

*The Guidelines*

## **Guideline 1: When to begin the work-up of a patient for the diagnosis of anaemia**

**A work-up for a diagnosis of anaemia (as outlined in Guideline 2) should be considered in patients with chronic renal failure (CRF) when:**

- **The haemoglobin (Hb) concentration is <11 g/dl (haematocrit <33%)\* in pre-menopausal females and pre-pubertal patients**
- **The Hb concentration is <12 g/dl (haematocrit <37%) in adult males and post-menopausal females**

*(Evidence level B)*

### **Commentary on Guideline 1: When to begin the work-up of a patient for the diagnosis of anaemia**

The definition of anaemia presents difficulties both at a mechanistic and at an operational level. These difficulties include the statistical significance of a single measurement of the venous Hb concentration, the original starting Hb concentration, the rate and amount of the decrease in Hb, and, finally, both the evident and the hidden effects of the anaemia at a metabolic and a clinical level. For the moment, a simple definition of anaemia using an arbitrary cut-off point, adjusted for sex and age, must be used. Eleven g/dl represents approximately 80% of the mean normal

Hb concentration for healthy females and 71% of the mean normal Hb concentration for healthy adult males and post-menopausal females (the lower end of the normal Hb range is >83% of the mean) [57].

In uraemic patients, there is wide variation in the level of renal function at which an Hb concentration of 11 g/dl may be reached. However, in a typical patient, it will be approximately when the glomerular filtration rate (GFR) decreases to <30 ml/min [8,10, 58–60], directly measured or calculated from the plasma creatinine using the Cockcroft-Gault formula [61] or, if these measurements are not available, when the plasma creatinine increases to >200–250 µmol/l. Some diabetic patients will have anaemia earlier than this, with a GFR of up to 45 ml/min [62], perhaps because of renal hyperfiltration and poor red cell deformability. However, it is the presence of anaemia, not the degree of renal function, which should prompt evaluation.

\* Measured by an automated cell counter in an accredited laboratory (see Appendix II), and in a pre-dialysis blood sample if the patient is already on haemodialysis.

## **Guideline 2: Evaluation of anaemia in uraemic patients**

**A. Evaluation of anaemia in uraemic patients begins with a general clinical evaluation designed to assess both the possible causes (e.g. gastrointestinal blood loss or uterine losses of blood in pre-menopausal women, hypothyroidism, haemoglobinopathies and nutritional deficiencies) and the clinical impact of anaemia. This evaluation should include the quantity of dialysis received in those patients on dialysis, and the nutritional status.**

*(Evidence level C)*

**B. Basic laboratory evaluation of anaemia should consist of measurement of the following:**

- Hb concentration
- Red blood cell indices (mean corpuscular volume and mean corpuscular Hb)
- Absolute reticulocyte count on a standardized machine (see Appendix II)
- Iron stores by measurement of the serum ferritin concentration
- Iron supply for erythropoiesis by the measurement of percentage red cell hypochromia (see Appendix II) or, where this is not available, by the transferrin saturation (TSAT), *measured on more than one occasion* (see Appendix II)
- C-reactive protein (CRP)

*(Evidence level B)*

**This work-up should be completed before consideration is given to starting treatment with epoetin.**

**C. A fuller work-up should also include the following, as indicated:**

- Serum B<sub>12</sub> and red cell folate concentrations
- Differential white blood count
- Tests for haemolysis (haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test)
- Serum and/or urine (where available) protein electrophoresis/immunoblotting
- Serum aluminium
- Bone marrow examination in selected cases
- Assessment of occult gastrointestinal blood loss (see Guideline 6)

*(Evidence level B)*

**Elements of this work-up will be necessary if there is clinical suspicion of primary haematological disorder (haemolysis, marrow dysplasia), macrocytosis, aluminium poisoning or occult blood loss.**

**Commentary on Guideline 2: Evaluation of anaemia in uraemic patients**

Evaluation of anaemia includes both a clinical assessment [63], which is directed towards a search for blood loss, haemoglobinopathies, hypothyroidism and haemolysis, and assessment of iron stores and availability [64,65], since iron is crucial to red cell production and to the response to epoetin; sometimes iron overload may be associated with macrocytosis [66]. Tests

recommended for iron assessment are outlined in more detail in Appendix II. In addition, some of those factors discussed in the Commentary on Guideline 14 as causes of hyporesponsiveness to epoetin [see Commentary Guideline 14 for references] may also be causes of anaemia: aluminium intoxication, chronic inflammation and/or infection, malignancies, malnutrition, myelodysplastic syndromes, hyperparathyroidism, and some medicines.

## **Guideline 3: Diagnosis of the anaemia of chronic renal failure**

**Anaemia is most probably the result of erythropoietin deficiency if:**

- **No cause for anaemia other than CRF is detected by the work-up detailed in Guideline 2, and**
- **Impairment of renal function is present as indicated by a GFR of < 30 ml/min in non-diabetic patients and < 45 ml/min in diabetic patients**

**Measurement of the plasma erythropoietin concentration is not usually indicated.**

*(Evidence level B)*

### **Commentary on Guideline 3: Diagnosis of the anaemia of chronic renal failure**

The diagnosis of renal anaemia is usually a diagnosis of exclusion, when no other cause of anaemia is found in a patient with CRF. Deficiency of erythropoietin is the main cause of the progressive decline in Hb concentrations experienced by patients with CRF [59,60], but inhibitors of red cell production have also been described in uraemia [61], and the role of iron defi-

ciency must not be neglected [67]. Although erythropoietin concentrations can be measured, in practice this is rarely necessary for the diagnosis of the anaemia of CRF.

The higher cut-off point for diabetic patients takes account of the hyperfiltration that is evident in some of these patients, and the fact that, in practice, these patients tend to develop anaemia at higher GFRs than non-diabetic patients; the earlier development of anaemia may also be related to the poorer deformability of the diabetic red cell envelope.

## Guideline 4: Indications for starting treatment with epoetin

**A. Not all patients with CRF will require treatment with epoetin. Many patients in advanced CRF and a proportion of patients on dialysis (ca. 20% of those on haemodialysis and ca. 40% of those on peritoneal dialysis) can maintain an Hb concentration > 10 g/dl (haematocrit > 30%) provided they are well dialysed, well nourished and their iron stores are supplemented. Some of these patients will have polycystic kidney disease. Very few patients with CRF, however, can maintain an Hb concentration > 12 g/dl without epoetin treatment.**

*(Evidence level B)*

**B. Epoetin treatment should be considered when the Hb concentration is consistently less than 11 g/dl (haematocrit < 33%) on repeated testing, and when other possible causes of anaemia have been excluded as detailed in Guideline 2, although an individual decision is required for each patient according to the clinical impact of the anaemia. This applies equally to patients with CRF on dialysis and to those not yet receiving dialysis.**

*(Evidence level C)*

**C. It may not be necessary to start epoetin therapy during the first three months after beginning peritoneal dialysis, because an increase in the Hb concentration (average 1–2 g/dl) often occurs during this period.**

*(Evidence level C)*

### Commentary on Guideline 4: Indications for starting treatment with epoetin

The impact of anaemia on the patient will vary with individual tolerance of anaemia, usual or desired level of physical activity, and presence of cardiovascular or respiratory disease (see Commentary on Guideline 1). There is, however, widespread agreement that symptoms usually begin when the Hb concentration is less than approximately 11 g/dl (haematocrit 33%), even though careful testing may show evidence of psychological and physiological impairment at Hb concentrations greater than 11 g/dl (see also Commentaries on Guidelines 1 and 5).

Not all uraemic patients require epoetin before or during dialysis to maintain an Hb concentration > 10 g/dl [68], but most will require epoetin therapy

to achieve higher Hb concentrations. There is abundant evidence, including data from prospective randomized studies, that quality of life [35,45,69–76], cardiovascular morbidity, exercise capacity, endocrine, immune and sexual function [17,18,20,26,27,30,43,77–102], together with hospitalization rates [10,102–104], are all improved both in pre-dialysis [19,73,105] and in uraemic patients already on dialysis if the Hb concentration is increased from lower levels to > 10–11 g/dl (haematocrit > 30–33%).

There are also several sets of data, which span the Hb concentrations discussed here, not only showing retrospective [36,46,48,106,107] and prospective [103] correlations between the severity of anaemia and survival in dialysed patients, but also suggesting that an improvement follows epoetin treatment [103,108]. However, prospective data suggesting that this mortal-

ity gradient can be diminished by increasing the Hb concentration are, as yet, lacking.

Much of the mortality (especially early mortality within 90 days) of patients placed on dialysis is cardiovascular [109,110], and it is becoming clear that this is pre-determined by events occurring *before* entry to dialysis. It is also becoming clear that anaemia, along with hypertension, is a major factor in these events [21,84,106,111–115]. Thus, early correction of anaemia has the potential to prevent or reverse some of the cardiovascular morbidity or mortality through reversal

of left ventricular hypertrophy, a major determinant of outcome, and hence also the potential to save money to offset the costs of earlier treatment by reducing interventions and hospitalizations later in the course of the patient's illness [84].

Despite some animal data to the contrary [116], there is growing evidence (although not yet from randomized trials) that correction of anaemia with epoetin in humans has no effect on the rate of progression of the primary renal disease (at least in non-diabetic patients) [73,105,117–127].

## Target Guideline 5: Target haemoglobin concentration for the treatment of the anaemia of chronic renal failure

A. For patients with standard causes of CRF (measured in a pre-dialysis sample in those on haemodialysis), the target is that  $\geq 85\%$  of the patient population should have an Hb concentration  $> 11$  g/dl (haematocrit  $> 33\%$ ). If this minimum concentration is attained or exceeded, it is likely that the *mean or median* for the total patient population will be 12–12.5 g/dl (see Preface 1.3).

(Evidence level A—but see commentary)

B. At the moment, no clear evidence exists either as to what the optimum Hb concentration above these levels may be, or as to whether there is a concentration above which costs and potential risks exceed benefit. Hence, *no upper limit* has been suggested, pending further data. Exact target Hb concentrations  $> 11$  g/dl will need to be established for individual patients.

C. Variations in the target Hb concentration may be required in patients with co-morbidity:

(a) Hb concentrations within the normal range are not recommended for *patients with cardiovascular disease*. In these patients, 11–12 g/dl should be aimed for, unless severe symptoms (e.g. angina) dictate otherwise.

(Evidence level A)

(b) Patients with sickle cell disease (homozygotes) should, where possible, be maintained at a total (HbF + HbS) Hb concentration between 7 and 9 g/dl.

(Evidence level B)

(c) Data to support variations in the target Hb concentration for *patients with diabetes mellitus or chronic hypoxaemic pulmonary disease* are lacking as yet, but there is widespread concern that the general target Hb concentration for non-diabetic patients recommended above may not be optimum for these groups of patients; controlled data are needed. Until data become available, it seems prudent not to increase the Hb concentration to normal in patients with diabetes, but to maintain it within the range of 11–12 g/dl. Whether hypoxaemic patients should have the same general target Hb concentration as that recommended for non-diabetic patients is

**unknown; similar constraints arise in those living at high altitude (> 1500 m).**

*(Evidence level C)*

**D. The recommended target Hb concentrations are for epoetin-iron therapy, and are not to be used as an indication for blood transfusion therapy (except in patients with sickle cell disease).**

*(Evidence level C)*

### **Commentary on Guideline 5: Target haemoglobin concentration for the treatment of the anaemia of chronic renal failure**

The target Hb concentration perhaps represents the most controversial single issue in the application of epoetin today [128–130]. It can be argued that, like any other endocrine deficiency, erythropoietin deficiency in CRF should be replaced fully as a matter of course. If this attitude is accepted, then it is up to those who argue for target Hb concentrations less than those within the normal range to demonstrate that there is no detriment to the patient in having a lower Hb concentration, both in terms of overt symptoms and hidden morbidity.

However, because of the high cost of epoetin and fears that an increase in Hb concentration to within the normal range would precipitate acute cardiovascular events [45,71,128,131], in practice the almost universal attitude has been the opposite: those who argue for a normal Hb concentration have had to show that it improves patients' quality of life and diminishes morbidity compared with lower Hb concentrations. Thus, the studies done hitherto have not fully addressed the question of what can be achieved in terms of costs and benefits by fully normalizing the Hb concentration in patients with CRF.

It seems likely that the relationship between all the deleterious events outlined in the Commentaries on Guidelines 1 and 4, on the one hand, and the Hb concentration, on the other hand, is a continuous one; however, the exact contour of the relationship and the point of optimum cost-benefit are unknown. Increasing the Hb concentration from lower levels to only 9–10 g/dl does not lead to a detectable improvement in quality of life [132–136], in contrast to the effect of increasing it to 10–11 g/dl or greater [35,45,69–76]; it should be noted, however, that no difference in quality of life was seen between Hb concentrations of 9–10 g/dl and Hb concentrations of 10–11 g/dl in two studies [133,137,138]. Whether further increases in the Hb concentration to >11 g/dl (haematocrit >33%)—still less than the lower limit of normal for normal adults—result in further improvements in quality and/or quantity of life remains undetermined [71,128,129–131,139–157], although the majority of these new studies (mostly available as abstracts or

preliminary reports) show that, as compared to only partial correction of anaemia, cardiovascular and exercise performance, cognitive functioning and sleep dysfunction can all be improved by normalization of the Hb concentration.

Fears are present [45,72,128,131], however, that normalization of the Hb concentration might lead to access thrombosis and, more seriously, to an increase in the number of cardiovascular events, in the short or long term [158–160]. These concerns are based on the high plasma fibrinogen concentrations and poorly deformable erythrocytes of uraemia, with consequent increased blood viscosity, added to altered platelet and endothelial physiology. Risks might be greater in precisely those patients who need higher Hb concentrations the most, i.e. in those with pre-existing cardiovascular disease. There is also some evidence that oxygen delivery to the brain is optimal at Hb concentrations of only 10–11 g/dl [161,162] because of compensatory vasodilatation; however, these data have been challenged [163–165], and a normal Hb concentration suggested as optimal. Other data are emerging which suggest that during epoetin treatment blood rheology improves [157,166], together with changes in the red cell envelope and metabolism of the younger circulating red cell population; all of these changes are associated with increased circulating red cell survival.

To date, no clear evidence of deleterious effects of normalising the Hb concentration in the majority of uraemic patients has emerged. However, in a recent large prospective randomized study in 1233 patients with clinical evidence of congestive heart failure or ischaemic heart disease [153], access thrombosis was more common in both PTFE grafts (48% thrombosis) and native vessel fistulae (26% thrombosis) in the patients whose target haematocrit was 42% (Hb concentration 13 g/dl), compared to those with a target haematocrit of 30% (Hb concentration 10 g/dl) (37% and 11% thrombosis, respectively) [D. Goodkin, personal communication]. However, these findings did not relate statistically either to the haematocrit or to epoetin dosage; in addition, these rates of thrombosis are high by European standards, even allowing for the age of the patients and the presence of vasculopathy (see also Guideline 18). It may be that the poor cardiac output of many of the patients included in this study was in part responsible for the results.

In a Swedish study of normalization of Hb, patients

whose Hb concentration was increased to 13.2 g/dl (haemodialysis patients) or 14.5 g/dl (pre-dialysis patients) showed a 5 mm increase in diastolic (but no change in systolic) blood pressure [167]. Of interest is that there was no improvement in exercise tolerance in these subjects compared with their previous Hb concentrations of 11.1 and 11.4 g/dl, respectively.

Data on the rates of new cardiovascular and cerebrovascular events in patients with and without previous cardiovascular disease who have been maintained at higher Hb concentrations are still insufficient to judge, but so far there is no suggestion that rates are increased in average pre-dialysis and dialysis patients. The study of 1233 patients with clinical evidence of congestive heart failure or ischaemic heart disease referred to in the previous paragraph [153] was terminated early because of more deaths in the 'normal-haematocrit' group (183 vs 150, risk ratio 1.3; 95% CI, 0.9–1.9). However, there were no statistically significant differences between the 'normal-haematocrit' and the 'low-haematocrit' groups either in the number of cardiovascular deaths (125 in the 'normal-haematocrit' group vs 112 in the 'low-haematocrit' group), or in the incidence of angina, coronary interventions, congestive heart failure or myocardial infarction over a period of 30 months (mean 14) until the premature termination of the trial. One population-based report [168] suggesting an increased incidence of cardiovascular death following the introduction of epoetin has been criticized on a number of grounds [169,170] and a further prospective population study [103] showed a lowered total mortality with increasing haematocrit together with a lower cardiovascular mortality with epoetin use.

Normalization of the Hb concentration usually requires not only an increase in the amount of epoetin required, which has varied from 30% [152] to 300% [153] in recent studies, but also increased dosage of iron. As a secondary consideration, the fiscal costs of these extra amounts of epoetin need detailed analysis, since costs of the extra epoetin required may be offset by decreased hospitalization rates. Possible dangers of infection in patients receiving greater amounts of iron are considered in more detail in Appendix III.

It is very difficult, therefore, to set a target Hb concentration with any confidence, except to state with some certainty that it should be  $\geq 10$  g/dl (haematocrit  $\geq 30\%$ ). What the cost-benefit of increasing the mean Hb concentration from 10 to 11 to 12 g/dl may be has not been tested adequately in completed, prospective, randomized controlled trials. Despite this relative absence of data, for the moment in this first version of the European guidelines, we have set a minimum target Hb concentration which is somewhat greater than that recommended previously, but we have made no statement about an upper limit. We also suggest that higher Hb concentrations may be inappropriate in some patients with vascular disease. These important points will be kept under review until the studies cited here are published in full, and more data accumulate.

Data on the optimum Hb concentration for *diabetic patients* that take into account their vasculopathy, retinopathy and abnormal blood rheology are lacking [171,172]. In general, however, it seems best to be cautious in increasing the Hb concentration to normal in these patients, and any increment in Hb should be slow. A recent paper [172] reported an association between epoetin use and increased peripheral vascular disease in patients with diabetes receiving peritoneal dialysis; more data are needed urgently in this important area, since diabetic patients comprise at least one quarter of European dialysis populations in most countries.

Data from *homozygous sickle cell patients* without uraemia suggest strongly that increasing their Hb concentration towards normal is deleterious, because of an increased incidence of sickle crises as the majority of the new Hb is HbS [173]. Hence, a much lower target Hb concentration is recommended for sickle cell homozygote patients with CRF, which corresponds to that normally experienced pre-CRF. Use of epoetin to achieve these concentrations will help maximize HbF concentrations without major increases in the concentration of HbS, in conjunction with treatments such as hydroxyurea [173]. However, very large doses of epoetin, which it will often be impossible to use because of cost, may be required to achieve these concentrations.

### Technical note

In the case of pre-dialysis patients and patients on peritoneal dialysis, the timing of the sample for measurement of Hb concentration is not critical. In haemodialysis patients, however, the immediate pre-dialysis venous sample underestimates the 'true' Hb concentration as a measure of total red cell mass, a discrepancy which increases the longer the interval since the last dialysis; and the immediate post-dialysis sample gives an overestimate due to haemoconcentration. Differences of as much as 1–2 g/dl may be seen across dialysis [174,175], depending upon fluid removal during dialysis and the timing of the post-dialysis sample. It is usual to employ the pre-dialysis sample (which we recommend), but its deficiencies and variability [176] should be recognized, and several estimates will normally be needed before making treatment decisions.

In the case of patients who attain Hb concentrations within the normal range who are receiving haemodialysis, it will be prudent to check the Hb concentration in an immediate post-dialysis sample as well as in the pre-dialysis sample.

These factors will be even more important in patients receiving convective treatments employing post-dilution, and pre-dilution (or combined pre- and post-) dilution techniques may be preferable in patients with normal Hb concentrations.

## **Target Guideline 6: Assessing and optimizing iron stores**

### **Target:**

**A. Patients with CRF should be in iron balance and have sufficient iron to achieve and maintain an Hb concentration of at least 11 g/dl (haematocrit of at least 33%) set as a target in Guideline 5.**

**B. To achieve and maintain this target Hb concentration, sufficient iron should be administered to attain the following in all patients:**

- serum ferritin  $\geq 100$   $\mu\text{g/l}$
- hypochromic red cells  $< 10\%$  (or TSAT  $> 20\%$ )

**In practice, to achieve these minimum criteria will mean aiming for optimal levels of:**

- serum ferritin 200–500  $\mu\text{g/l}$
- hypochromic red cells  $< 2.5\%$  (or TSAT of 30–40%)

*(Evidence level B)*

### **Treatment strategies to achieve the target:**

**C. Many patients not yet on dialysis and some CAPD patients, usually not receiving epoetin, can be maintained on oral iron because blood loss and the degree of anaemia are less severe than in patients on haemodialysis. Moreover, intravenous therapy is inconvenient in most of these patients unless family practitioners with the appropriate back-up and facilities are available to deal with this situation.**

**D. In contrast, very few—if any—patients on haemodialysis can be maintained in iron balance using oral iron.**

*(Evidence level B)*

**E. In patients in whom:**

- hypochromic red cells are  $< 10\%$  (or TSAT is  $> 20\%$ ) and serum ferritin  $> 100$   $\mu\text{g/l}$ , yet the Hb concentration is  $< 10$  g/dl, as well as in
- patients requiring comparatively large doses of epoetin to maintain an Hb concentration of 11–12 g/dl (haematocrit 33–37%)

**the following should be looked for:**

1. occult intestinal blood loss
  2. increased CRP
- If both parameters are negative or within the normal range, the dose of epoetin should be increased by 50%.

- **If hypochromic red cells are > 10%, 1000 mg of intravenous iron should be given over a period of 6–10 weeks. If determination of hypochromic red cells is not feasible, the patient's response to 1000 mg intravenous iron over a period of 6–10 weeks should be observed.**

*(Evidence level B)*

**F. CRF patients are unlikely to respond to iron with a further increase in Hb concentration and/or a further reduction in the epoetin dose required to maintain a given Hb concentration if the percentage of hypochromic red cells decreases to < 2.5% (or TSAT increases to  $\geq$  50%) and/or serum ferritin increases to > 800  $\mu$ g/l.**

*(Evidence level B)*

### **Commentary on Guideline 6: Assessing and optimizing iron stores**

Iron stores (normally 800–1200 mg [177–179]) in health are almost entirely recycled through biologically active compounds such as haemoglobin, with only about 1 mg of iron being lost each day. Since the iron in a normal Western diet approximates to 15 mg/24 h, iron deficiency is rare in the absence of blood loss. However, iron stores are frequently diminished in patients on dialysis, as a result of increased blood loss and poor iron absorption. In addition, annual blood loss from dialysis and samples for tests varies, but has been calculated to be approximately 2500 ml in patients on haemodialysis [180,181]. This represents a loss of at least 1000 mg of iron each year in addition to the usual gastrointestinal losses of 1 mg/day, which may be increased in uraemia; in some patients, losses as high as 6–7 l/year (3000 mg iron) have been recorded [179].

With modern dialysers, this loss is mainly from sampling, since contemporary devices show only 2–5 ml blood loss per dialysis (300–750 ml annually) [182]. In contrast, annual blood loss is only about 250 ml (100 mg iron) in patients with chronic renal insufficiency or on peritoneal dialysis who have no dialysis-associated losses and generally have fewer blood samples taken. Women whose menstrual cycle returns have additional uterine losses, often worsened by the haemostatic defect of uraemia and anticoagulation for dialysis, which have not been adequately studied. In normal children, gastrointestinal losses are greater, and increase still further in those on dialysis; dialysis-related losses are also proportionately greater [183].

Demand for available iron is increased further by the use of epoetin [184]: during the first three months of treatment with epoetin, approximately 1000 mg of supplemental iron will be needed, of which 400 mg replaces blood loss. There is evidence that the demand for iron is higher, the higher the target Hb concentration. The need for iron to achieve the full effect of

epoetin amounts to synergy between the two forms of treatment.

Unfortunately, no single test, or combination of tests, allows discrimination of either iron deficiency or iron overload with complete confidence. The best available tests are the serum ferritin concentration as an index of iron stores [185] and the percentage of hypochromic red cells in the circulation [186–189] as an index of the availability of these stores.

Iron deficiency [177,190,191] may be considered *absolute* when stores are depleted, as indicated by a serum ferritin concentration < 20  $\mu$ g/l [185]; and *functional* when serum ferritin concentrations are normal, but insufficient iron can be made available to meet the needs of increased erythropoiesis and the Hb concentration fails to increase as expected with usual doses of epoetin [191–193].

Throughout these guidelines, the preferred assessment of iron availability is the *percentage of hypochromic red cells* in the circulation [186,187], measured on a suitable analyser, which is normally < 2.5%, rising to > 10% in iron deficiency. The percentage transferrin saturation with iron (TSAT) [190], measured on several occasions, may be used as a substitute if measurement of hypochromic red cells is not available; < 20% saturation usually indicates iron deficiency, although many exceptions are encountered, in part because of variation in TSAT from day to day [194–204]. The reasons for these choices are given in Appendix II, together with a discussion of problems of interpretation which may arise; several recent reviews of the subject are available [205–207].

During inflammation, both ferritin and percentage hypochromic red cells (or TSAT) may be normal, but iron is not available. Some measure of acute phase reaction, such as the C-reactive protein, will aid this diagnosis (see Guideline 14).

The value of testing for occult blood in the faeces in detection of gastrointestinal bleeding from discrete lesions in uraemic patients has never been systematically evaluated, but a high proportion of uraemic patients on haemodialysis will show positive results that are not the result of bleeding from discrete lesions, and liberal use of gastroscopy will be needed.

## **Guideline 7: Frequency of monitoring iron stores and availability during treatment and follow-up**

**A.** As for initial assessment of anaemia (see Guideline 2), iron stores should be assessed regularly by measurement of serum ferritin, and iron supply by hypochromic red cells (see Guideline 6 and Appendix II). If the latter test is not available, then measurement of the TSAT on more than one occasion can be used as a substitute.

*(Evidence level B)*

**B.** In CRF patients with a stable Hb concentration not treated with epoetin, whose percentage of hypochromic red cells is <10% (TSAT  $\geq$  20%) and serum ferritin is  $\geq$  100  $\mu$ g/l, iron stores should be determined every 3–6 months. A sustained reduction in the Hb concentration and a decrease in the mean corpuscular volume are indications for investigation.

*(Evidence level C)*

**C.** During initiation of epoetin therapy and while increasing the epoetin dose in order to achieve an increase in the Hb concentration, the percentage of hypochromic red cells (or TSAT) and the serum ferritin should be checked every 4–6 weeks in patients not receiving intravenous iron, and at least once every 3 months in patients receiving intravenous iron, until the target Hb concentration is reached.

*(Evidence level C)*

**D.** Following attainment of the target Hb concentration, percentage hypochromic red cells (or TSAT) and serum ferritin should be determined at least once every 3–6 months.

*(Evidence level C)*

**E.** Intravenous iron therapy must be discontinued for at least one week (if the individual dose is > 100 mg) prior to performing these measurements.

*(Evidence level B)*

**F.** TSAT should not persistently exceed 50% or serum ferritin 800  $\mu$ g/l if iron toxicity is to be avoided (see Appendix III).

### **Commentary on Guideline 7: Frequency of monitoring iron stores and availability during treatment and follow-up**

No hard data are available and the suggestions are those thought reasonable by the Working Party. A Dutch survey of local practice is available for comparison [208].

## **Guideline 8: Administration of supplemental iron**

**A. Supplemental iron should be administered to prevent iron deficiency and to maintain adequate iron stores, so that CRF patients can achieve and maintain an Hb concentration > 11 g/dl with or without epoetin therapy.**

*(Evidence level A)*

**B. Most patients on haemodialysis will require at least one dose of intravenous iron every two weeks to achieve and maintain an Hb concentration > 11 g/dl (haematocrit > 33%). The intravenous iron should be given by slow infusion during the last 2 h of dialysis.**

*(Evidence level A)*

**(A variety of iron formulations and dosing schedules can be used for administration of intravenous iron; for details, see Appendix III.)**

**C. Most patients in whom the serum ferritin concentration is > 800 µg/l, and the percentage of hypochromic red cells is < 10% (or TSAT is > 20%) will achieve or exceed an Hb concentration of 11 g/dl (haematocrit 33%). A few patients with spuriously elevated serum ferritin concentrations (e.g. from inflammation or liver disease) will require low doses of iron and frequent monitoring.**

**D. In patients in whom the serum ferritin is ≥ 800 µg/l (or TSAT is ≥ 50%), intravenous iron should be withheld for up to three months, as long as there are no signs of functional iron deficiency (percentage of hypochromic red cells is < 10%), at which time the iron parameters should be re-measured before intravenous iron is resumed.**

**E. When the serum ferritin has declined to ≤ 800 µg/l (or TSAT to < 50%) and the percentage of hypochromic red cells has increased to > 10%, intravenous iron can be resumed at a dose reduced by one-third to one-half.**

*(Evidence level C)*

**F. It is anticipated that once optimal Hb concentrations and iron stores are achieved, the required maintenance dose of intravenous iron in haemodialysis patients may vary from 25 to 100 mg/week. The goal in haemodialysis patients is to provide a weekly dose of intravenous iron that will allow the patients to maintain the target Hb concentration at a safe and stable iron level, regularly monitoring iron status (see Guideline 7).**

*(Evidence level C)*

**G. Oral iron is superfluous for CRF patients receiving maintenance doses of intravenous iron, since iron absorption is negligible once the serum ferritin is increased to, or greater than, normal.**

*(Evidence level B)*

**H. Uraemic patients with progressive renal insufficiency not yet receiving dialysis, and those on CAPD, can be given oral iron in the form of ferrous salts at a daily dose of 100–200 mg of elemental iron for adults (usually 200 mg elemental iron in three divided doses or a single dose at night), and 2–3 mg/kg for paediatric patients in 2–3 divided doses, without concomitant food or other medicines.**

*(Evidence level B)*

**I. Some uraemic patients with progressive renal insufficiency, and others on CAPD, particularly if they are receiving epoetin, will not be able to maintain adequate iron stores with oral iron. Therefore, iron must be administered intravenously and repeated as needed. Intravenous iron should be administered slowly (30 min–2 h), using veins that will not be used for haemodialysis vascular access (see Appendix III).**

*(Evidence level A)*

### **Commentary on Guideline 8: Administration of supplemental iron**

The object of iron supplementation is to maintain iron stores adequate to sustain a higher Hb concentration, while avoiding iron overload and its deleterious consequences discussed in Appendix III. The data for iron use in haemodialysis patients are given in more detail in the NKF-DOQI<sup>®</sup> guidelines, and a consensus has emerged, upon which their recommendations and those in Guideline 8 are based.

In *haemodialysis patients* (as in normal subjects), oral iron is poorly absorbed [209–223], and it has been shown in a number of studies, including randomized controlled trials, to be incapable of maintaining iron balance in the long term [191,192,194,197,199,209,211,224–227]. In addition, oral iron is often poorly tolerated, with consequent poor compliance. Thus, in almost every haemodialysis patient, parenteral iron will be needed. Extra costs of the intravenous iron preparation are likely to be offset by reduced epoetin requirements [228].

Detailed guidance on the administration of intravenous iron is given in Appendix III, in which data in favour and against various regimens of administration as well as side effects and risks of iron overload are discussed. At the moment, which iron preparation is used depends upon local availability and, so far, no regimen has emerged clearly as the best in terms of

costs and benefits, although a trend towards more frequent administration of lower dosages has been noted [216,229–269].

Comparable detailed data are lacking for iron administration to patients with *progressive renal insufficiency* and on *peritoneal dialysis*, although the tendency in recent years has been to use intravenous iron more frequently and earlier in these patients; there is also some evidence that the use of epoetin can be avoided altogether in a proportion of such patients [194]. However, our recommendation remains that oral iron should be tried in the first instance; despite the demonstrated poor absorption [209–212,217–222] (not only in pre-dialysis patients and those on CAPD, but also in those patients receiving haemodialysis), more than half of pre-dialysis and CAPD patients are able to maintain iron balance, perhaps because of the lower blood/iron losses in these patients groups as compared with haemodialysis patients.

There are no clear data as to which preparation of oral iron should be used, and although ferrous sulphate or gluconate frequently give rise to side effects, neither ferrous fumarate nor iron polymers have been demonstrated to be superior insofar as side effects are concerned and both are equally poorly absorbed [209,217]. To minimize side effects, the dose can be administered either in divided doses or on an empty stomach at bed-time. Food [270] and some medicines (for example, calcium salts given to avoid osteodystrophy [271]) markedly depress iron absorption.

## Appendix I: Designation of strength of available evidence to support guidelines

The method employed to assess the quality of evidence in this document is that developed by the US Agency for Health Policy and Research [7]. This method assesses the quality of evidence as follows:

- Ia evidence obtained from meta-analysis of several randomized controlled trials;
- Ib evidence obtained from at least one randomized controlled trial;
- IIa evidence obtained from at least one well-designed controlled study without randomization;
- IIb evidence obtained from at least one other type of well-designed quasi-experimental study;
- III evidence obtained from well-designed, non-experimental descriptive studies such as comparative studies, correlation studies and case studies;
- IV evidence obtained from expert reports or opinions and/or clinical experiences of respected authorities.

Three grades of support (A, B and C) are then derived from this classification:

A=evidence obtained from meta-analysis of several randomized controlled trials (quality of evidence Ia) or from at least one randomized controlled study (quality of evidence Ib);

B=evidence obtained from well-conducted clinical studies, but no randomized clinical trials (evidence levels IIa, IIb, III). Evidence may be extensive but is essentially descriptive;

C=evidence obtained from expert committee reports or opinions, and/or clinical experience of respected authorities (evidence level IV). This grading indicates

either an absence of directly applicable studies of good quality and the need for further studies, or general advice on good practice which is not evidence-based by its nature.

This method of grading is not without its problems. In particular, it elevates *any* randomized study above all other data, even though a number of controlled trials show bias in patient selection, and/or employ inadequate numbers of subjects to answer the question tested, especially if the absence of an effect is found (inadequate power). As ethical constraints are now present in performing fully controlled studies. e.g. in which one group of patients have a successful treatment such as epoetin withheld, our ability to gather first rate information in some areas is limited.

The particular problems with Grade C recommendations have been indicated in the Preface: this category includes several disparate entities: first, areas where there is an absence of data, and only opinion can guide. Here there are many levels of 'opinion', from individual prejudice, on the one hand, to the carefully and communally considered advice of groups of experts in a field in the light of their clinical experience and knowledge of the area, on the other. Second, some guidelines will relate to aspects of clinical practice which by their nature are unsuitable for investigation by randomized controlled trials—for example, many ethical questions.

Nevertheless, this grading system represents a widely used scale of assessment, although a need clearly remains for improved tools for grading of evidence.

## Appendix II: Haematology methodology

AII.1 Hb concentration is a primary parameter which can be directly measured, for which there is an international standard, and which is not influenced by differences in technology. In contrast, the haematocrit is not directly derived by automated cell counters, has no recognized international standard and may differ with different technologies. Hb concentration should, therefore, be used in preference to the haematocrit, as is the case in most European laboratories and in these guidelines. In the guidelines approximate haematocrit equivalents have been indicated in parentheses where appropriate.

In this document, Hb concentrations are expressed in g/dl because most clinicians are familiar with this method of presentation; to convert g/dl to g/l, multiply by 10. It should be noted, however, that other units, such as mmol/l, are used in some countries in the European Union, e.g. Denmark and The Netherlands; to convert g/dl to mmol/l, multiply by 0.62.

AII.2 All blood counts should be carried out on properly standardized, controlled and maintained automated counters in an accredited laboratory. In the United Kingdom and some other European countries accreditation is granted by an independent body, CPA (Clinical Pathology Accreditation Ltd).

AII.3 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 greater than 50%, and results obtained in this way must not be compared to automated counts.

AII.4 The percentage of hypochromic red cells in the circulation [186–189,537,538,539] is a direct reflection of the proportion of cells with suboptimal Hb content. This may be expressed either in terms of the Hb concentration (cells with an Hb concentration of <28 g/dl) or by content (cells with an individual Hb content of <26 pg). This measurement does not reflect the level of iron stores. A percentage of hypochromic cells of <2.5% is normal, 2.5–10% represents an

indeterminate area, and >10% indicates definite functional iron deficiency. However, the analyser methodology for this measurement is presently available in fewer than half of renal units throughout Europe (Bayer H-1, H-2, H-3 or Advia 120).

AII.4.1 Where analysis of hypochromic red cells is not available, then the transferrin saturation (TSAT) [190,194] can be used. This measurement has disadvantages as well as advantages [195–204,540,541]. There is day to day variation, the concentration of transferrin varies with nutrition in parallel with the serum albumin [542], and is further influenced by cytokine production during acute and chronic inflammatory reactions, including those due to bio-incompatible dialyser membranes and intraperitoneal inflammation. TSAT is calculated from serum iron  $\times 100$ , divided by TIBC; or serum iron ( $\mu\text{g/dl}$ )  $\times 70.9$  divided by transferrin concentration (mg/dl).

AII.4.2 Other methods of assessment of iron availability, such as the Hb content of reticulocytes [543–546], zinc protoporphyrin concentrations [547–549] and circulating transferrin receptors [550–554] are under evaluation, but none has been as carefully studied as hypochromic red cells in the circulation. While reticulocyte Hb concentrations appear to have possible application, plasma concentrations of soluble transferrin receptor have not proved reliable so far.

AII.5 In patients who are not receiving either iron therapy or blood transfusion, the serum ferritin concentration is a valid but indirect reflection of the level of iron stores [185,205–207,555]. During epoetin therapy, this relationship may be altered but serum ferritin may still be used to monitor iron stores. Immediately after intravenous iron therapy, serum ferritin levels may be unreliable as a reflection of iron stores for up to 2 weeks, especially if larger intermittent doses are used. Finally, serum ferritin may be increased during inflammation or liver disease, without being the result of any change in iron status.

## Appendix III: Use of intravenous iron in patients receiving epoetin

There is increasing evidence that regular intravenous iron supplementation can enhance the haemopoietic response to epoetin and hence reduce epoetin dosage requirements [194,197–200,202–204,230,231,266] (*Evidence level A*). As discussed in Guidelines 6 and 7, in almost all patients on haemodialysis, iron supplementation represents the only way to keep up with losses of iron associated with the dialysis procedure and to maintain iron balance. In addition, some patients with progressive renal insufficiency who are not yet on dialysis, or who are on peritoneal dialysis, will require intravenous iron instead of oral iron to maintain iron balance, or will benefit from this approach [194].

The optimum regimen for intravenous iron is not clear, however, and various protocols are used throughout Europe. At the moment, there is no evidence that any one regimen is better than any other, and the regimen used should be designed to suit the requirements of the individual unit and/or patient.

Two major factors, however, determine which iron preparation can be given.

### (i) Availability of intravenous iron preparations in different countries

Availability of intravenous iron preparations is not uniform throughout the European Union, or the rest of Europe. Depending on the country, one or more of the following intravenous iron preparations are currently available: iron dextran, iron sucrose (also known as hydroxysaccharate and iron(III)-hydroxide sucrose complex), iron sodium gluconate.

### (ii) Maximum recommended dosages

According to the manufacturers' recommendations, the *maximum* doses of the various intravenous iron preparations are as follows:

- iron dextran: 1000 mg
- iron sucrose: 500 mg
- iron sodium gluconate: 62.5 mg

## Reactions to intravenous iron

All iron therapies may be followed by a vasoactive reaction, especially with larger doses administered rapidly [236,242,269]. This is not allergic in origin, but relates to the administration of free iron itself, and there are no reported fatalities with this type of reac-

tion. Another form of reaction reported with iron sodium gluconate is severe upper loin and abdominal pain [241].

Iron dextran may also show a low but significant incidence of anaphylactic reactions due to pre-formed anti-dextran antibodies (4/573, 0.7% [246]), which are occasionally severe enough to be fatal [243,246]. Thus, if iron dextran is used, a test dose is required. For all other iron preparations, a test dose is unnecessary.

## Iron toxicity [539,556]

In the pre-epoetin era, dialysis patients were frequently overloaded following polytransfusion; in one British unit in 1979 [210], more than 50% of patients had serum ferritin concentrations >1000 µg/l. In such patients [557,558], as well as in non-uraemic individuals [406,559], tissue deposition of iron was observed together with cell damage, associated with plasma ferritin concentrations >1000–2000 µg/l. Few data are available to allow estimation of a safe upper limit of serum ferritin in patients receiving only intravenous iron treatment, without transfusions, as so few comparisons have been made between histological iron stores and ferritin concentrations in this type of patient [247,560,561]. Most authors favour a figure between 600 and 1000 µg/l; provisionally, we recommend 800 µg/l as a safe upper limit, remembering that falsely elevated ferritin concentrations may be seen in inflammatory states. Most of the excess iron is in reticuloendothelial cells [233] and thus is unavailable to cause parenchymal cell damage. Possession of haemochromatosis-linked MHC alleles has been proposed [562] and denied [563] as facilitating tissue deposition.

Concern exists about the ability of excess iron to increase quantities of hydroxyl radicals and thus increase oxidative damage in patients with atheromatous or inflammatory disease, diabetes mellitus or chronic hepatitis. At the moment, these concerns remain theoretical; however, the apparent potentiating effect of a relationship between excess iron and the incidence and severity of a variety of infections [563–571], at least in part due to inhibition of phagocytosis [264,565,567,569,572], is a problem of immediate concern. Many of these studies, however, relate to severe transfusion-induced iron overload. A recent 1000-patient multicentre study [573] failed to show a relationship between infection rates and ferritin concentrations or administration of epoetin; in contrast,

significantly greater mean corpuscular Hb concentrations were noted in those patients without bacteraemic episodes—the only laboratory parameter showing a positive correlation. One recent study [263] suggests a greater incidence of infections when more frequent low-dose iron injections were used, but this needs confirmation. In view of these uncertainties, we recommend that, as a precaution, intravenous iron should be discontinued in patients with bacteraemia.

The relationship between iron overload and infections is complex and uncertain, and it is by no means established that the iron itself is the culprit, since anaemia itself [570], transfusions [574] and secondary splenic dysfunction all increase infection risk. However, it has been shown that removal of iron with desferrioxamine or epoetin treatment leads to improvement in phagocytic function [512,575]—even though plasma ferritin concentrations still remained greater than 1000 µg/l.

Finally, a relationship between iron status and an excess incidence of neoplasia has been described [539], although it seems unlikely that this is of significance at the levels of overload induced by therapeutic use of iron.

### Modality of renal replacement therapy and dosage schedule

Intravenous iron can be given either as a single bolus at longer intervals or (in patients on haemodialysis) in the form of a small dose at every dialysis session. The latter schedule may result in a better response and lower costs, but may also be associated with an increased incidence of infection [263], and no consensus has yet emerged.

It is convenient to give regular boluses of intravenous iron into the dialysis lines during each dialysis session in haemodialysis patients; this is clearly impractical for most CAPD and pre-dialysis patients, who have neither ready vascular access nor the wish to be burdened with regular hospital visits.

### Suggested regimens

#### A. Haemodialysis patients

- i. 20–40 mg of iron sucrose or iron sodium gluconate every dialysis session
- ii. 100–200 mg of iron sucrose, iron dextran, once every week
- iii. 1000 mg of iron dextran as a slow infusion during dialysis.

#### B. CAPD and pre-dialysis patients

- i. 200–500 mg of iron sucrose as an intravenous infusion in a 100–500 ml saline solution over 1–4 hours
  - ii. 200–1000 mg of iron dextran as an intravenous infusion in a 250 ml saline solution over 1–2 hours
- Iron sodium gluconate is impractical in CAPD and pre-dialysis patients because of dosage restrictions.

### Monitoring the response to intravenous iron

Epoetin therapy will typically increase erythropoietic activity up to twice its normal or baseline level, leading to a requirement for iron during this correction phase of up to 50 mg/24 h. Nomograms to calculate the iron deficit are available but have limited value, and although monitoring the change in Hb concentration is the best assessment, changes occur slowly; the reticulocyte count will immediately indicate changes in effective erythropoietic activity. Changes in the proportion of hypochromic red cells, more particularly hypochromic reticulocytes, will reflect immediate changes in iron supply to erythrocytes.

A steady increase in serum ferritin concentration will indicate that a significant proportion of the intravenous iron has been sequestered in the reticuloendothelial iron stores. Serum ferritin concentrations of 100–200 µg/l or greater are probably adequate to support normal erythropoiesis (**Evidence level B**); in general, intravenous iron should not be given to patients whose serum ferritin is >1000 µg/l (**Evidence level C**). Repeat ‘top-up’ infusions every few months will be required in a large proportion of patients receiving epoetin (**Evidence level B**).