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Nephrology
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SECTION I. Anaemia evaluation

Guideline I.1: Which patients should be evaluated and when should work-up begin?

Recommendation

I. All patients with chronic anaemia associated with chronic kidney disease (CKD) should be investigated for possible treatment, irrespective of the stage of kidney disease and requirement for renal replacement therapy.

A work-up for a diagnosis of anaemia should be considered in patients with CKD when haemoglobin (Hb) concentration falls below the mean –2 SD (i.e. <95%) Hb level of the normal population, adjusted for age and sex:

- **<11.5 g/dl in adult female patients**
- **<13.5 g/dl in adult male patients**
- **<12.0 g/dl in adult male patients aged >70 years.** (***Evidence level B***)

Rationale and commentary

How is anaemia defined?

There is some uncertainty over the definition of anaemia both in the scientific literature and in clinical practice. A rational approach seems to be to define anaemia as an Hb level below 5% of that of the total population [1]. However, the normal distribution of Hb values depending on age, gender, ethnicity and altitude of living is not entirely clear (see Appendix A for a more detailed discussion of this issue). Therefore, on the basis of the available evidence, this guideline proposes that Hb values in individuals living below 1500 m altitude are considered below normal if they are <11.5 g/dl in women, <13.5 g/dl in adult men younger than 70 years and <12.0 g/dl in men above the age of 70.

These values are close to those found in a definition of anaemia introduced by the World Health Organization several decades ago (<12 g/dl in women and <13 g/dl in men). However, in clinical practice, individuals frequently are only considered to be anaemic when their Hb values fall considerably lower than these threshold values.

Variations in the definition of anaemia aside, there are at least two reasons to start a work-up for anaemia in all patients with Hb levels below the normal range, rather than at a more severely reduced Hb concentration. First, a decline in Hb to below the normal range may indicate a potentially serious underlying disease that should be excluded. Secondly, there is increasing evidence that even moderate reductions of Hb levels are associated with adverse outcomes (see below).

Although the diagnosis of renal anaemia involves consideration of the degree of anaemia and the severity and type of kidney disease (see Guideline I.3), work-up for anaemia should be initiated in all CKD patients solely on the basis of an abnormally low Hb value.

What is the prevalence of anaemia in patients with CKD?

In CKD patients not on dialysis, anaemia is under-recognized and many start dialysis with very low Hb concentrations [2,3]. The traditional view has been that anaemia becomes more common and severe with decreasing renal function [4]. However, more recent data indicate that anaemia starts much earlier during the progression of CKD [5,6]. Although it varies, the degree of renal insufficiency at which the Hb concentration drops below 11 g/dl is typically when renal function falls below a glomerular filtration rate (GFR) of 30 ml/min (CKD stage 4, see Appendix C) [4,7–10]. GFR is measured directly, or calculated from the plasma creatinine using the Cockcroft–Gault formula (see Appendix C) [11]; or, if both these measurements are unavailable, when the plasma creatinine increases above 200–500 μmol/l [2.26–5.66 mg/dl]. Some patients, particularly diabetic patients, can develop anaemia earlier or more severely than other patients, at GFR levels of up to 45 ml/min [12–14]. In fact, anaemia has been found to be two to three times more prevalent in patients with diabetes compared with the general population at all levels of GFR [15]. This may be due to the renal hyperfiltration in poorly treated diabetic patients, or to reduced red cell deformability. Consequently, it is the presence of anaemia, and not the degree of renal function, that should prompt evaluation.

In addition, there are many factors that can affect the work-up of patients with anaemia, including loss of iron and folate. Iron losses are much greater in haemodiaysis (HD) patients than in any other group, and so iron stores may be lower in patients undergoing HD. The age of a patient is important in deciding when to investigate as normal Hb levels decrease with age (see

Appendix A). This latter factor is of particular significance as >50% of patients on HD are >60 years of age.

The development of anaemia is also complicated by co-morbidity associated with underlying disease (see commentary to Guideline I.3).

Other factors that may cause variations are altitude of residence, smoking and ethnicity. Patients who reside above 1000 m have increased Hb concentrations and the optimum Hb concentration may be higher. Smoking increases Hb by up to 1.5 g/dl without improving O_2 exchange, and this may worsen vascular disease. Although not a source of major difference, black patients have lower Hb and higher ferritin levels than Caucasian patients.

The timing of investigation and treatment of anaemia should be based solely on the Hb concentration. However, in renal anaemia, the level of renal function and the concentration of erythropoietin should also be considered. Hb concentration is preferable to the haematocrit (Hct) level since it is a primary parameter that can be measured directly (see Appendix A).

What are the consequences of not addressing anaemia in early stages of CKD?

If left untreated, chronic anaemia has serious consequences in terms of impaired quality of life and increased risk of cardiac complications. In the past, patients were only treated for anaemia once they started dialysis. At this point, most patients were already anaemic and suffering from anaemia's many physical and psychological consequences. Some of these early conditions may be serious and, if allowed to develop, partly irreversible (e.g. left ventricular hypertrophy and fibrosis) [16]. Therefore, there may be a case for earlier treatment, perhaps when the Hb concentration falls below the normal range (see Guideline II.1). There is prospective epidemiological evidence that earlier treatment reduces mortality during the first year on dialysis [17]. Also, it has been shown that a lower Hb at the start of dialysis significantly increases the risk of cardiovascular complications and death in the first year of dialysis and early intervention might help prevent such complications [12,16].

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Guideline I.2: What is the appropriate work-up to investigate anaemia in chronic kidney disease?

Recommendation

I. An initial clinical and laboratory evaluation should be completed prior to considering the commencement of treatment with an erythropoiesis-stimulating agent (ESA) in patients with chronic kidney disease (CKD), to evaluate possible causes of anaemia superimposed on relative erythropoietin deficiency.
(*Evidence level C*)

Assessment of anaemia should involve laboratory measurement of the following parameters:

- **haemoglobin (Hb) concentration—to assess the degree of anaemia**
- **red blood cell indices [mean corpuscular volume (MCV) and mean corpuscular Hb (MCH)]—to assess the type of anaemia**

- **absolute reticulocyte count—to assess erythropoietic activity**
- **plasma/serum ferritin concentration—to assess iron stores**
- **functional iron available for erythropoiesis by the measurement of either:**
  - **percentage of hypochromic red blood cells (HRC)**
  - **plasma/serum transferrin saturation (TSAT)**
  - **reticulocyte Hb content (CHr)**
- **plasma/serum C-reactive protein (CRP)—to assess inflammation.**
  (***Evidence level B***)

In patients on dialysis, the frequency and the received dose of dialysis should also be evaluated.
(***Evidence level C***)

Rationale and commentary

Anaemia can develop in CKD patients for a variety of reasons other than erythropoietin deficiency. The basic, recommended laboratory evaluation provides information regarding the degree of anaemia, the type of anaemia, erythropoietic activity, inflammation, iron stores and functional iron available for erythropoiesis. Measurement of plasma erythropoietin concentration is usually not indicated (see commentary to Guideline I.3).

Plasma/serum CRP is the best parameter for monitoring inflammation and the acute phase reaction in CKD patients [1–3]. Inflammation and high CRP levels are associated with anaemia and increased requirements for ESAs. Inflammation also has several effects on iron metabolism and iron parameters [4].

Recommendation

II. A more extensive work-up may also include the following, as indicated by the initial clinical and laboratory evaluation:

- **assessment of occult gastrointestinal blood loss**
- **serum B_{12} and red cell folate concentrations**
- **serum/plasma intact parathyroid hormone (iPTH) concentration**
- **differential white blood count and platelets**
- **tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test)**
- **plasma/serum and/or urine protein electrophoresis/immunoblotting**
- **serum aluminium**
- **Hb electrophoresis and bone marrow examination in selected cases.**
  (***Evidence level B***)

Rationale and commentary

A fuller work-up should be performed as indicated by the initial clinical and/or laboratory evaluation, and particularly if there is clinical suspicion of occult blood loss, macrocytosis, primary haematological/oncological disorder (haemolysis, multiple myeloma, marrow dysplasia) or aluminium accumulation. Although the utility of screening for gastrointestinal bleeding using occult blood tests has yet to be proven in larger populations with CKD, such bleeding is common and the test is simple, widely used and inexpensive [5].

In addition, deficiencies of folic acid and vitamin B_{12} (both water soluble and therefore dialysable vitamins) are well-defined causes of anaemia associated with macrocytosis [6]. In patients on a low-protein diet and dialysis patients with malnutrition, folate intake may often be lower than the recommended 1 mg/day (which is five-fold higher than the RDA). However, in CKD patients without obvious folate or vitamin B_{12} deficiency, there is no strong evidence that routine supplementation has an effect on anaemia or that it enhances the overall response to ESAs [7].

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Guideline I.3: Diagnosis of renal anaemia

Recommendation

I. A diagnosis of anaemia most likely to be due to erythropoietin deficiency should be considered if:

- **there is significant impairment of renal function AND**

- **no cause for anaemia other than chronic kidney disease (CKD) is detected during work-up.** (***Evidence level B***)

Rationale and commentary

The proportion of patients with renal anaemia in a given population depends on a number of factors including the population studied, the definition of anaemia and the degree of renal failure. In the NHANES III (the Third National Health and Nutrition Examination Survey) study [1], only 1% of participants with a glomerular filtration rate (GFR) >60 ml/min were found to suffer from anaemia [as defined in this study as a haemoglobin (Hb) concentration <12 g/dl in men or <11 g/dl in women]. However, in a cohort of patients with CKD, 25% of patients with a GFR >50 ml/min had Hb <12 g/dl [2].

Data describing the relative contributions of different causes of anaemia (erythropoietin deficiency, blood loss, inflammation, iron deficiency, medications, etc.) in the early stages of CKD are lacking. However, the most important reason for a progressive decline in Hb concentrations in patients with CKD is probably a relative deficiency of erythropoietin. Other possible causes of low Hb levels include inhibition of red cell production, iron deficiency (possibly as a result of inappropriate nutrition) and inflammation. Adequate iron is essential for red blood cell production and response to erythropoietic protein.

The development of anaemia is also complicated by co-morbidity associated with underlying disease. For example, diabetic patients develop severe anaemia earlier in the course of renal failure than non-diabetic patients [3]. Hypertensive patients, especially those with severe heart failure, atrial fibrillation or with chronic obstructive pulmonary disease, also have different rheology and thrombotic indices. Pre-existing anaemia during normal renal function and relative resistance to treatment is common in patients with haemoglobinopathies such as sickle cell disease and thalassaemia, neoplasia (especially myeloid neoplasia) and inflammatory disorders such as inflammatory arthritis. In addition, patients who are taking (or have taken) cytotoxic drugs for vasculitis, autoimmune disorders and some forms of primary glomerulonephritis may have hyporesponsive bone marrows.

The diagnosis of renal anaemia in a patient with CKD is, classically, a diagnosis of exclusion, reached when no other cause of anaemia is found.

In practice, it is rarely considered necessary to measure the level of erythropoietin in order to reach a diagnosis of renal anaemia. However, when Hb levels are low and renal function is only mildly impaired (GFR 60–120 ml/min), plasma erythropoietin levels should be shown to be inappropriate before a diagnosis of renal anaemia is made. In fact, the higher the level of renal function, the more important it is to consider additional tests (such as a full haematological work-up, the measurement of erythropoietin or endoscopy), or an assessment of adequate nutrition, in order to assess possible causes of anaemia other than CKD (see Guideline I.2).

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

The original European Best Practice Guidelines (EBPG) for the Management of Renal Anaemia in Patients with Chronic Renal Failure were published in 1999, following the decision by the ERA-EDTA in 1998 to create clinical practice guidelines to aid nephrologists in providing optimal care for their patients. Since the publication of the original guidelines, more than 3000 papers relating to the management of anaemia of chronic kidney disease (CKD) have been published. Since 1999, there have been major changes in the field of anaemia management including research related to iron administration and evaluation, available erythropoietic agents, adjunctive therapies, adverse events [e.g. pure red cell aplasia (PRCA)], peritoneal dialysis and appropriate target haemoglobin (Hb). With this in mind, it was deemed necessary to update/revise the current guidelines.

Working group

The revised guidelines were developed by the EBPG II working group that was chaired by Professor Francesco Locatelli (Lecco, Italy). All working group members were experts in the management of renal anaemia. Editorial and organizational support was provided by Thomson Gardiner-Caldwell Communications, a medical education agency with experience in clinical practice guidelines development and CKD.

Literature search

One of the key elements in the creation of evidence-based guidelines is a systematic literature review. In this section, we describe the methodology used to conduct the literature search for the evidence base of the revised EBPG guidelines. In line with other evidence-based guidelines projects, only published data were considered.

At the outset of the guidelines project, an appropriate search strategy was developed in consultation with a medical information specialist to maximize the retrieval of articles relevant to the guidelines that had been published subsequent to the release of the original guidelines in 1999 (Search terms set A). This initial search was performed in MEDLINE and EMBASE and covered the period between January 1998 and March 2003.

Following the initial meeting of the EBPG II working group, additional searches were performed. After consultation with the members of the working group, a comprehensive search of MEDLINE and EMBASE in relation to renal anaemia was performed based on the Cochrane Renal Groups randomized controlled trial (RCT) search criteria (Search terms set C). The MEDLINE search covered the period from January 1979 through January 2003, while the EMBASE search covered the period from January 1983 through January 2003. Both searches excluded foreign language and non-human studies, as well as editorials and abstracts. This was followed by an accessory search for transplant-related articles (Search terms set B).

Pre-specified search criteria are rarely sufficiently accurate to capture all the relevant articles. For this reason, selected journals were also hand-searched by a search coordinator.

All the above searches were continued to capture any relevant articles published while the guidelines were being prepared.

Title, abstract and article review

Upon completion of the initial literature searches, a search coordinator reviewed the ~5100 titles identified for relevance to the guideline topics/questions. The process of selecting articles for use in creating the evidence base for the revised guidelines occurred in three stages: title review, abstract review and article review. Specific rejection criteria were developed for each of these stages. A team of researchers, trained in the review process and supervised by the search coordinator, conducted the review.

Title review

The search coordinator reviewed the titles of each article identified by the literature search and made an initial decision to accept or reject each title. During this stage of the review, an article was rejected if: (i) it was

clearly a letter, editorial or case report; or (ii) it clearly did not include a group, condition or outcome of interest. In addition, each accepted title was assigned to one or more guideline topic areas. Full papers were ordered for titles deemed of possible interest/relevance.

Abstract review

The abstract review was similar to that for the title review. An article was excluded during the abstract review if: (i) it was a review, letter or editorial; (ii) it did not relate directly to the treatment of renal anaemia; (iii) it did not include an outcome of interest; or (iv) it did not include a group or condition of interest. Full articles were obtained for relevant abstracts.

Article review

The search coordinator briefly reviewed each article to confirm its relevance, assigned it to the appropriate guideline(s), then passed the article on to a member of the research team for review. One researcher reviewed each article. To assess the consistency of the reviews, a number of randomly selected articles were reviewed by a second researcher. The search coordinator was available for consultation throughout the review process.

Each article was assessed for relevance to the guideline topic, eligibility for inclusion in the evidence base for that guideline and methodological quality. A standardized 'data extraction' form containing pre-specified inclusion criteria and outcomes of interest for each guideline was used to record details of trial randomization, blinding, description of withdrawals/dropouts and numbers lost to follow-up. Relevant content was also abstracted and entered into evidence tables on the data extraction form; separate tables were created for interventions and outcomes. The use of data extraction forms standardized the data presented in each paper, making it easier for the working group members to assess the quality of the evidence. During the data extraction process, a simple evidence grade was assigned to each paper based on the following scale:

i. Prospective randomized or quasi-randomized, controlled trial or meta-analysis of several such trials, or a Cochrane systematic review.
ii. Uncontrolled, non-randomized open study.
iii. Case studies or expert opinions (reviews).

Articles containing information relevant for two or more guidelines were reviewed in duplicate, using the appropriate data extraction form for each guideline.

Expert review

As a final review step, copies of the list of accepted articles for each guideline question were sent to each working group member. The experts were asked to comment on the inclusiveness of the article list, and any additional articles suggested by the working group members were obtained and sent through the same review and data extraction process as the other references.

Formulation of the guideline recommendations

Once all the selected papers from the initial literature searches had been reviewed and abstracted using the data extraction forms, the references, along with the corresponding data extraction forms for each guideline, were reviewed and analysed by the working group members assigned to that guideline. Where evidence was available from RCTs and systematic reviews, recommendations were based on these. Where there was a lack of evidence from high-quality studies, recommendations were based on the best available evidence or expert opinion.

A draft version of each guideline was then produced from these recommendations and reviewed by the entire working group. Several complete drafts of the set of guidelines and appendices were produced and reviewed by the working group. The working group assessed the evidence base for each recommendation and assigned an evidence level to each using the following scale:

A. Evidence from at least one good, randomized or quasi-randomized, controlled trial or meta-analysis of several such trials, or a Cochrane systematic review.
B. Evidence from several uncontrolled, non-randomized open studies.
C. Case studies or expert opinions (reviews).

Due to the nature of the subject matter in Guideline IV.2: Antibody-mediated pure red cell aplasia (PRCA), this guideline was not subjected to evidence-based grading.

Open review

To ensure the highest level of accuracy, quality and thoroughness, input was sought from the membership of the ERA-EDTA on the revised guidelines. Individuals participating in the 'Open Review' logged on to the ERA-EDTA's website (www.era-edta.org) and followed the links to the Open Review of the EBPG. Each reviewer was then asked to rate the recommendations and rationale for each guideline as either 'acceptable' or 'unacceptable', and to leave a brief comment. Conducting the Open Review online allowed the working group rapidly to aggregate and analyse the responses and eliminated the postage costs associated with mailed surveys. The Open Review was available from 20 October 2003 until 2 November 2003.

Search terms set A

MEDL 1	CHRONIC ADJ RENAL ADJ FAILURE OR CHRONIC ADJ KIDNEY ADJ DISEASE OR RENAL ADJ DIALYSIS OR PREDIALYSIS OR PRE-DIALYSIS OR PRE ADJ DIALYSIS OR CHRONIC ADJ RENAL ADJ INSUFFICIENCY OR END ADJ STAGE ADJ RENAL ADJ DISEASE
MEDL 2	KIDNEY ADJ FAILURE ADJ CHRONIC OR CHRONIC ADJ KIDNEY ADJ FAILURE OR PERITONEAL ADJ DIALYSIS
MEDL 3	1 OR 2
MEDL 4	3 AND (ANAEMIA OR ANEMIA OR ANEMIC OR ANAEMIC)
MEDL 5	3 AND ERYTHROPOIETIN
MEDL 6	3 AND EPOETIN
MEDL 7	3 AND (NESP OR NOVEL ADJ ERYTHROPOIESIS ADJ STIMULATING ADJ FACTOR)
MEDL 8	3 AND (HAEMATOLOG$4 OR HEMATOLOG$4)
MEDL 9	3 AND (HAEMATOCRIT OR HEMATOCRIT)
MEDL 10	3 AND (LVH OR LEFT ADJ VENTRICULAR ADJ HYPERTROPHY)
MEDL 11	3 AND (CARDIOVASCULAR ADJ MORBIDITY)
MEDL 12	3 AND CARDIOVASCULAR AND MORBIDITY
MEDL 13	11 OR 12
MEDL 14	3 AND (HAEMOGLOBIN OR HEMOGLOBIN)
MEDL 15	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 13 OR 14

Search terms set B

This search was run in Medline then repeated in EMBASE, language was limited to English and publication date was later than 1997:

1. chronic ADJ renal ADJ failure OR chronic ADJ kidney ADJ disease OR renal ADJ dialysis OR predialysis OR pre-dialysis OR pre ADJ dialysis OR chronic ADJ renal ADJ insufficiency OR end ADJ stage ADJ renal ADJ disease
2. kidney ADJ failure ADJ chronic OR chronic ADJ kidney ADJ failure OR peritoneal ADJ dialysis
3. 1 OR 2
4. 3 AND (anaemia OR anemia OR anemic OR anaemic)
5. 3 AND transplant$
6. 3 or 4 or 5

Search terms set C

Medline RCT Strategy

No.	Search term
1	PT = CLINICAL-TRIAL$ OR PT = CONTROLLED-CLINICAL-TRIAL OR PT = RANDOMIZED CONTROLLED-TRIAL
2	PT = CONTROLLED-CLINICAL-TRIAL OR PT = RANDOMIZED-CONTROLLED-TRIAL
3	randomized ADJ controlled ADJ trials
4	random ADJ allocation
5	double-blind ADJ method
6	double ADJ blind ADJ method
7	single-blind ADJ method
8	single ADJ blind ADJ method
9	2 OR 3 OR 4 OR 6 OR 8
10	animal NOT (animal AND human)
11	9 NOT 10
12	PT=CLINICAL-TRIAL$
13	exp ADJ clinical ADJ trials OR experimental ADJ clinical ADJ trials
14	(clinic$ ADJ trial$).TI,AB.
15	cross-over ADJ studies
16	cross ADJ over ADJ studies
17	crossover OR cross-over OR cross ADJ over
18	((singl$ OR doubl$ OR trebl$ OR tripl$) ADJ (blind$ OR mask$)).TI,AB.
19	placebos
20	placebo$.TI,AB.
21	random$.TI,AB.
22	research ADJ design
23	12 OR 13 OR 14 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24	23 NOT 10
25	11 OR 24
26	chronic ADJ renal ADJ failure OR chronic ADJ kidney ADJ disease OR renal ADJ dialysis OR predialysis OR pre-dialysis OR pre ADJ dialysis OR chronic ADJ renal ADJ insufficiency OR end ADJ stage ADJ renal ADJ disease
27	kidney ADJ failure ADJ chronic OR chronic ADJ kidney ADJ failure OR peritoneal ADJ dialysis
28	26 OR 27
29	28 AND (anaemia OR anemia OR anemic OR anaemic)
30	25 AND 29
31	limit set 30 YEAR > 1979

Embase RCT strategy

No.	Search term
32	exp ADJ clinical ADJ trial OR experimental ADJ clinical ADJ trial
33	comparative ADJ study
34	drug ADJ comparison
35	major ADJ clinical ADJ study
36	randomization
37	crossover ADJ procedure
38	double ADJ blind ADJ procedure
39	single ADJ blind ADJ procedure
40	double ADJ blind ADJ procedure
41	placebo
42	prospective ADJ study
43	((clinical OR controlled OR comparative OR placebo OR prospective OR randomi$4) ADJ (trial OR study)).TI,AB.
44	((clinical OR controlled OR comparative OR placebo OR prospective OR randomi$4) ADJ (trial OR study)).TI,AB.
45	((clinical OR controlled OR comparative OR placebo OR prospective OR randomi$4) ADJ (trial OR study)).TI,AB.
46	((clinical OR controlled OR comparative OR placebo OR prospective OR randomi$4) ADJ (trial OR study)).TI,AB.
47	(random$ ADJ (allocat$ OR allot$ OR assign$ OR basis$ OR divid$ OR order$)).TI,AB.
48	((singl$ OR doubl$ OR trebl$ OR tripl$) ADJ (blind$ OR mask$)).TI,AB.
49	(crossover$ OR cross ADJ over$).TI,AB.
50	32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49
51	chronic ADJ renal ADJ failure OR chronic ADJ kidney ADJ disease OR renal ADJ dialysis OR predialysis OR pre-dialysis OR pre ADJ dialysis OR chronic ADJ renal ADJ insufficiency OR end ADJ stage ADJ renal ADJ disease
52	kidney ADJ failure ADJ chronic OR chronic ADJ kidney ADJ failure OR peritoneal ADJ dialysis
53	51 OR 52
54	53 AND (anaemia OR anemia OR anemic OR anaemic)
55	50 AND 54
56	limit set 55 YEAR > 1983

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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

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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