the antibody [534–536].