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Nephrology
Dialysis
Transplantation

Appendix I: European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

Note: Appendices and Preface referred to in the text, below, may be found in 'European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure.' *Nephrol Dial Transplant* 1999; 14 [Supplement 5]. An explanation of 'evidence levels' as referred to in the Guidelines is given at the end of this Appendix.

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*)
*Measured by an automated cell counter in an accredited laboratory (see Appendix II in *Nephrol Dial Transplant* 1999; 14, Supplement 5), 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; *Nephrol Dial Transplant* 1999; 14, Supplement 5);
- iron *stores* by measurement of the serum ferritin concentration;
- iron *supply* for erythropoiesis by the measurement of percentage red cell hypochromia (see Appendix II in *Nephrol Dial Transplant* 1999; 14, Supplement 5) or, where this is not available, by the transferrin saturation (TSAT), *measured on more than one occasion* (see Appendix II in *Nephrol Dial Transplant* 1999; 14, Supplement 5);
- 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_{12} 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.

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 glomerular filtration rate (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*)

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 ($\sim$20% of those on haemodialysis and $\sim$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 3 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*)

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 $\geqslant$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 in *Nephrol Dial Transplant* 1999; 14, Supplement 5).
(*Evidence level B*)
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*)

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 $\geqslant$100 μg/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 μg/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 main-

tained 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 μg/l, yet the Hb concentration is <11 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 of 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 $\geqslant 50\%$) and/or serum ferritin increases to >800 μg/l.

(*Evidence level B*)

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 8 and Appendix II in *Nephrol Dial Transplant* 1999; 14, Supplement 5). 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 $\geqslant 20\%$) and serum ferritin is $\geqslant 100$ μg/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, the percentage of 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 1 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 μg/l if iron toxicity is to be avoided (see Appendix III in *Nephrol Dial Transplant* 1999; 14, Supplement 5)

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 2 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 in *Nephrol Dial Transplant* 1999; 14, Supplement 5).

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 $\geqslant 800$ μg/l (or TSAT is $\geqslant 50\%$), intravenous iron should be withheld for up to 3 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 $\leqslant 800$ 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 (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 is 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 in *Nephrol Dial Transplant* 1999; 14, Supplement 5).
(*Evidence level A*)

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 dose requirements may be higher than those associated with intravenous and subcutaneous administration.
(*Evidence level B*)

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) three 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: 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*)

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*)

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*)

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 and 9–12).
(*Evidence level C*)
C. Patients with a slowly failing transplant (e.g. from chronic rejection) should be treated exactly as other patients in 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*)

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 ($\sim$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. α- and β-thalassaemias, sickle cell anaemia);
- folate or vitamin B_{12} deficiency;
- multiple myeloma, myelofibrosis;
- other malignancy;
- malnutrition;
- haemolysis;
- drug intake (e.g. high dose ACE inhibitor or AT_1 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.

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*)

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*)

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 disalysis, 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*)

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.

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 (US Department of Health and Social Service and Agency for Health Care Policy and Research. *Acute Pain Management: Operative or Medical Procedures and Trauma*. AHCPR publication 92–0038, Rockville, MD: 1992). 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 and 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 is some areas is limited.

The particular problems with Grade C recommendations have been indicated in the Preface of *Nephrol Dial Transplant* 1999; 14, Supplement 5: 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.