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Nephrology
Dialysis
Transplantation

SECTION IV. Failure to respond to treatment

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

Recommendation

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

Rationale and commentary

Resistance to ESA therapy is usually relative rather than absolute, so the term 'hyporesponsiveness' is often used to describe the need for a greater than usual dose of ESA to produce an otherwise expected increase in Hb concentration. The definition of resistance to ESAs is a continued need for >20 000 IU/week (300 IU/kg/week) or 1.5 μg/kg of darbepoetin alfa (~100 μg/week) [1]. This is >2.5 times the average ESA dose [1–4], so most (>90%) iron-replete patients given ESA would be expected to respond to a lower dose. However, the true incidence of resistance to ESAs, as defined above, is not known, since in surveys on the use of different doses, a considerable percentage of patients were below the target Hb level of 11 g/dl [5].

Recommendation

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

Compliance should also be checked in patients self-administering an ESA.
(***Evidence level C***)

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

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

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

Rationale and commentary

The most common causes of resistance to ESAs are iron deficiency, either absolute or functional, and inflammation [6–8]. However, there are numerous possible causes, and their frequency differs in various settings, making it impracticable to construct a treatment algorithm. The following points should be considered when investigating target failure.

Blood loss should always be suspected in patients who need a higher dose of ESA to maintain a stable Hb concentration, in patients whose Hb concentration is declining, and in patients who fail to increase iron stores, even after i.v. iron administration.

Pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor-α can negatively influence the maturation of red cell precursors [9,10], leading to anaemia and hyporesponsiveness to ESAs.

The influence of ACE inhibitors and angiotensin receptor antagonists on Hb concentrations and patients' responses to ESAs are controversial. A range of studies, mostly observational, have either suggested or dismissed an effect [11–27].

There are reports of numerous other causes of hyporesponsiveness to ESAs. Briefly these include: high plasma intact parathyroid hormone (iPTH) concentrations (especially with histological osteitis fibrosa) [22,28–36], aluminium intoxication (leading to

microcytic anaemia) [29,37–40], haemoglobinopathies (sickle cell disease and α- and β-thalassaemias) [41–45], malignancy [46,47], haemolysis (mechanical, immunological or linked to disorders of the red cell membrane) [48] and response to cytotoxic agents [47,49].

Sometimes (with haemoglobinopathies or chronic inflammatory disease for example) it is not possible to remove the cause of hyporesponsiveness to ESAs. Data from studies in critically ill patients suggest that ESA resistance can be overcome with high doses [50,51], but the cost of treatment may preclude the use of ESAs at these doses.

When no underlying medical cause of hyporesponsiveness to ESAs can be found, clinicians must rely on the mainstay treatments used to manage chronic kidney disease before the advent of ESA therapy (namely minimizing blood loss and sampling, optimization of dialysis and nutrition). Attention to dialysis and nutrition should also underpin treatment of anaemia with ESAs in uraemic patients.

References

1. Eschbach JW. The anemia of chronic renal failure: pathophysiology and the effects of recombinant erythropoietin. *Kidney Int* 1989; 35: 134–148
2. Jacobs C, Horl WH, Macdougall IC *et al*. European best practice guidelines 9–13: anaemia management. *Nephrol Dial Transplant* 2000;15 [Suppl 4]: 33–42
3. Vanrenterghem Y, Barany P, Mann JF *et al*. Randomized trial of darbepoetin alfa for treatment of renal anemia at a reduced dose frequency compared with rHuEPO in dialysis patients. *Kidney Int* 2002; 62: 2167–2175
4. Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J. Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). *Nephrol Dial Transplant* 2003; 18: 362–369
5. Valderrabano F. Anaemia management in chronic kidney disease patients: an overview of current clinical practice. *Nephrol Dial Transplant* 2002; 17 [Suppl 1]: 13–18
6. Hörl WH, Jacobs C, Macdougall IC *et al*. European best practice guidelines 14–16: inadequate response to epoetin. *Nephrol Dial Transplant* 2000; 15 [Suppl 4]: 43–50
7. Richardson D. Clinical factors influencing sensitivity and response to epoetin. *Nephrol Dial Transplant* 2002; 17 [Suppl 1]: 53–59
8. Macdougall IC, Cooper A. The inflammatory response and epoetin sensitivity. *Nephrol Dial Transplant* 2002; 17 [Suppl 1]: 48–52
9. Krantz SB. Pathogenesis and treatment of the anemia of chronic disease. *Am J Med Sci* 1994; 307: 353–359
10. Pereira BJ. Balance between pro-inflammatory cytokines and their specific inhibitors in patients on dialysis. *Nephrol Dial Transplant* 1995; 10: 27–32
11. Onoyama K, Sanai T, Motomura K, Fujishima M. Worsening of anemia by angiotensin converting enzyme inhibitors and its prevention by antiestrogenic steroid in chronic hemodialysis patients. *J Cardiovasc Pharmacol* 1989; 13: S27–S30
12. Sanchez JA. ACE inhibitors do not decrease rHuEpo response in patients with end-stage renal failure. *Nephrol Dial Transplant* 1995; 10: 1476–1477
13. Conlon PJ, Albers F, Butterly D, Schwab SJ. ACE inhibitors do not affect erythropoietin efficacy in haemodialysis patients. *Nephrol Dial Transplant* 1994; 9: 1358
14. Hess E, Sperschneider H, Stein G. Do ACE inhibitors influence the dose of human recombinant erythropoietin in dialysis patients? *Nephrol Dial Transplant* 1996; 11: 749–751
15. Walter J. Does captopril decrease the effect of human recombinant erythropoietin in haemodialysis patients? *Nephrol Dial Transplant* 1993; 8: 142
16. Dhondt AW, Vanholder RC, Ringoir SM. Angiotensin-converting enzyme inhibitors and higher erythropoietin requirement in chronic haemodialysis patients. *Nephrol Dial Transplant* 1995; 10: 2107–2109
17. Ertürk S, Ates K, Duman N, Karatan O, Erbay B, Ertug E. Unresponsiveness to recombinant human erythropoietin in haemodialysis patients: possible implications of angiotensin-converting enzyme inhibitors. *Nephrol Dial Transplant* 1996; 11: 396–397
18. Morrone LF, Di Paolo S, Logoluso F *et al*. Interference of angiotensin-converting enzyme inhibitors on erythropoiesis in kidney transplant recipients: role of growth factors and cytokines. *Transplantation* 1997; 64: 913–918
19. Gossmann J, Thurmann P, Bachmann T *et al*. Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients. *Kidney Int* 1996; 50: 973–978
20. Abu-Alfa AK, Cruz DN, Mahnensmith RL *et al*. ACE inhibitors do not induce Epogen® resistance in hemodialysis patients: a prospective crossover study. *J Am Soc Nephrol* 1997; 8: 225A
21. Cruz DN, Perazella MA, Abu-Alfa AK, Mahnensmith RL. Angiotensin-converting enzyme inhibitor therapy in chronic hemodialysis patients: any evidence of erythropoietin resistance? *Am J Kidney Dis* 1996; 28: 535–540
22. Albitar S, Genin R, Fen-Chong M, Serveaux MO, Bourgeon B. High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. *Nephrol Dial Transplant* 1998; 13: 1206–1210
23. Navarro JF, Macia ML, Mora-Fernandez C *et al*. Effects of angiotensin-converting enzyme inhibitors on anemia and erythropoietin requirements in peritoneal dialysis patients *Adv Perit Dial* 1997; 13: 257–259
24. Macia M, Mora J, Chahin E *et al*. Higher erythropoietin (EPO) requirements in peritoneal dialysis patients treated with angiotensin-converting enzyme inhibitors (ACEI). *J Am Soc Nephrol* 1997; 8: 269A
25. Ikeda Y, Sakemi T, Ohtsuka Y, Kuwahara M, Fujisaki N. Drug-related low responsiveness to recombinant human erythropoietin therapy in three patients with end-stage renal disease. *Nephrol Dial Transplant* 1997; 12: 371–372
26. Kuriyama S, Tomonari H, Tokudome G *et al*. Antiproteinuric effects of combined antihypertensive therapies in patients with overt type 2 diabetic nephropathy. *Hypertens Res* 2002; 25: 849–855
27. Foote EF, Germick D. Angiotensin receptor blockers and epoetin resistance. *Semin Dial* 2003; 16: 79–80
28. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. *N Engl J Med* 1993; 328: 171–175
29. Grützmacher P, Ehmer B, Limbach J *et al*. Treatment with recombinant human erythropoietin in patients with aluminium overload and hyperparathyroidism. *Blood Purif* 1990; 8: 279–284
30. Muirhead N, Hodsman AB, Hollomby DJ, Cordy PE. The role of aluminium and parathyroid hormone in erythropoietin resistance in haemodialysis patients. *Nephrol Dial Transplant* 1991; 6: 342–345
31. Goicoechea M, Gomez-Campdera F, Polo JR *et al*. Secondary hyperparathyroidism as cause of resistance to treatment with erythropoietin: effect of parathyroidectomy. *Clin Nephrol* 1996; 45: 420–421
32. Mandolfo S, Farina M, Malberti F *et al*. Parathyroidectomy (PTX) and erythropoietin (rHuEPO) response in anaemic patients with ERSD. *Nephrol Dial Transplant* 1997; 12: A192

33. Seyrek N, Paydas S, Sagliker Y. Improvement of anemia and secondary hyperparathyroidism with erythropoietin treatment in hemodialysis patients. *Nephron* 1996; 73: 338–339
34. Rault R, Magnone M. The effect of parathyroidectomy on hematocrit and erythropoietin dose in patients on hemodialysis. *ASAIO J* 1996; 42: M901–M903
35. Goicoechea M, Vazquez MI, Ruiz MA, Gomez-Campdera F, Perez-Garcia R, Valderrabano F. Intravenous calcitriol improves anaemia and reduces the need for erythropoietin in haemodialysis patients. *Nephron* 1998; 78: 23–27
36. Ismail N. Use of erythropoietin, active vitamin D3 metabolites, and alkali agents in predialysis patients. *Semin Nephrol* 1997; 17: 270–284
37. Steffen HM, Brunner R, Muller R *et al*. Peripheral hemodynamics, blood viscosity, and the renin–angiotensin system in hemodialysis patients under therapy with recombinant human erythropoietin. *Contrib Nephrol* 1989; 76: 292–298
38. Rosenlof K, Fyhrquist F, Tenhunen R. Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; 335: 247–249
39. Grützmacher P, Ehmer B, Messinger D, Kulbe KD, Scigalla P. Effect of aluminum overload on the bone marrow response to recombinant human erythropoietin. *Contrib Nephrol* 1989; 76: 315–321; discussion 322–323
40. Casati S, Passerini P, Campise MR *et al*. Benefits and risks of protracted treatment with human recombinant erythropoietin in patients having haemodialysis. *BMJ* 1987; 295: 1017–1020
41. Tomson CR, Edmunds ME, Chambers K, Bricknell S, Feehally J, Walls J. Effect of recombinant human erythropoietin on erythropoiesis in homozygous sickle-cell anaemia and renal failure. *Nephrol Dial Transplant* 1992; 7: 817–821
42. Steinberg MH. Erythropoietin for anemia of renal failure in sickle cell disease. *N Engl J Med* 1991; 324: 1369–1370
43. Roger SD, Macdougall IC, Thuraisingham RC, Raine AE. Erythropoietin in anemia of renal failure in sickle cell disease. *N Engl J Med* 1991; 325: 1175–1176
44. Cheng IK, Lu HB, Wei DC, Cheng SW, Chan CY, Lee FC. Influence of thalassemia on the response to recombinant human erythropoietin in dialysis patients. *Am J Nephrol* 1993; 13: 142–148
45. Lai KN, Wong KC, Li PK, Lui SF. Use of recombinant erythropoietin in thalassemic patients on dialysis. *Am J Kidney Dis* 1992; 19: 239–245
46. Macdougall IC, Coles GA, Williams JD. Inhibition of a response to r-HuEPO in the presence of infection or malignancy. *Erythropoiesis* 1992; 3: 29–30
47. Abels RI. Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. *Semin Oncol* 1992; 19: 29–35
48. Evers J. Cardiac hemolysis and anemia refractory to erythropoietin: on anemia in dialysis patients. *Nephron* 1995; 71: 108.
49. Samol J, Littlewood TJ. The efficacy of rHuEPO in cancer-related anaemia. *Br J Haematol* 2003; 121: 3–11
50. Corwin HL, Gettinger A, Rodriguez RM *et al*. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999; 27: 2346–2350
51. Corwin HL, Gettinger A, Pearl RG *et al*. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002; 288: 2827–2835

Guideline IV.2: Antibody-mediated pure red cell aplasia

Due to the nature of the subject matter, this guideline was not subjected to evidence-based grading.

Recommendation

I. Pure red cell aplasia (PRCA) should be strongly suspected if a patient treated with an erythropoiesis-stimulating agent (ESA) for $\geq$4 weeks has:

- **a sudden, rapid decline in haemoglobin (Hb) concentration of $\sim$0.5–1 g/dl/week despite ongoing ESA therapy, or requires transfusion of 1–2 units of red blood cells per week to maintain Hb level AND**
- **normal platelet and white cell counts AND**
- **a reticulocyte count $< 10 \times 10^9$/l.**

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

Rationale and commentary

PRCA is a progressive, severe, isolated anaemia, typified by a sudden onset and an almost complete absence of red blood cell precursors from an otherwise normal bone marrow [1]. Acquired PRCA is rare. It usually arises spontaneously; however, it can be associated with thymoma, lymphoid proliferation, or an immune-related disorder such as systemic lupus erythematosus or rheumatoid arthritis [2,3]. Occasionally, PRCA can be secondary to drug-induced impairment of erythroid progenitor cells or viral infections such as B19 parvovirus or hepatitis B virus.

In ESA-induced PRCA, neutralizing anti-erythropoietin antibodies develop in patients undergoing treatment with an ESA. These antibodies cross-react with the patient's residual endogenous erythropoietin, leading to a form of anaemia more severe than that occurring before the start of ESA therapy. Three cases have also been reported of PRCA arising from anti-erythropoietin antibodies in patients never treated with an ESA [4–6].

In the first 10 years of ESA therapy, there were only four reports of ESA-associated PRCA [7–10]. However, there has been a sudden increase in cases since 1998 [11]. To date, there have been $\sim$200 cases of suspected or proven PRCA. The estimated incidence is two per 10 000 patients on subcutaneous (s.c.) ESA therapy, whereas no cases have been confirmed in patients receiving ESAs solely via the intravenous (i.v.) route. Future incidence is difficult to predict, but, even with the increased incidence of PRCA since 1998, other causes of loss of ESA efficacy are still far more likely than PRCA.

Research with other biopharmaceuticals indicates that administering recombinant proteins s.c. usually has a higher risk of immunogenicity than the i.v. route of administration [12–15]. However, administration via the s.c. route alone appears insufficient to trigger an immune response to ESAs, and there seem to be clear differences in immunogenic potential among the different brands of ESAs. A report covering a series of patients [11], as well as post-marketing data from ESA manufacturers [16], shows a significantly higher

incidence of PRCA associated with the s.c. use of the Eprex® brand of epoetin alfa (sold outside the USA) than with any of the other products.

PRCA is unlikely to be the cause of falling Hb concentrations in patients who have been on ESA therapy for <4 weeks, although the possibility cannot be excluded. One month is the shortest interval reported so far between the start of therapy and loss of efficacy due to PRCA [17]. Patients have typically been on ESA therapy for 6–18 months before the appearance of the condition.

The decreased Hb concentration and increased requirement for transfusion in patients with PRCA typically reflect a drop in the red blood cell count due to the normal decay of existing cells, combined with a lack of new cell production following erythropoietin neutralization ($\sim 1\%$ loss of cells per day, corresponding to a drop in Hb concentration of between 0.5 and 1.0 g/dl per week). To date, the presence of anti-erythropoietin antibodies has usually been found to be associated with total neutralization of erythropoietin; there are no reports of partial neutralization of erythropoietin leading to a correspondingly slower decline in Hb concentration. In addition, no neutralizing anti-erythropoietin antibodies have been reported in patients lacking signs of PRCA. Therefore, less severe forms of anaemia are unlikely to be due to PRCA.

The reticulocyte count should be $<10 \times 10^9$/l to confirm a diagnosis of PRCA. It is likely that a fall in reticulocyte count would be detected before a fall in Hb concentration, but the use of regular reticulocyte count monitoring has not been validated in this clinical setting [18].

Other observations have also been linked to PRCA:

- serum ferritin and serum transferrin concentrations rise markedly in patients with PRCA, reflecting a decreased use of iron as red blood cell production ceases.
- white cell and platelet counts usually remain within the normal range, but a small decline in platelet count has been observed at the onset of PRCA which may reflect a stimulatory role of erythropoietin on megakaryocytes or more complex interactions between different precursor cell lines.
- skin reactions have been observed both separately and associated with PRCA in patients being treated with s.c. ESAs [19].

Recommendation

II. A confirmed diagnosis of PRCA due to anti-erythropoietin antibodies requires the presence of the following:

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

Rationale and commentary

If PRCA is strongly suspected, using the above criteria, bone marrow aspiration should be performed. Evidence of erythroid hypoplasia (normal cellularity with $<5\%$ erythroblasts and evidence of a block in red blood cell precursor maturation) on the smear would confirm a diagnosis of PRCA. Bone marrow histology is not usually required for a diagnosis.

Antibody testing is the key to determining whether PRCA is caused by ESA therapy [3]. Although there is currently no single, standardized assay used to detect anti-erythropoietin antibodies, there are two types of assays commonly used for determining such antibodies: binding assays and bioassays. Enzyme-linked immunosorbent assays (ELISAs), radioimmunoprecipitation assays (RIPs) and the biosensor immunoassay (BIAcore) are all binding assays. If different assays are not standardized and regularly compared, positive results of both RIPs and ELISAs should, ideally, be confirmed by a second, different assay. Only bioassays, which involve growing erythroid-dependent erythroid colonies or cell lines can identify the neutralizing capacity of anti-erythropoietin antibodies. However, the anti-erythropoietin antibodies reported to date in patients with PRCA have usually been neutralizing [11]. Therefore, although confirming the neutralizing activity of anti-erythropoietin antibodies in each patient is desirable, it appears not to be essential for a diagnosis of ESA-induced PRCA.

Recommendation

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

Rationale and commentary

Every attempt should be made to confirm a suspected diagnosis of PRCA. However, if the diagnosis is unconfirmed because of inconclusive results, a patient may need to be treated as having PRCA and the case should be reported to health authorities.

The antibodies induced by the recombinant protein cross-react with both endogenous erythropoietin and other forms of the recombinant protein [3,11]. In addition, erythropoiesis was not found to improve in patients with PRCA who switched ESAs because of loss of efficacy prior to a diagnosis of PRCA. It is not advisable to continue with ESA therapy in patients with anti-erythropoietin antibodies as it can lead to severe anaphylactic reactions [19]. In addition, switching brands of ESA in patients with suspected PRCA would make it difficult to determine which brand was responsible for the condition, if a diagnosis of PRCA was later confirmed.

Immunosuppressive therapy

Stopping ESA therapy alone does not appear to be sufficient to induce recovery from PRCA [20]. Patients can exhibit a full recovery under immunosuppressive therapy, but different regimens have not been compared prospectively. The most rapid and consistent recovery has been observed after kidney transplantation.

As there are few data about the outcome of treatment with an erythropoietic agent in patients who have recovered from PRCA, no recommendations can be given at the present time about restarting ESA therapy in these patients.

References

1. Krantz SB. Pure red-cell aplasia. *N Engl J Med* 1974; 291: 345–350
2. Casadevall N. Antibodies against rHuEPO: native and recombinant. *Nephrol Dial Transplant* 2002; 17 [Suppl 5]: 42–47
3. Eckardt K-U, Casadevall N. Pure red-cell aplasia due to anti-erythropoietin antibodies *Nephrol Dial Transplant* 2003; 18: 865–869
4. Peschle C, Marmont AM, Marone G *et al*. Pure red cell aplasia: studies on an IgG serum inhibitor neutralizing erythropoietin. *Br J Haematol* 1975; 30: 411–417
5. Casadevall N, Dupuy E, Molho-Sabatier P *et al*. Brief report: autoantibodies against erythropoietin in a patient with pure red cell aplasia. *N Engl J Med* 1996: 334: 630–633
6. Linardaki GD, Boki KA, Fertakis A, Tzioufas AG. Pure red cell aplasia as presentation of systemic lupus erythematosus: antibodies to erythropoietin. *Scand J Rheumatol* 1999; 28: 189–191
7. Montagnac R, Boffa GA, Schillinger F, Guillaumie J. Sensibilisation à l'erythropoiétine humaine recombinante chez une hémodialysée. *Presse Med* 1992; 21: 84–85
8. Bergrem H, Danielson BG, Eckardt KU, Kurtz A, Stridsberg M. A case of antierythropoietin antibodies following recombinant human erythropoietin treatment. In: Bauer C, Koch KM, Scigalla P, Wieczorek L, eds. *Erythropoietin: Molecular Physiology and Clinical Applications*. Marcel Dekker, New York; 1993: 265–273
9. Peces R, de la Torre M, Alcàzar R, Urra JM. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med* 1996; 335: 523–524
10. Prabhakar SS, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol* 1997; 47: 331–335
11. Casadevall N, Nataf J, Viron B *et al*. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002b; 346: 469–475
12. Porter S. Human immune response to recombinant human proteins. *J Pharm Sci* 2002; 90: 1–11
13. Schellenkens H. Bioequivalence and immunogenicity of biopharmaceuticals. *Nature Rev Drug Discov* 2002; 1: 457–462
14. Kontsek P, Liptakova H, Kontsekova E. Immunogenicity of interferon-alpha 2 in therapy: structural and physiological aspects. *Acta Virol* 1999; 43: 63–70
15. Perini P, Facchinetti A, Bulian P *et al*. Interferon-beta (INF-beta) antibodies in interferon-beta1a- and interferon-beta1b-treated multiple sclerosis patients. Prevalence, kinetics, cross-reactivity, and factors enhancing interferon-beta immunogenicity in vivo. *Eur Cytokine Netw* 2001; 12: 56–61
16. Locatelli F, Alijama P, Barany P *et al*. Erythropoiesis-stimulating agents and antibody-mediated pure red cell aplasia: where are we now and where do we go from here? *Nephrol Dial Transplant* 2004; 19: 288–293
17. Gershon SK, Luksenburg H, Coté TR, Braun MM. Pure red-cell aplasia and recombinant erythropoietin. *N Engl J Med* 2002; 346: 1584–1586
18. Cavill I, Williams JD. Benefits of recombinant human erythropoietin. *Lancet* 2002; 360: 1606–1607
19. Weber G, Gross J, Kromminga A *et al*. Allergic skin and systemic reactions in a patient with pure red cell aplasia and anti-erythropoietin antibodies challenged with different epoetins. *J Am Soc Nephrol* 2002; 13: 2381–2383
20. Verhelst D, Rossert J, Casadevall N *et al*. Treatment of antibody-mediated pure red cell aplasia. *Lancet* 2004: in press

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Appendix C: Tables, conversions and abbreviations

This appendix contains the following supplemental information:

- Tables
- Formulae for calculating the glomerular filtration rate (GFR)
- Conversion factors for haemoglobin (Hb)
- Abbreviations used throughout the guidelines

Tables

Table 1. Definition of the five stages of chronic kidney disease (CKD)

Stage	Description	GFR (ml/min/1.73 m^2)	Action
	At increased risk	≥90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment, treatment of co-morbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild decrease in GFR	60–89	Estimating progression
3	Moderate decrease in GFR	30–59	Evaluating and treating complications
4	Severe decrease in GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uraemia present)

Reprinted from [1] with permission from the National Kidney Foundation.

Table 2. New York Heart Association classification of congestive heart failure patients

Class	Description
I	Patients with documented heart disease of any type who are completely symptom free
II	Slight limitation of physical activity; symptoms (shortness of breath, chest pain) occur only with more than ordinary physical activity
III	Marked limitation of physical activity; symptoms occur even with ordinary physical activity (e.g. eating meals)
IV	Severe limitation of physical activity; symptoms occur even at rest (e.g. in a sitting or lying position)

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Formulae for calculating the GFR

The following formulae can be used to calculate the GFR.

Cockcroft–Gault formula

If using μmol/l as a measure of serum creatinine, use the following formula:

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight in kg}\,(\times 0.85 \text{ if female})}{0.810 \times \text{serum creatinine (μmol/l)}}.$$

If using mg/dl for serum creatinine, use the following formula:

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight in kg}\,(\times 0.85 \text{ if female})}{72 \times \text{serum creatinine (mg/dl)}}.$$

To convert μmol/l to mg/dl, multiply by 0.0113.
To convert mg/dl to μmol/l, multiply by 88.4.

MDRD formula

The MDRD formula below is derived from the Modification of Diet in Renal Disease Trial [3].

$$\begin{aligned}\text{GFR} = {} & 170 \times \text{serum creatinine concentration}^{-0.999}_{(\text{mg/dl})} \\ & \times \text{age}^{-0.176} \\ & \times 0.762 \text{ (if female)} \\ & \times 1.18 \text{ (if race is black)} \\ & \times \text{blood urea nitrogen concentration}^{-0.17} \\ & \times \text{serum albumin concentration}^{+0.318}\end{aligned}$$

A GFR calculator using the MDRD formula can also be found on the National Kidney Foundation K/DOQI website: www.kdoqi.org. GFR can be calculated by inputting the required laboratory and demographic data.

Conversion factors for Hb

Throughout these guidelines, Hb concentrations are expressed in g/dl. To convert g/dl to g/l, multiply by 10. Other units, such as mmol/l, are used in some countries in Europe, including Denmark and The Netherlands. To convert g/dl to mmol/l, multiply by 0.62.

Abbreviations used throughout the guidelines

AGE = advanced glycosylation end
CHr = reticulocyte Hb content
CKD = chronic kidney disease
CRP = C-reactive protein
CVD = cardiovascular disease
DST = donor-specific transfusion
ESA = erythropoiesis-stimulating agent
ESRD = end-stage renal disease
FID = functional iron deficiency
GFR = glomerular filtration rate
Hb = haemoglobin
Hct = haematocrit
HD = haemodialysis
HLA = histocompatibility leukocyte antigens
HRC = hypochromic red blood cells
iPTH = intact parathyroid hormone
KDQ = Kidney Disease Questionnaire
MCH = mean corpuscular haemoglobin
MCV = mean corpuscular volume
PD = peritoneal dialysis
PRCA = pure red cell aplasia
PTFE = polytetrafluoroethylene
QOL = quality of life
TBIC = total iron-binding capacity
sTfR = soluble transferrin receptor
TSAT = transferrin saturation
VO_2max = maximal rate of oxygen consumption
ZPP = zinc protoporphyrin

References

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39 [Suppl 1]: S1–S266
2. The Criteria Committee for the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Little, Brown & Co., Boston; 1994: 253–256
3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470