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2008 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in Chronic Kidney Disease

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Abstract: The Japanese Society for Dialysis Therapy (JSDT) guideline committee, chaired by Dr Y. Tsubakihara, presents the Japanese guidelines entitled "Guidelines for Renal Anemia in Chronic Kidney Disease." These guidelines replace the "2004 JSDT Guidelines for Renal Anemia in Chronic Hemodialysis Patients," and contain new, additional guidelines for peritoneal dialysis (PD), non-dialysis (ND), and pediatric chronic kidney disease (CKD) patients.

Chapter 1 presents reference values for diagnosing anemia that are based on the most recent epidemiological data from the general Japanese population. In both men and women, hemoglobin (Hb) levels decrease along with an increase in age and the level for diagnosing anemia has been set at <13.5 g/dL in males and <11.5 g/dL in females. However, the guidelines explicitly state that the target Hb level in erythropoiesis stimulating agent (ESA) therapy is different to the anemia reference level. In addition, in defining renal anemia, the guidelines emphasize that the reduced production of erythropoietin (EPO) that is associated with renal disorders is the primary cause of renal anemia, and that renal anemia refers to a condition in which there is no increased production of EPO and serum EPO levels remain within the reference range for healthy individuals without anemia, irrespective of the glomerular filtration rate (GFR). In other words, renal anemia is clearly identified as an "endocrine disease." It is believed that defining renal anemia in this way will be extremely beneficial for ND patients exhibiting renal anemia despite having a high GFR. We have also emphasized that renal anemia may be treated not only with ESA therapy but also with appropriate iron supplementation and the improvement of anemia associated with chronic disease, which is associated with inflammation, and inadequate dialysis, another major cause of renal anemia.

In Chapter 2, which discusses the target Hb levels in ESA therapy, the guidelines establish different target levels for hemodialysis (HD) patients than for PD and ND patients, for two reasons: (i) In Japanese HD patients, Hb levels following hemodialysis rise considerably above their previous levels because of ultrafiltration-induced hemoconcentration; and (ii) as noted in the 2004 guidelines, although 10 to 11 g/dL was optimal for long-term prognosis if the Hb level prior to the hemodialysis session in an HD patient had been established at the target level, it has been reported that, based on data accumulated on Japanese PD and ND patients, in patients without serious cardiovascular disease, higher levels have a cardiac or renal function protective effect, without any safety issues. Accordingly, the guidelines establish a target Hb level in PD and ND

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patients of 11 g/dL or more, and recommend 13 g/dL as the criterion for dose reduction/withdrawal. However, with the results of, for example, the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) study in mind, the guidelines establish an upper limit of 12 g/dL for patients with serious cardiovascular disease or patients for whom the attending physician determines high Hb levels would not be appropriate.

Chapter 3 discusses the criteria for iron supplementation. The guidelines establish reference levels for iron supplementation in Japan that are lower than those established in the Western guidelines. This is because of concerns about long-term toxicity if the results of short-term studies conducted by Western manufacturers, in which an ESA cost-savings effect has been positioned as a primary endpoint, are too readily accepted. In other words, if the serum ferritin is <100 ng/mL and the transferrin saturation rate (TSAT) is <20%, then the criteria for iron supplementation will be met; if only one of these criteria is met, then iron supplementation should be considered unnecessary.

Although there is a dearth of supporting evidence for these criteria, there are patients that have been surviving on hemodialysis in Japan for more than 40 years, and since there are approximately 20 000 patients who have been receiving hemodialysis for more than 20 years, which is a situation that is different from that in many other countries. As there are concerns about adverse reactions due to the overuse of iron preparations as well, we therefore adopted the expert opinion that evidence obtained from studies in which an ESA cost-savings effect had been positioned as the primary endpoint should not be accepted unquestioningly.

In Chapter 4, which discusses ESA dosing regimens, and Chapter 5, which discusses poor response to ESAs, we gave priority to the usual doses that are listed in the package inserts of the ESAs that can be used in Japan. However, if the maximum dose of darbepoetin alfa that can currently be used in HD and PD patients were to be used, then the majority of poor responders would be rescued.

Blood transfusions are discussed in Chapter 6. Blood transfusions are attributed to the difficulty of managing renal anemia not only in HD patients, but also in end-stage ND patients who respond poorly to ESAs. It is believed that the number of patients requiring transfusions could be reduced further if there were novel long-acting ESAs that could be used for ND patients.

Chapter 7 discusses adverse reactions to ESA therapy. Of particular concern is the emergence and exacerbation of hypertension associated with rapid hematopoiesis due to ESA therapy.

The treatment of renal anemia in pediatric CKD patients is discussed in Chapter 8; it is fundamentally the same as that in adults. **Key Words:** Chronic dialysis, Erythropoiesis stimulating agent, Guidelines, Hemoglobin, Non-dialysis Chronic kidney disease, Pediatric chronic kidney disease, Quality of life, Renal anemia, Serum erythropoietin concentration.

Renal anemia is a major complication in patients with chronic kidney disease (CKD), particularly dialysis patients, and is a problem that has yet to be conquered. However, the feeling has been that this problem had been solved by the development of recombinant human erythropoietin (rHuEPO), which became available for use by dialysis patients in Japan in 1990, and immediately began to be used by approximately 80% of patients with unprecedented efficacy. Then, in 1994, an additional indication was approved for non-dialysis (ND) CKD patients, yielding a dramatic reduction in blood transfusions given when starting dialysis and affording various other beneficial effects, including suppression of the progression of renal failure and an improvement in patient quality of life (QOL). An improved vital prognosis following the start of dialysis was also reported. Moreover, new problems were identified with the target hemoglobin (Hb) levels in ESA therapy and also with the criteria for the concomitant use of iron preparations. In order to find solutions to these problems, clinical studies were conducted, and guidelines based thereon were formulated and revised in various countries and regions around the world. Although the majority of the guidelines of different countries and regions cite virtually identical evidence, differences may be seen. In all of the guidelines outside of Japan, the target Hb levels for ESA therapy in hemodialysis (HD), peritoneal dialysis (PD), and ND patients are almost identical.

In 2001, there was a groundswell of momentum for the preparation of guidelines in Japan as well, and the First Renal Anemia Treatment Guideline Preparation Working Group (WG) of the Japanese Society for Dialysis Therapy (JSDT), chaired by Professor F. Gejyo, was formed. The working group first assessed the Western guidelines that had already been prepared, as well as the evidence on which they had been based, and then explored what data were available in Japan. However, since there was virtually no evidence that was suitable for citing in Japan, the use of the Western guidelines was one option that was considered. On the other hand, given that the dialysis and blood collection methods that are used in the West in HD patients are different than those used in Japan, the working group decided against adopting the Western guidelines in their present form. There was also considerable debate about whether or not to

handle PD and ND patients in the same way as HD patients, whose Hb values change markedly from before to after hemodialysis. In the end, renal anemia treatment guidelines were established only for HD patients. The working group also proposed preparing its own evidence on HD patients. Although this is not usually how guidelines are prepared, there was no other way of preparing Japan-specific guidelines, and this plan was accepted by all the members of the working group. In order to prepare the evidence, the results of the statistical surveys conducted by the JSDT Committee of Renal Data Registry (CRDR) at the end of each year at all dialysis facilities in Japan were analyzed retrospectively. Based on the evidence obtained, finally, in 2004, the "Guidelines for Renal Anemia in Chronic Hemodialysis Patients" were completed.

The following year, in December 2005, in addition to revising the 2004 guidelines, the Second Renal Anemia Treatment Guidelines Working Group, chaired by Dr Y. Tsubakihara, was formed for the purpose of preparing renal anemia treatment guidelines for PD, ND, and pediatric CKD patients. Most of the members of the first working group were retained, and JSDT CRDR members and hematology specialists were added. In addition, in order to prepare guidelines for ND, PD, and pediatric CKD patients, the cooperation of the Japanese Society of Nephrology (JSN), the Japanese Society of Peritoneal Dialysis (JSPD), and the Japanese Society for Pediatric Nephrology (JSPN) was obtained. Each society was invited to send a representative to join the working group as a member, and a working group with 16 members was thereby formed. In January 2006, at a meeting with the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Guideline Preparation Committee members, we were reminded anew of the differences in the patient backgrounds between the patient populations in the large-scale clinical studies conducted in the US and the patients that we see in the clinical setting in Japan. We therefore determined that, as a matter of policy, as had been done by the First Working Group, we would emphasize Japanese evidence wherever possible.

We then initiated a search of the literature and communications amongst ourselves, held 13 meetings of the working group, exchanged opinions with the Japan Bio-Iron Society (JBIS) regarding the use of iron preparations, held a public hearing with JSDT members, posted the draft guidelines on the JSDT home page, compiled numerous opinions, including those of JSDT members, reported the overall framework at the JSDT Annual Meeting in June 2008, obtained approval, and published the guidelines in that same year, in the October issue of *J Jpn Soc Dial Ther*, the Japanese-language journal of the JSDT.

In these guidelines, the cited papers are divided into three levels, A, B, and C, in order of decreasing strength of the evidence contained therein. So that the recommendations shown in the boxes in the guidelines are easier to understand, they have also been divided into three levels: Strong Recommendation; Moderately Strong Recommendation; and Opinion (recommendation as the committee's opinion). Furthermore, evidence from Japan and recommendation levels that are based on evidence from Japan are indicated by asterisks.

It is our sincere hope that these guidelines contribute to the improved treatment of anemia in CKD patients in Japan. In the future, these guidelines should be revised as necessary as new evidence is obtained, and after giving due consideration to the opinions of JSDT, JSN, JSPD, and JSPN members and other relevant parties.

CHAPTER 1

Diagnosis, criteria, and treatment of renal anemia

1. Hemoglobin (Hb) levels in healthy adults depend on age, gender, and race. Therefore, the criteria for anemia must be established considering these factors. (Table 1-1).
2. "Hb levels" should be used as reference values for diagnosis of anemia (Strong recommendation).
3. In diagnosing anemia, various disorders causing anemia must be differentiated. Mean corpuscular volume (MCV) is a useful index (Opinion).
4. The primary cause of renal anemia is decreased erythropoietin (EPO)-producing capacity associated with renal disorder. The diagnosis of renal anemia is made for the first time when no other diseases causing anemia are found. In some non-dialysis (ND) patients, measurement of serum EPO level may be useful (Opinion*).

1. General diagnostic criteria for anemia

The reference values for diagnosis of anemia in Japanese are Hb levels of <13.5 g/dL (hematocrit [Ht] levels <40%) in adult males and <11.5 g/dL in adult females (Ht levels <35%) (Recommendation*).

(1) Definition of anemia. Anemia is not a disease name but a condition in which the Hb level is decreased. Hb transports oxygen to each body tissue; therefore, when anemia occurs, oxygen supply to tissues is reduced, and the physical function is influenced in accordance with the severity of anemia.

TABLE 1-1. *Mean hemoglobin levels in Japanese males and females and the criteria for anemia*

	Miwa Hematology, 3rd edition (1)	Chronological scientific (2)	
	19–60 years	60–69 years	70–79 years
Male g/dL (Mean ± SD)	15.3 ± 0.9	13.8 ± 0.9	13.5 ± 1.2
Female g/dL (Mean ± SD)	13.3 ± 0.9	12.5 ± 1.0	12.2 ± 0.9
Reference Levels for Diagnosis			
Male g/dL (Mean – 2SD)	13.5	12.0	11.1
Female g/dL (Mean – 2SD)	11.5	10.5	10.4

SD, standard deviation.

(2) Diagnostic criteria. There have been few textbooks which provide diagnostic criteria for anemia based on measurement results in healthy Japanese. When mean – 2SD (standard deviation) values of Hb or Ht levels in Japanese judged to be healthy by certain standards are defined as reference values for diagnosis of anemia, the values are as shown in Table 1-1 and 1-2 (1,2) (Level B*). As indicated in the tables, the reference values for diagnosis of anemia differ between males and females and among the age groups. Table 1-3 lists common reference values for diagnosis of anemia in Europeans and Americans which are provided in the European Best Practice Guidelines (EBPG) (3) and US (K/DOQI) (4) guidelines for renal anemia (hereinafter abbreviated as the European and US guidelines).

In Japan, the "2004 Japanese Society for Dialysis Therapy Guideline for Renal Anemia in Chronic Hemodialysis Patients" (2004 Guideline) (5) also specified the diagnostic reference values, but they were revised as shown in Table 1-1 and 1-2 because of revisions to the supporting data. The provided age-specific Japanese diagnostic reference values for both males and females aged 60 years or older tend to be lower than those in Europe and the US.

In blood tests with an automatic analyzer which is now commonly used, the red blood cell count, Hb level, and MCV are obtained as measured values, and the Ht level as a calculated value. Unlike Hb levels which remain relatively constant after blood sampling, the values of MCV and Ht change due to various influences occurring with time after sampling (3) (Level A). Therefore, unless Ht levels are measured directly, the use of Hb levels in diagnosing anemia is recommended.

TABLE 1-2. *Mean hematocrit levels in Japanese males and females and the criteria for anemia*

	Miwa Hematology, 3rd edition (1)	Chronological scientific (2)	
	19–60 years	60–69 years	70–79 years
Male % (Mean ± 2SD)	45.0 ± 2.5	42.0 ± 2.8	40.9 ± 3.6
Female % (Mean ± 2SD)	40.0 ± 2.5	37.6 ± 3.1	36.9 ± 2.9
Reference Levels for Diagnosis			
Male % (Mean—2SD)	40.0	36.4	33.7
Female % (Mean—2SD)	35.0	31.4	31.1

TABLE 1-3. *European Best Practice Guidelines (EBPG) (3) and Kidney Disease Outcomes Quality Initiative (K/DOQI) (4) criteria for anemia*

	EBPG	K/DOQI
Adult male	Hb level <13.5 g/dL	Hb level <13.5 g/dL
Adult female	Hb level <11.5 g/dL	Hb level <12.0 g/dL
Male aged >70 years	Hb level <12.0 g/dL	

Hb, hemoglobin.

TABLE 1-4. *Differential diagnosis of anemia*

Microcytic	iron-deficiency anemia, ACD, sideroblastic anemia, thalassemia, atransferrinemia
Normocytic	renal anemia, hemolytic anemia, aplastic anemia, PRCA, myelodysplastic syndrome, ACD, leukemia
Macrocytic	renal anemia, megaloblastic anemia (Vitamin B12 deficiency, folic acid deficiency), hepatopathy, hypothyroidism, aplastic anemia, myelodysplastic syndrome, and drug-related disorders in DNA synthesis

ACD, anemia of chronic disease; PRCA, pure red cell aplasia.

2. Differential diagnosis of anemia and examination items

In diagnosing anemia, various disorders causing anemia must be differentiated. In the differential diagnosis of anemia, the type of anemia should be classified into microcytic, normocytic, and macrocytic categories based on MCV. (Opinion).

In diagnosing renal anemia, differentiation of various diseases causing anemia is needed. To make a differential diagnosis of anemia in clinical practice, classification of microcytic, normocytic, and macrocytic categories based on MCV is clinically useful. The disorders classified according to MCV values are shown in Table 1-4.

The examination items necessary for the differentiation of the individual diseases are summarized in Table 1-5. The items include a peripheral blood test, parameters of iron metabolism, biochemistry, a serological test, serum EPO level, bone marrow examination, and vitamin/hormone measurements. It is important to select the examination items in accordance with disorders to be differentiated.

3. Definition of renal anemia

1. Renal anemia refers to anemia caused by decreased renal EPO-producing capacity due to renal disease.
2. Other causes of renal anemia include shorter lifespan of red blood cells, hypo-responsiveness of erythroid progenitor cells to EPO, malnutrition, and residual blood in the dialysis blood circuit in hemodialysis (HD) patients.

In a limited sense, renal anemia refers to a condition in which the Hb level cannot be maintained above the reference value because of decreased EPO-producing capacity of the kidney which is not attributable to causes other than renal disease (Level B*) (6,7). However, in broadly-defined renal anemia, causes other than the decreased EPO-producing capacity due to renal disease (such as shorter life span of red blood cells) are also taken into consideration. In Japan, it is reasonable to regard values in Table 1-1 and 1-2 as the reference values of Hb depending on the sex and age.

Reference values of a decrease in glomerular filtration rate (GFR) at which the incidence of renal anemia abruptly increases are approximately serum creatinine (Cr) of 2 mg/dL or more, or creatinine clearance (Ccr) of less than 20 to 35 mL/min (chronic kidney disease [CKD] stage 4 to 5) (8–10) (Level C). In patients with diabetic nephropathy, renal anemia is known to occur at an earlier stage than in those with non-diabetic nephropathy, and the rough indication of such occurrence is Ccr of less than 45 mL/min (3) (Level C).

However, the presence of renal anemia cannot be ruled out even in patients with relatively higher GFR. Given that "renal anemia is an endocrine disease", factors responsible for anemia other than decreased renal EPO production due to renal disease must be excluded before diagnosing renal anemia. Nevertheless, in most cases, renal anemia may be diagnosed when a decrease in GFR is within the ranges described above and no other causes of anemia (particularly, iron deficiency anemia, etc.) are found.

Although measurement of serum EPO level is considered to be of less diagnostic significance in patients with end stage renal failure (3–5), it should be con-

TABLE 1-5. *Useful examination items for the differential diagnosis of anemia*

1. RBC, Hb, Ht, and MCV
2. Reticulocytes
3. Parameters of iron metabolism (Fe, UIBC, Ferritin, and TSAT)
4. Leukocyte count, WBC fraction, and platelet count
5. Occult blood in stool
6. Blood biochemistry, CRP, and protein fraction
7. Serum EPO level
8. Bone marrow test
9. Vitamin B_{12}, folic acid, Zn, and Cu
10. Coombs' test and haptoglobin
11. Blood aluminum level
12. Thyroid function
13. Parathyroid function (intact PTH)
14. Others

TSAT (%) = [serum iron (μg/dL)/TIBC (μg/dL)] × 100; CRP, C-reactive protein; EPO, erythropoietin; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; PTH, parathyroid hormone; RBC, red blood cell; TSAT, transferrin saturation; UIBC, unsaturated iron binding capacity; WBC, white blood cell.

sidered when no other causes of anemia are found despite a relatively mild decrease in GFR (3,6) (Level B). The national health insurance in Japan covers such measurement when conducted before the start of treatment with erythropoiesis stimulating agents (ESAs). Renal anemia can be diagnosed when, although the GFR is relatively preserved, the Hb level is low and no other causes of anemia or no increased serum EPO level is observed. Re-analysis of data from Japanese clinical studies of recombinant human erythropoietin (rHuEPO) in ND patients (conducted by Chugai Pharmaceutical Co., Ltd. and Kirin Pharma Company, Ltd.; both studies included patients with Cr of 2 mg/dL or more, or Ccr of 30 mL/min, or less and Hb of less than 10 g/dL) revealed that the mean ± standard deviation (SD) of serum EPO level in 422 patients was 22.7 ± 12.1 mIU/mL (range 5.0 to 151.0 mIU/mL) and that the mean + 2SD was 46.9 mIU/mL (7). In ND patients with Hb levels of less than 10 g/dL and lower serum EPO levels than this value, renal anemia is suspected irrespective of GFR (Level C*).

In Japan, most laboratory testing companies use the radioimmunoassay (RIA) method to measure the EPO level, while the enzyme-linked immunoassay (ELISA) method is mainly used in Europe and the US. Since there have been no studies which addressed cross validation of these methods, data obtained from the different methods cannot be simply compared. The values previously described are based on RIA. The method used for measurement should be confirmed prior to outsourcing the test. In the laboratory testing companies below, all use the identical reagent (Recombigen EPO kit*). Slight differences in their reference values (healthy individuals without anemia) are considered to cause no problem in measurement (as of September 2008).

1. SRL, Inc. (Tokyo, Japan): 8–36 mIU/mL
2. Mitsubishi Chemical Medience Corp. (Tokyo, Japan): 9.1–32.8 mIU/mL
3. BML, Inc. (Tokyo, Japan): 29.0 mIU/mL or lower
4. FALCO biosystems Ltd. (Tokyo, Japan): 9.1–32.8 mIU/mL
5. Health Sciences Research Institute, Inc. (Tokyo, Japan): 8–36 mIU/mL
6. Koto Biken Medical Laboratory (Ibaraki, Japan): 8.0–36.0 mIU/mL

*Manufactured and distributed by: Mitsubishi Kagaku Iatron, Inc.

Reference material for calibration: WHO 2nd IRP (HUM, urinary/Bioassay 67/343 (194).

4. Treatment of renal anemia

1. When a definite diagnosis of renal anemia is reached and criteria for treatment are met, ESA therapy should be started (Strong recommendation).
2. Treatment with iron preparations required for erythropoiesis should be used concomitantly (Strong recommendation).
3. In maintenance HD patients, efforts should be made to purify the dialysate, and adequate dialysis should be conducted (Strong recommendation).
4. In patients with malnutrition or inflammation, aggressive treatment for them should be conducted (Strong recommendation).

The first-line treatment of renal anemia is ESAs. Anabolic steroids covered by the national health insurance in Japan should not be used because of adverse reactions (4) (Level A). In special cases, including those where no ESA preparations can be used, anabolic steroids should be used after adequate informed consent is obtained. Causes of renal anemia include uremic toxin or endotoxin, malnutrition, shorter life span of red blood cells due to inflammation and other factors, poor responsiveness of erythroid progenitor cells to EPO, and residual blood in the hemodialysis circuit of HD patients. The EBPG recommends that adequate dialysis doses should be Kt/V of 1.2/week or more for HD patients and 1.8/week or more for PD patients (3) (Level B). However, the more recent PD guidelines published in Europe and the US (11,12) recommend Kt/V of 1.7 or more as the minimum target.

In HD patients, purification of the dialysate and long-term dialysis are effective not only in treating renal anemia but also in improving survival prognosis (3) (Level B). Since malnutrition and inflammation are also among the causative factors of renal anemia, treatment for these events should be conducted in combination with ESA therapy (3) (Level B). In addition, hemodiafiltration (HDF) is believed to be more effective than ordinary HD (3) (Level B).

CHAPTER 2

Target Hb level and criteria for starting ESA therapy

HD patients

1. We recommend that ESA therapy in patients undergoing HD should target an Hb level of 10 to 11 g/dL in blood samples collected in the supine position before HD at the beginning of the week (2 days from the last dialysis) (Moderately strong recommendation*). Hb levels exceeding 12 g/dL should be the criteria for dose reduction or interruption of ESAs (Opinion*).

2. When the Hb level is less than 10 g/dL in several test results following a diagnosis of renal anemia, ESA administration should be initiated. (Opinion*).
3. In relatively young patients with high activity levels, an Hb level of 11 to 12 g/dL should be maintained. (Opinion*). Hb levels exceeding 13 g/dL should be the criteria for dose reduction or interruption of ESAs (Opinion*). When the Hb level is less than 11 g/dL in several test results, ESA administration should be initiated. (Opinion*).

PD and ND patients

1. We recommend that ESA therapy in PD and ND patients should target an Hb level of 11 g/dL or higher (Moderately strong recommendation *). If the Hb level exceeds 13 g/dL, dose reduction or interruption should be considered (Opinion*).
2. When the Hb level is less than 11 g/dL in several test results following a diagnosis of renal anemia, ESA administration should be initiated. (Opinion*).
3. If the patient has a history of serious cardiovascular disease or complications or if it is medically necessary, dose reduction or interruption should be considered if the Hb level exceeds 12 g/dL (Moderately strong recommendation*).

1. Background of setting the target Hb level (Ht level) for ESA therapy

Although the Europe and US guidelines for renal anemia (3,4) provide identical target Hb levels for HD, PD, and ND patients, the 2004 Guideline (5) restricted its application to HD patients, and the setting of Hb levels for PD and ND patients was postponed. This was primarily because Hb levels in HD patients vary depending on hemoconcentration due to fluid removal caused by HD (13,14). In the US, an increase of 1 to 3 g/dL of Hb levels after HD has been reported (13) (Level B). In addition, it is known that the dry weight (DW) of Japanese HD patients is less than that of Westerners and that many Japanese patients have high weight gain rates (15) (Level B). Therefore, it is expected that the change of Hb levels between pre-HD and post-HD is larger in Japanese patients than in Europeans and Americans. Taking such changes of Hb levels into consideration, the Europe and US guidelines recommend that sampling for Hb levels in HD patients should be conducted midweek as the weight gain is smaller (4). However in Japan, most institutions conduct blood sampling at the beginning of the week, and the statistical survey data by the Japanese Society for Dialysis Therapy (JSDT) are also based on this sampling schedule. Therefore, the increase in Hb after HD cannot be disregarded. At the end of 1997, the statistical survey results by the JSDT showed that the percentage of patients with Ht levels of 40% or higher reached 12.7% after HD compared to 2.0% before HD (16) (Level A*).

For these reasons, the 2004 Guidelines in Japan restricted its application to HD patients (5). Another major reason for such a restriction was that there was very little information on PD or ND patients. Compared to anemia treatment in Europe and the US, circumstances such as limitations of types and doses of ESAs covered by the national health insurance resulted in markedly lower Hb levels (17). Furthermore there were no large-scale studies to set the target Hb level. After 2004, the target Hb level in the US K/DOQI guidelines was revised twice. In the update in 2006 (4), the upper limit of Hb levels was removed as in the EBPG (3) (although it included the statement that there is no evidence to recommend that Hb levels be maintained at 13 g/dL or higher). In 2007, the guideline was revised again based on the results of large-scale, randomized, controlled trials (RCTs), including the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study in ND patients published at the end of 2006 (18) in addition to consideration of the US Food and Drug Administration (FDA) alert (13). In this update, given the Hb target should be set by taking the conditions of individual patients into account, it was specified that the Hb target should generally be in the range of 11 to 12 g/dL and should not be greater than 13 g/dL. The EBPG recommends that the target Hb level should be higher than 11 g/dL, without setting the upper limit. However, it also states that the target Hb level for patients with congestive heart failure and severe cardiovascular disease should be 11 to 12 g/dL (3) (Level A).

Looking back on changes in Japanese anemia treatment after the publication of the 2004 Guidelines, the results of the statistical surveys by the JSDT at the end of 2005 and 2006 (19,20) revealed that approximately 40% of HD patients still had Hb levels of less than 10 g/dL as the lower limit of the Hb target recommended by the 2004 Guidelines (Level A*). This implied that the 2004 Guidelines had not been understood or adequately penetrated. In addition, in association with the revision of medical treatment fees for HD patients in 2006, the cost of ESAs was included in a flat payment system. Because of this event, the survey results at the end of 2006 showed that as compared to the survey at the end of 2005 (19), the used dose of rHuEPO had decreased (20) and that patients with severe anemia tended to have higher iron stores. Given such influence of this flat payment system, more efficient ESA therapy will be pursued further in the future. On the other hand, a long-acting ESA, darbepoetin alfa (DA), has been approved also in Japan for the treatment of renal anemia in HD and PD patients and clinical studies in ND patients are being conducted presently. In addition, clinical studies of another long-acting ESA, continuous erythropoietin receptor activator (CERA),

are also ongoing in HD, PD, and ND patients. Before publication of the 2004 Guidelines, the Japanese target Hb levels for HD, PD, and ND patients were all approximately 10 g/dL (Ht: approximately 30%), which was the target Hb level specified in the package insert of rHuEPO. The same criteria were also recommended in the report on HD patients by the 1990 Health Sciences Research Committee (chairperson; Yoshihei Hirasawa) (21). However, the Japanese clinical studies of DA provided higher target Hb levels than before separately in HD, PD and ND patients based on the Europe and US guidelines. In these studies, no safety issues were observed, and favorable results were reported in QOL and cardiac function. As a result, an increased Hb (Ht) target of approximately 11 g/dL (33%) was provided in the package insert of DA. The results of these studies targeting higher Hb levels are important for they were obtained from Japanese patients with chronic kidney disease (CKD). Therefore, this Guideline acknowledged these findings to change the criteria for ESA dose reduction or interruption in HD patients and also to set target Hb levels for PD and ND patients.

2. Target Hb level for HD patients

In the Europe and US guidelines, the target Hb levels are set at 11 to 12 g/dL or higher, based on the results of several endpoints, including survival rate, morbidity, left ventricular mass index (LVMI), QOL, physical activity level, number (length) of hospitalizations, other cognitive abilities, metabolic function, and sleep pattern (3,4) (Level B).

On the other hand, a slight ethnic difference is observed in the normal Hb (Ht) level between Japanese and Westerners, and it is slightly lower in the Japanese elderly (see Chapter 1). However, there are only a few studies that address the setting of Hb target for rHuEPO therapy in Japanese that are worth citing. In the annual statistical survey results by the JSDT, evaluation of independent factors affecting 1-year survival revealed that the optimal Ht level was 30 to 35%. However, this evaluation was limited to the short-term prognosis of 1-year survival and the evaluated Ht range was divided into intervals as broad as 5%. For these reasons, the Ht level with an interval of 5% is considered inappropriate for recommendation.

In this context, using the statistical survey data by the JSDT, we stratified Ht levels obtained at the end of 1995 (55 855 patients, including non-rHuEPO users) into 3% intervals as in Europe and the US to examine the effect of Ht levels on 5-year survival. The result revealed that the relative risk (RR) of Ht levels between 27 and 33% was lowest when adjusted by age, sex, primary disease, weight gain rate, and Kt/V (Table 2-1). Analyses by age and primary disease also indicated that survival prognosis was most favorable in the group with Ht levels between 30 and 33%, although a slight difference was observed between the results of these analyses (5) (Level B*).

TABLE 2-1. *Influence of the hematocrit (Ht) level prior to hemodialysis (HD) at the end of 1995 on the 5-year survival rate* (5) *(corrected by age, gender, underlying disease, Kt/V urea, and percent weight loss during HD)*

Ht level prior to HD (%)	RR (95%CI)	*P*-value
<24	1.714 (1.610–1.82)	0.0001
24 ≤ <27	1.219 (1.159–1.28)	0.0001
27 ≤ <30	1.026 (0.980–1.07)	0.2722
30 ≤ <33	1.000 (control)	control
33 ≤ <36	1.112 (1.050–1.178)	0.0003
36 ≤ <39	1.254 (1.156–1.362)	0.0001
39≤	1.306 (1.185–1.440)	0.0001

CI, confidence interval; RR, relative risk.

Hirasawa et al. retrospectively investigated a 3-year prognosis in 2654 Japanese maintenance dialysis patients receiving rHuEPO at 22 institutions, based on mean Ht levels divided into 3% intervals. Evaluation of the survival prognosis using the Ht levels adjusted by age, sex, primary disease, concomitant disease, albumin (Alb) level, and other parameters revealed that the prognosis was most favorable in the group with Ht levels between 30 and 33% (Table 2-2) (23) (Level B*).

Taken together, the results described above suggested that the target Hb level for rHuEPO therapy is 10 to 11 g/dL (Ht level: 30 to 33%) (5) when evaluated in terms of survival prognosis, (Level B*). However, when limited to younger individuals aged 35 to 45 years, analysis of 5-year survival using the statistical data by the Japanese Society for Dialysis Therapy revealed that the RR in the group with Ht levels of 33 to 36% was as low as 0.78, with no significant difference compared to the group with Ht levels between 30 and 33% because of the limited number of patients. Therefore, the 2004 Guidelines recommended the Hb level of 11 to 12 g/dL (Ht level of 33 to 36%) only for relatively younger, active individuals with fewer arteriosclerotic lesions (5) (Level C*).

It was presumed that the difference in the target Hb level (Ht level) between the Japanese and Europe or US guidelines could be explained by differences in the ethnicity, day of blood sampling, body position during blood sampling, and other factors. To test this hypothesis, two types of additional studies below were conducted.

TABLE 2-2. *Influence of the hematocrit (Ht) level/patient characteristics on the 1-year and 3-year mortality rates*

	1-year mortality rate			3-year mortality rate		
Background factor	RR	95%CI	*P*-value	RR	95%CI	*P*-value
Group1 (Ht ≥ 36%)	0†	0†	0.9694	0.915	0.405–2.072	0.8321
Group2 (33% ≤ Ht < 36%)	0.605	0.320–1.146	0.1231	1.111	0.816–1.514	0.5036
Group3 (30% ≤ Ht < 33%)	0.447	0.290–0.689	0.0003	0.677	0.537–0.855	0.001
Group4 (27% ≤ Ht < 30%)	1					
Group5 (Ht < 27%)	1.657	1.161–2.367	0.0054	1.604	1.275–2.019	<0.0001
Age:1-year increase	1.029	1.016–1.043	<0.0001	1.048	1.039–1.056	<0.0001
Gender:Female	0.85	0.620–1.167	0.3159	0.758	0.629–0.913	0.0036
Underlying disease						
Diabetic nephropathy	0.958	0.671–1.368	0.815	1.354	1.114–1.647	0.0024
Complications						
Heart failure	1.224	0.883–1.696	0.2256	1.596	1.319–1.932	<0.0001
Occlusive arteriosclerosis	1.281	0.844–1.944	0.2456	1.639	1.302–2.063	<0.0001
Cerebrovascular diseases	1.683	1.142–2.480	0.0085	1.522	1.211–1.913	0.0003
Digestive disorders	1.190	0.870–1.628	0.2759	0.907	0.753–1.093	0.3051
Hepatobiliary system disorders	1.438	0.978–2.117	0.0651	1.264	0.997–1.603	0.0528
Cancer	1.725	0.943–3.156	0.0768	2.716	1.910–3.862	<0.0001
Alb						
<3.5 g/dL	1					
≥3.5 g/dL	0.424	0.307–0.585	<0.0001	0.603	0.501–0.726	<0.0001

†No deaths among $N = 36$. This table is quoted from the study described by Hirasawa et al. (23). Alb, albumin; CI, confidence interval; RR, relative risk.

In the JSDT survey of the current status, most of the Ht levels were obtained at the beginning of the week, while in Europe and the US, results of blood sampled at midweek are used. Therefore, it is expected that there is an influence from a difference in the weight gain rate between Japan and Western countries. In this context, a comparison between peripheral blood data obtained on Monday and Wednesday from the same patient was conducted in 247 Japanese patients undergoing HD three times weekly (Monday, Wednesday, and Friday) at a single institution. The result showed that the Ht level on Monday corresponded to 99.1% of that on Wednesday (Table 2-3) (5) (Level C*).

In addition, it is known that the patient's body position during blood sampling affects the Ht level. A study conducted in Japan has shown that in HD patients' blood sampled in a supine position had a greater decrease in Ht levels than in healthy individuals (24). In Europe and the US, many HD patients receive dialysis while sitting in a chair bed, whereas those in Japan receive dialysis in a supine position. Thus, the body position during blood sampling is different. In this context, in 99 HD patients with little residual renal function who were receiving dialysis three times weekly at four institutions, peripheral blood was taken while they were in a sitting position shortly after admission to the laboratory test room. Data on these peripheral blood samples were compared to those obtained after they rested in a supine position for approximately 10 min. The result revealed that the Ht level of the blood samples in a supine position was 94.3% of that in a sitting position (Table 2-4) (5) (Level C*).

TABLE 2-3. *Differences between the days of blood collection* (5). *(Comparison of the hematological data between Monday and Wednesday of the same week in 247 patients undergoing dialysis on Monday, Wednesday and Friday)*

	Monday	Wednesday	Difference
BW (kg)	53.1 ± 0.7	52.6 ± 8.9	0.6
Hb level (g/dL)	10.4 ± 1.0	10.5 ± 1.3	0.15
Ht level (%)	32.3 ± 3.5	32.6 ± 4.4	0.36
TP (g/dL)	6.7 ± 0.5	6.7 ± 0.5	0.05

Values are reported as Mean ± SD. BW, body weight; Hb, hemoglobin; Ht, hematocrit; TP, total protein.

A simple calculation with the two factors described above revealed that Ht levels of 33 to 36% in Europe and the US correspond to those of 30.8 to 33.6% in Japan.

However, the studies on the survival prognosis mentioned above were all retrospective and based on Ht levels during a certain period.

In order to set target Hb levels, large-scale, prospective RCTs with endpoints such as survival prognosis and QOL will be needed in the future.

Although not an RCT, there is a report on the results of a prospective, open-label clinical study in which DA was administered for approximately one year to 513 HD patients in maintenance phase receiving rHuEPO (25). In this study, a target Hb level

TABLE 2-4. *Comparison of the Ht level between the sitting position and the supine position in patients undergoing HD* (5)

Results	Sitting position	Supine position
Cr level (mg/dL)	10.9 ± 2.8	10.9 ± 2.8
BUN (mg/dL)	74.4 ± 12.4	74.0 ± 12.2
Hb level (g/dL)	10.7 ± 1.0	10.1 ± 0.9 (94.4%)
Ht level (%)	33.2 ± 3.0	31.3 ± 2.9 (94.3%)
TP (g/dL)	6.7 ± 0.5	6.3 ± 0.5 (94.0%)

Examination in Osaka prefecture Hospital and three other hospitals. Examination was conducted in 99 patients with little residual renal function who were undergoing HD three times a week in four hospitals, and from whom informed consent was obtained. We collected blood via the venous route in the sitting position immediately after arrival, and via the arterial route about 10 min after they were placed in the supine position. The levels were compared. Values are reported as Mean ± SD. BUN, blood urea nitrogen; Cr, reatinine; Hb, hemoglobin; Ht, hematocrit; TP, total protein.

higher than that recommended by the 2004 Guideline was used; specifically, the study Hb target was set at 11 to 12 g/dL (10 to 13 g/dL as therapeutic window). The mean Hb level after the start of the DA treatment was maintained at approximately 11 g/dL, but no safety issues were observed. In addition, we compared the medical outcomes study 36-item short-form health survey (SF-36) of QOL assessment at the start of DA treatment and when the Hb level increased to 11g/dL or higher. The result revealed that all scores showed a tendency toward an increase after the DA treatment. Particularly in patients in whom the Hb level increased by 1 g/dL or greater and reached 11 g/dL or higher, the score of vitality significantly increased as compared to those in whom the Hb level increased by less than 1 g/dL and remained lower than 11 g/dL (26) (Level B*). These results may suggest that target Hb levels for HD patients which are higher than the conventional reference value cause no safety issues and are more useful.

Based on these clinical study results, the package insert of DA states the target Hb level of approximately 11 g/dL, which is higher than the conventional target of approximately 10 g/dL. This explains the current double structure of Japanese target Hb level for ESA therapy in the package inserts, which consists of approximately 10 g/dL for rHuEPO and approximately 11 g/dL for DA.

In a prospective, open-label clinical study in which 145 HD patients in maintenance phase on rHuEPO received CERA for approximately one year, the Hb target was set at 10 to 12 g/dL. The result showed that the mean Hb level after the CERA administration was maintained at approximately 11 g/dL, and no safety issues were observed (27) (Level B*).

In the 2004 Guidelines, the Hb targets were strictly set within narrow ranges; 10 to 11 g/dL and 11 to 12 g/dL for active younger patients. However, Hb levels of patients vary by various factors, and the variation range of approximately 1 g/dL is considered acceptable in clinical practice. Although it is important to pay attention to the upper limit of Hb levels during the ESA use, excessive adherence to this upper limit may cause Hb levels to be maintained at a relatively lower level. This probably leads to the result mentioned above that the number of patients with Hb levels of less than 10 g/dL have not yet decreased. As described above, the clinical study results of DA and CERA have shown no safety issues with the high therapy range of Hb from 10 to 13 g/dL. Therefore, as criteria for dose reduction or interruption, in addition to target Hb levels, we decided to recommend Hb levels are more than 12 g/dL, and more than 13 g/dL for active younger patients with mild vascular lesions.

A large-scale, prospective, observational study of rHuEPO is being conducted presently in HD patients to investigate Hb targets from the viewpoint of survival prognosis (22). This result is notable, but a RCT in HD patients to investigate Hb targets is also needed in Japan.

3. Target Hb level for PD and ND patients

The Europe and US guidelines for renal anemia (3,13) provide the same Hb targets for HD, PD, and ND patients. However, there is no scientific evidence for handling these patient subgroups equally, since Hb levels of PD and ND patients are more stable than those of HD patients which change before and after HD. However, only a few studies have been conducted regarding target Hb levels for PD or ND patients in Japan. Earlier clinical studies of rHuEPO in Japanese ND patients have suggested that an increase in Hb levels to approximately 12 g/dL or higher would be useful in improving cardiac function (28) or protecting renal function (29). An increase in Ht levels to a range of 32% to 39% by a dose increase of rHuEPO has been reported to significantly improve LVMI without safety issues (28) (Level B*). In other research which prospectively investigated effects on the renal function in ND patients randomized to rHuEPO group or untreated group, it has been reported that deterioration of the renal function (as evaluated by doubling of Cr) was significantly prevented in the rHuEPO group (the Ht level increased from 27% to 32%) compared to that in the untreated group (29) (Level A*). Furthermore, in postmarketing clinical studies of rHuEPO in ND

patients, increasing Ht levels from 28% to a range of 33 to 36% has been reported to improve LVMI and QOL (30,31) (Level B*).

As described above, intravenous administration of DA in HD and PD patients was approved in 2007, and clinical study results in PD and ND patients with higher target Hb levels than before has been reported. Regarding PD patients, in a clinical study of intravenous DA in rHuEPO-treated and treatment-naïve patients, it has been reported that Hb levels of approximately 11 g/dL could be maintained as in HD patients, without safety issues (32). In another clinical study of intravenous and subcutaneous DA with the Hb target of 11 to 13 g/dL, it has been reported that Hb levels maintained at approximately 12 g/dL caused no safety issues (33) (Level B*). Regarding ND patients, in a clinical study of subcutaneous DA in those without serious cardiovascular complications, the target Hb level was set at 12 to 13 g/dL. The Hb levels were increased from approximately 10 g/dL to 12 g/dL (12 to 16 weeks after treatment), and as a result, a significant improvement in QOL and LVMI was reported without safety issues (34). This study was continued for a long period of time, during which the Hb level was maintained at approximately 12 g/dL. Consequently, LVMI showed further improvement at week 32 (35) (Level B*). Subsequently results of a long-term randomized controlled clinical study in groups with target Hb levels of 11 to 13 g/dL (DA group) and 9 to 11 g/dL (rHuEPO group) were reported (36,37). Among the DA group patients in this study, Hb levels of 11 to 13 g/dL were the target for those who had no serious concomitant diseases and 11 to 12 g/dL for those who had serious concomitant cardiovascular diseases. The result revealed that, after anemia correction, the Hb level was maintained at approximately 12 g/dL in the DA group and at approximately 10 g/dL in the rHuEPO group. Concerning efficacy, QOL (SF-36) and LVMI significantly improved in the DA group (target Hb level set at 11 to 13 g/dL) compared to the rHuEPO group (target level set at 9 to 11 g/dL) (36). Concerning safety (37), there was no difference between the two groups (Level A*).

Furthermore, in a clinical study of subcutaneous and intravenous CERA in ND patients without serious cardiovascular complications, in which the target Hb level was set at 11 to 13 g/dL, the Hb levels were increased from approximately 9 g/dL to 12 g/dL. After maintaining 12 g/dL for 1 year, no safety issues were observed (Level B*) (38).

The results of rHuEPO, DA, and CERA in Japan have shown that the Hb levels of 11 g/dL or higher cause no safety issue and improve QOL and cardiac function. Therefore, as in the European and US guidelines, it is reasonable to set the Japanese Hb target at 11 g/dL or higher. In addition, since increased Hb levels are expected to produce benefits such as improvement in QOL and LVMI, it is considered possible to set the Hb target at 12 g/dL or higher if those with serious cardiovascular complications are excluded.

In setting the upper limit of target Hb levels or criteria for dose reduction or interruption, it is also necessary to consider the recent European and US large-scale RCTs which investigated effects of Hb levels maintained within a normal range on survival prognosis, occurrence of concomitant cardiovascular diseases, renal function, and others. In the past, a US clinical study (Normal Hematocrit study [NHCT]) in HD patients with concomitant cardiac failure and ischemic cardiac disease was discontinued for ethical reasons since the mortality in the group with Hb levels maintained at approximately 14 g/dL (Ht levels; 42%) before HD tended to be higher than that in the group with the Hb levels maintained at approximately 10 g/dL (Ht; 30%) before HD (39) (Level A). Based on this result, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines recommended that the upper limit of Hb targets be 12 g/dL (40).

In the CHOIR study reported in November 2006 (18), 1400 or more ND patients were followed in a RCT in which target Hb levels of two groups were set at 13.5 g/dL and 11.3 g/dL. The intention to treat (ITT) analysis revealed a significantly more frequent occurrence of events (composite endpoint of death, myocardial infarction, hospitalization due to cardiac failure, and stroke) in the group with the Hb target of 13.5 g/dL (Level A). In the Cardiovascular Risk Reduction by Early Treatment with Epoetin Beta (CREATE) study in 600 or more European ND patients reported as another RCT at the same time (41), two groups were investigated; one group had the target Hb level of 13 to 15 g/dL and the other group had the target Hb level of 10.5 to 11.5 g/dL. The result revealed no significant differences in the primary endpoint of cardiovascular events between the groups. For the secondary endpoint of the renal function, dialysis was initiated in significantly more patients in the group with the Hb level of 13 to 15 g/dL, although no difference was observed in a decrease in the estimated GFR. QOL improved significantly in the group with the Hb level of 13 to 15 g/dL, which supports results previously reported (Level A). However, placing importance on the results of the domestic CHOIR study, the FDA placed an emphasis on the results from the CHOIR

study and issued an alert that the upper limit of Hb levels during the ESA use should be 12 g/dL (42). These results from the European and US large-scale RCTs suggest that it is not preferable to correct anemia to a normal level equally for all ND patients. More recently published meta-analysis results, including these three large studies (43), reported a significant increase of risk of death, shunt occlusion, and uncontrolled blood pressure in the patient group with higher Hb levels (defined as 12 g/dL or higher) (Level A).

In response to the evidence above, the statement on the upper limit of Hb levels in the 2006 K/DOQI Guidelines (4), "there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater", was changed as follows in 2007: "the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL, and the Hb target should not be greater than 13.0 g/dL" (13). The Europe guidelines have not been revised as of September 2008.

During the course of developing this guideline, we conducted in-depth discussions on the upper limit of Hb targets and criteria for dose reduction or interruption of ESAs in consideration of overseas circumstances. In the CHOIR study, almost one-third of the participants had a history of myocardial infarction, stroke, undergoing of coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) or limb amputation. This indicates that this study population included many patients with serious cardiovascular complications (18). Although there have been no accurate data on the prevalence of serious cardiovascular complications in Japanese ND patients, the incidence and seriousness of such diseases in the CHOIR study were much higher than those from the preliminary results of the Japanese large-scale, prospective, observational study of rHuEPO (22). This result shows that the patient characteristics in the CHOIR study were very different from those in average Japanese ND patients (Table 2-5) (Level B*). In addition, at a hearing of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) held in the US in September 2007 regarding target Hb levels, the ITT analyses of both of the CHOIR study (ND patients) and NHCT study (39) (HD patients) revealed a poorer prognosis in the high Hb group. However, in results of the analysis with actually-achieved Hb levels, a more frequent occurrence of events was observed in patients who had poor achievement in the target Hb level (Fig. 2-1). This indicates that a lower response to rHuEPO results in a poor prognosis (44) (Level A). This finding was presumed to be associated with hyporesponsiveness to ESAs or treatment with high-dose ESAs. Subsequently, the secondary analysis of the CHOIR trial results revealed the following findings: (1) among patients randomized to the high Hb group, those who achieved higher Hb levels had a better prognosis; (2) patients who had received higher maximum doses (20 000 IU or higher) per administration had a poorer prognosis than those who had received lower maximum doses (less than 20 000 IU). In a Cox hazard model analysis adjusted for these factors, the association between the assigned target Hb level and prognosis was lost, and the use of high doses of ESAs was the most satisfactory explanation for the poorer prognosis. Based on these results, it has been reported that no association could be observed between higher Hb targets and the poor prognosis (45) (Level A).

It has also been reported that with Hb variability (hemoglobin cycling), particularly when Hb levels abruptly decrease, cardiovascular complication occur most frequently (44) (Fig. 2-2) (Level A). In other words, this finding probably indicates that the events often develop when abrupt dose reduction or interruption of rHuEPO, or unresponsiveness to rHuEPO occurs. These facts suggest that the poorer prognosis is an expected result in patients with serious cardiovascular complications who require a high-dose rHuEPO to increase Hb or those in a status which causes unresponsiveness to rHuEPO. Considering all these reports, we concluded that at present, the evidence to set the upper limit of Hb targets at 12 g/dL for all PD and ND patients in Japan is weak.

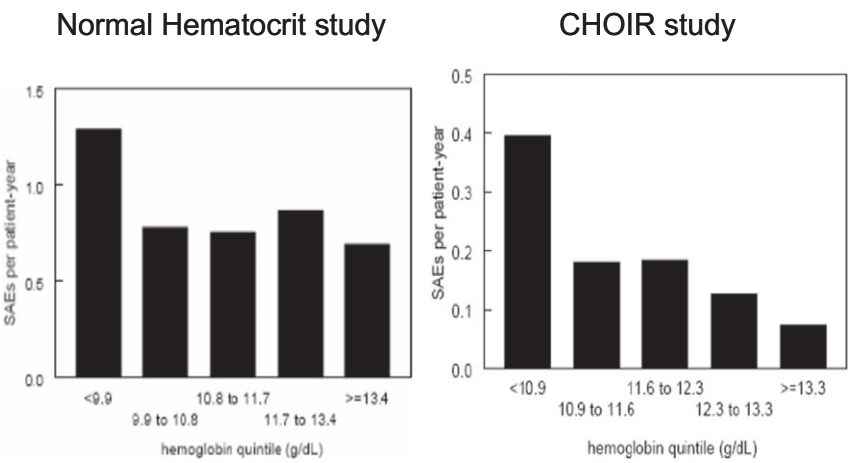
However, it is considered necessary to pay careful attention to patients with serious cardiovascular complications and other high risk patients among the Japanese patient population. As described previously, it has been reported in the clinical studies of DA in Japan that correction of anemia to Hb levels of approximately 12 g/dL resulted in significant improvement in QOL and cardiac function and that the target Hb level of 11 to 13 g/dL (criterion for discontinuing ESAs: 14 g/dL) caused no safety issues (33–37) (Level A*). Giving consideration to these results, we recommend 13 g/dL as a criterion for dose reduction or interruption for PD and ND patients, without setting an upper limit of Hb targets. However, for patients with serious cardiovascular complication, those at high risk of cardiovascular events, and those who would benefit from the opinion of the physician, we decided for safety reasons to recommend that dose reduction or interruption be considered if the Hb level exceeds 12 g/dL.

TABLE 2-5. *The demographic and baseline characteristics of the patients in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study (18) and the Japan Erythropoeitin Treatment Study for Target Hemoglobin (JET) study (22)*

	CHOIR study	
	High Hb group ($N = 715$)	Low Hb group ($N = 717$)
Hypertension (%)	95.8†	93.2
Myocardial infarction (%)	16.4	15.0
CABG (%)	17.4†	13.5
PCI (%)	10.9	11.9
Congestive heart failure (%)	24.4	22.9
Atrial fibrillation (%)	9.4	8.6
Stroke (%)	9.8	10.0
Peripheral vascular disease (%)	16.4	16.4
Myocardial infarction, stroke, CABG, PCI, or amputation of a lower limb (%)	36.3	34.5

	JET study ($N = 1949$; at the time of HD introduction)	
	Anamnesis/treatment history	Complication
Hypertension (%)	–	70.8
Myocardial infarction (%)	3.6	1.1
CABG (%)	2.4	–
PTCA (%)	2.8	–
Stent (%)	1.7	–
Congestive heart failure (%)	5.4	10.2
Arrhythmia (%)	1.5	3.4
Cerebral vascular disease (%)	12.6	2.9
Peripheral vascular disease (%)	1.4	3.5
Gangrene of a lower limb (%)	–	0.9
PTA (%)	0.3	–
Myocardial infarction, CABG, PTCA, Stent, or Cerebral vascular disease in the History/Treatment (%)	18.4	
Myocardial infarction, Cerebral vascular disease, Gangrene of a lower limb, CABG, PTCA, or Stent in the Complication or Treatment (%)	12.2	

†Had significant high-frequency compared to low Hb group. Hb, hemoglobin; HD, hemodialysis; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.



(http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4315b1-01-FDA.pdf)

FIG. 2-1. The relation between all serious adverse events and dynamic hemoglobin (Hb) level (by the quintile) for the Normal Hematocrit Study (NHCT) and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study (44).

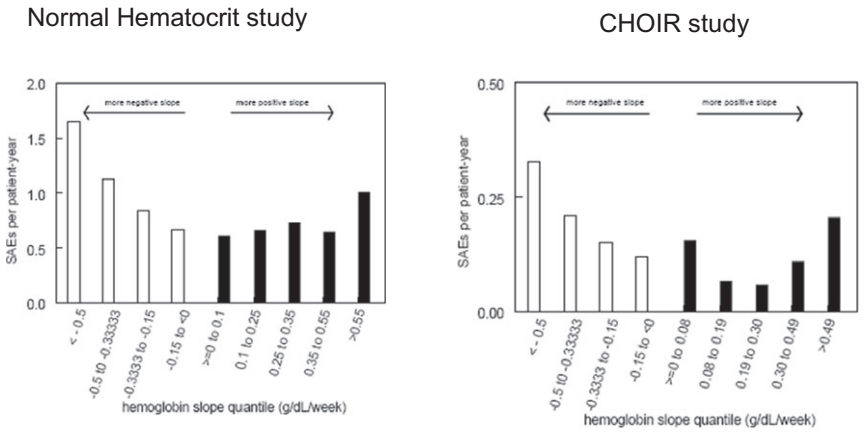


FIG. 2-2. The relation between all serious adverse events rate and hemoglobin (Hb) rate of change for the Normal Hematocrit Study (NHCT) and the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study; the risk of crisis was higher when variation of Hb level was high. The risk is especially high when Hb decreases more than 0.5 g/dL per week. On the contrary, when the elevation was less than 0.5g/dL, there was no increase in risk (44).

(http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4315b1-01-FDA.pdf)

4. Criteria for starting ESA therapy

The criteria for starting ESA therapy in HD, PD, and ND patients should be diagnosed renal anemia with Hb levels of less than the individual target values in more than one assessment.

It has been pointed out that ND patients are caught in a vicious cycle, in which renal failure, cardiac failure, and anemia are closely related to one another as risk factors and worsen the condition (cardio-renal anemia syndrome) (46). Anemia correction with ESA therapy is expected to break this cycle and prevent aggravation of renal and cardiac failures. In the recent large-scale, controlled clinical studies in ND patients such as the CHOIR study (18), the CREATE study (41), and the Anemia Correction in Diabetes (ACORD) study (47), no benefits of higher Hb levels (more than 13 g/dL in all studies) have been observed in improving survival prognosis, cardiac function, renal function, or others functions compared to lower Hb levels (10.5 to 11.5 g/dL). This result also suggests that there is no reason to actively support starting ESA therapy at Hb levels of 11 g/dL or higher.

CHAPTER 3

Evaluation of iron status and administration of iron therapy

1. Transferrin saturation (TSAT) and serum ferritin levels should be used for evaluation of iron status in chronic kidney disease (CKD) patients on ESA therapy. Iron should be given to CKD patients with TSAT ≤20% and serum ferritin levels ≤100 ng/mL (Opinion*).
2. Iron status should be assessed at least every 3 months. At the start of ESA therapy and in the cases below target Hb levels, more frequent examinations should be considered (Opinion).
3. For HD patients, iron should be administered intravenously and slowly via the dialysis circuit at the end of dialysis session. Recommended frequency of iron administration is up to once a week for 3 months or a total of 13 times (at every dialysis session) with consideration of Hb levels (Opinion*). Re-evaluation should be conducted 1 week or more after the final administration of iron (Moderately strong recommendation). Attention is needed for conditions in which intravenous iron is contraindicated or should be administered carefully.
4. For PD and ND patients, administration of oral iron is recommended (Opinion*). However, if oral iron administration is difficult or may not be sufficient to improve functional iron deficiency, it should be changed to intravenous administration (Strong recommendation).

1. Criteria for administration of iron therapy during ESA therapy

Iron should be given to CKD patients with TSAT ≤20% and serum ferritin levels ≤100 ng/mL (Opinion*).

(1) Evaluation of iron status and definition of iron overload in CKD patients on ESA therapy. Serum ferritin levels are useful to assess iron deficiency. In patients with anemia and serum ferritin levels of <12 ng/mL, they are diagnosed with iron deficiency anemia (48) (Level A*). However, even if patients have normal or high serum ferritin levels, iron deficiency cannot be ruled out. Serum ferritin levels change by various reasons such as inflammatory disease, infection, hepatic disease, and malignant tumor. Therefore in patients with iron deficiency anemia, if any of these diseases coexists, the serum ferritin levels do not necessarily decrease (49). For these reasons, the diagnostic criteria for iron deficiency in CKD patients with various underlying diseases or complications are not definite.

After the clinical use of ESAs, many studies have been conducted mainly in Europe and the US regard-

ing criteria for administration of iron therapy while receiving ESA treatment. Demand of iron in the body should be assessed from the viewpoints of both its role and distribution (48). Evaluation of iron status and iron supplementation necessary and sufficient for erythropoiesis is important to achieve and maintain the target Hb level for ESA therapy and optimize ESA doses. On the other hand, avoidance of iron overload is considered important from the viewpoint of prophylaxis against aggravation of viral hepatitis, infection susceptibility, organ disorder, and other adverse reactions.

In HD patients, annual iron loss from dialysis has been calculated to be approximately 1 g or more per year including residual blood in the circuit or dialyzer and blood sampling (50) (Level C*). Administration of iron therapy is required to maintain appropriate erythropoiesis. In order to obtain sufficient benefits of ESAs, it is essential to maintain iron supplementation that can compensate for iron losses, in addition to a supply which meets iron demand for Hb synthesis so that adequate erythropoiesis is ensured (51–54) (Level B).

PD and ND patients differ from HD patients in aspects such as the absence of residual blood in the circuit or dialyzer. To obtain sufficient benefits of ESAs, it is essential to maintain iron supplementation which meets iron demand for Hb synthesis. However, in PD and ND patients, intravenous iron supplementation is more difficult than in HD patients in terms of hospital visit frequency, creation of vascular access, and other problems. The importance of iron supplementation in PD patients undergoing ESA therapy has also been elucidated in Japan (55) (Level C*).

In any conditions, measurement of serum ferritin levels and TSAT should be conducted at least every 3 months, and more frequent testing and iron supplementation should be considered if necessary (4) (Level B).

(2) Criteria for administration of iron therapy. Since erythropoiesis stimulates and induces Hb synthesis, the demand for iron increases during ESA therapy. This demand is fulfilled by iron absorbed from the gastrointestinal tract or visceral iron stores. However, if the supply of iron available for Hb synthesis is not sufficient, erythropoiesis occurs despite sufficient iron stores. In the increased erythropoiesis condition by ESA therapy, the demand of iron for Hb synthesis may exceed the supply despite adequate iron in the body. This condition is known as functional iron deficiency or relative iron deficiency (56). To obtain sufficient benefits of ESAs and to provide effective ESA therapy, an appropriate diagnosis of functional iron deficiency and iron supplementation are needed.

MCV is commonly used as an easy-to-use diagnostic marker to determine the need for iron supplementation during ESA therapy. However, the sensitivity and specificity are both insufficient. In this context, the following indices are used to determine the need for administration of iron therapy: e.g. [1] TSAT $\leq$20%; [2] serum ferritin level $\leq$100 ng/mL; [3] reticulocyte Hb content <32.2 pg/cell; [4] a persistent tendency of a decrease in MCV over 4 to 5 months (3–5). Among these indices, measurement of reticulocyte Hb content is not covered by the national health insurance in Japan. Therefore, TSAT and serum ferritin levels are used as standard indices to determine administration of iron therapy (3–5) (Level C).

$$\text{TSAT}\,(\%) = [\text{serum iron}\,(\mu g/dL)/\text{total iron binding capacity}\,(\text{TIBC})(\mu g/dL)] \times 100$$

For PD and ND patients, few clinical trials for iron supplementation have been performed to date. Serum ferritin levels and TSAT are used as criteria in the Europe and US guidelines. In Japan, measurement of reticulocyte Hb content is not covered by the national health insurance, and serum ferritin levels and TSAT are the standard indices. The K/DOQI guideline states that the following indices should be maintained: ferritin levels >200 ng/mL and TSAT >20% for HD patients; ferritin levels >100 ng/mL and TSAT >20% for PD and ND patients (4) (Level C).

In Japan, we have little evidence of iron administration, and we should avoid using serum ferritin levels alone as an index of iron evaluation in patients with renal failure because it may lead to iron overload. Therefore, this guideline recommends that the criteria for administration of iron therapy during ESA therapy are serum ferritin levels $\leq$100 ng/mL and TSAT $\leq$20%.

(3) Diagnosis of iron overload. The diagnosis of iron overload should be reached appropriately to prevent and decrease adverse reactions to iron overdose. Previous Europe and US guidelines suggested that Hb levels of 11 to 12 g/dL could often be maintained by continuing administration of iron therapy as long as TSAT remained <50% and serum ferritin levels remained <800 ng/mL (40,57). The recent K/DOQI guideline provides an opinion that there is insufficient evidence to recommend routine administration of intravenous iron if serum ferritin levels

TABLE 3-1. *Sensitivity and specificity of markers of iron deficiency/iron overload* (5)

	Sensitivity/specificity	Remarks
Parameter of functional iron deficiency		
TSAT (%) (<20%)	Control	A parameter of available iron
Ferritin (ng/mL) (<100 ng/mL)	84.2%/31.4%	A parameter of stored iron
HYPO (%) (>2.5%)	39.1%/35.6%	A parameter of erythrocyte level
(>10%)	86.5%/20.6%	
CHr (pg) (<32.2 pg)	76.5%/73.4%	A parameter of reticulocyte level
sTfR (ng/mL) (>1200 ng/mL)	40.5%/33.9%	This parameter reflects iron deficiency and amount of erythroblast
Parameter of iron overload		
TSAT (%) (>50%)	Control	A parameter of available iron
Ferritin (ng/mL) (>800 ng/mL)	46.7%/99.4%	A parameter of stored iron
HYPO (%) (<10%)	0%/90%	A parameter of erythrocyte level
CHr (pg) (>33 pg)	61.5%/65%	A parameter of reticulocyte level
sTfR (ng/mL) (<1000 ng/mL)	52.4%/36.2%	This parameter reflects iron deficiency and amount of erythroblast

CHr, reticulocyte hemoglobin content; HYPO, The rate of hypochromic erythrocyte; sTfR, soluble transferrin receptor; TSAT, transferrin saturation.

exceed 500 ng/mL (4) (Level C). This is due to a lack of long-term evidence regarding the safety of serum ferritin targets greater than 500 ng/mL.

Evidence of diagnostic criteria for iron overload in PD and ND patients is also insufficient.

In any conditions, it cannot easily be recommended to continue iron supplementation until TSAT and serum ferritin levels approach values as high as 50% and 800 ng/mL, respectively, because of possible iron overload (57–60) (Level B). Indeed, increased risk for developing infection, endocrine disorder, and other events has been reported in patients with iron overload of this degree (61–63) (Level C). A recent review on administration of iron (63) indicates based on many cited references that these risks are of concern when the serum ferritin levels are >500 ng/mL and that clinical evidence of iron overload are insufficient when the levels are lower than this level. However, these cited references all originate from Europe and the US, and it is unknown whether they can be extrapolated to Japanese CKD patients.

We recommend that intravenous administration of iron should be performed temporarily as a safer method. We should monitor iron status at least every 3 months, and administer iron if iron status meets the criteria for administration of iron therapy (64–66), rather than to maintain iron within the target ranges (67–69) (Level C).

TSAT and serum ferritin levels are both unsatisfactory in sensitivity and specificity (70) when used as a diagnostic method for iron overload, and a simple diagnosis of iron is not achievable (Table 3-1) (5) (Level C*). However, from the current point of view, to use serum ferritin levels and TSAT for diagnosis of iron overload is the only available option. Therefore, the establishment of acceptable ranges has to rely on insufficient evidence, taking the balance between increase in Hb levels and safety into consideration.

It has been reported that administration of iron therapy in compliance with the Europe and US guidelines (TSAT >20% and serum ferritin levels >100 ng/mL) increased risk for bacteremia in HD patients (71). A report demonstrated that after 10-week administration of intravenous iron in HD patients with serum ferritin levels <100 ng/mL, both the serum ferritin level and 8-hydroxy-2′-deoxyguanosine (8-OHdG), an oxidative stress marker, markedly increased, although the Ht level increased by 5% (72) (Level B*). These reports indicate that special attention needs to be paid to iron overload status.

The Guideline for HD patients established in 2004 recommended the following diagnostic criteria for iron deficiency: serum ferritin levels ≤100 ng/mL and TSAT ≤20%. The statistical survey results by the JSDT at the end of 2005 (19) revealed that the serum ferritin level was 191.5 ± 327.7 ng/mL (mean ± SD), but that patients with levels less than 100 ng/mL accounted for 34.7%. After ESAs were included in a flat payment system in 2006, the usage of rHuEPO decreased with the increase of iron usage. Consequently, the serum ferritin level increased to 241.4 ± 384.0 ng/mL (mean ± SD), and the percentage of patients with the level <100 ng/mL decreased to 29.4%. The clinical impact of such an increase in the usage of iron is unknown, but there are many concerns.

This guideline recommends the values previously described, taking these circumstances into consideration.

2. Administration of iron therapy

HD patients
1. The optimal intravenous iron dose is 40 to 50 mg via the dialysis circuit slowly at the end of dialysis session (Opinion*). Recommended frequency of administration is up to once a week for 3 months or a total of 13 times (at every dialysis session) with consideration of Hb levels (Opinion*). Re-evaluation should be conducted 1 week or more after the final administration of iron (Moderately strong recommendation). Attention is needed for conditions in which intravenous iron is contraindicated or should be administered carefully.

PD and ND patients
1. Administration of oral iron is recommended (Opinion*). However, if oral iron administration is difficult or may not be sufficient to improve functional iron deficiency, it should be changed to intravenous administration (Strong recommendation).
2. The optimal oral iron dose is 100 (73) to 200 (210) mg/day. For intravenous iron, 40 to 120 mg/day should be slowly administered with close monitoring at the hospital visit (Opinion*).

(1) Selection of iron preparations and the administration route. Iron is available in oral and intravenous forms. The subcutaneous administration route is also recommended in Europe and the US, but not in Japan. Since overdose of any dosage forms could cause iron overload, strict monitoring of iron status is needed.

Because the payment of EPO for HD outpatients was included in a flat payment system in 2006, the amount of administered EPO decreased, but we did not observe a decrease of Hb levels (20). On the other hand, evidence has been provided that patients with more severe anemia have higher serum ferritin levels and TSAT. Dialysis Outcomes and Practice Pattern Study (DOPPS), known as an international observational study, has also revealed that the risk of death was higher in institutions with high doses of intravenous iron supplementation. This fact suggests that we should perform intravenous iron supplementation more carefully. However, intravenous iron administration is often needed to treat functional iron deficiency during abrupt erythropoiesis induced by ESA therapy. Available intravenous iron preparations in Japan are saccharated ferricoxide (64), chondroitin sulfate/iron colloid (65) (manufacture was discontinued on May 9, 2008, and only the product in stock is available), and cideferron (66).

The K/DOQI guidelines state that the route of iron administration can be either oral or intravenous in patients with PD or ND (4) (Level C). Oral iron is easier to use from the clinical viewpoints of patient visit frequency and creation of vascular access and is also often effective (67) (Level A). Available oral iron preparations are sodium ferrous citrate (74), ferrous fumarate (75), and ferrous sulfate hydrate (76). In package insert of all of these, careful administration to patients with gastrointestinal disorder or paroxysmal nocturnal hemoglobinuria is stated. However, oral iron is often not effective in correcting functional iron deficiency status and in such cases, intravenous iron should be used.

(2) The optimal dose of iron and the frequency of administration. When the criteria for administration of iron therapy as mentioned above are fulfilled and there are no contraindications to iron administration (see below), 100 (105*) to 200 (210*) mg/day of oral iron should be administered (*iron content of ferrous sulfate hydrate). When functional iron deficiency does not improve or when no iron overload or improvement in Hb levels is observed, oral iron should be switched to intravenous iron.

For intravenous administration of iron to HD patients, saccharated ferricoxide (1 A, 2 mL, 40 mg of iron), chondroitin sulfate/iron colloid (1 A, 10 mL, 40 mg), or cideferron (1 A, 2 mL, 50 mg of iron) should be administered slowly up to once a week for 3 months or 13 times via the dialysis circuit at the end of each dialysis session. In this case, the total administered dose is 520 mg (40 mg × 13 times) or 650 mg (50 mg × 13 times). To avoid iron overload, when intravenous iron is administered to patients with ordinary iron deficiency anemia, the total Hb iron deficit must always be calculated by the formula below, and by adding the deficit of iron stores (500 mg) the total iron dose should be determined.

$$\text{Total Hb iron deficit} = (16 - \text{the patient's Hb level before iron administration}) / 100 \times \text{body weight (kg)} \times 65 \times 3.4 \ (48)$$

When this formula is applied to HD patients, the total Hb iron deficit can be calculated as follows, if the target Hb level is 12 g/dL:

$$\text{Total Hb iron deficit} = (12 - \text{the patient's Hb level before iron administration}) / 100 \times \text{body weight (kg)} \times 65 \times 3.4$$

Assuming that the patient has an Hb level of 8 g/dL and body weight of 60 kg, the amount of iron required to increase the Hb level to 12 g/dL is approximately 530 mg. Clinically, iron requirement is determined by adding the Hb iron content in the sampled blood and residual blood in the dialyzer (approximately 167 mg/month assuming that the amount of iron lost for 1 year is 2000 mg) to the amount above. This is almost the same amount as that

of iron supplied by intravenous iron administration once a week for 3 months or 13 doses of intravenous iron after each dialysis session.

Since abrupt shock symptoms could occur immediately after intravenous administration of any iron preparation (77–80), it is recommended that, particularly at the first dose, half a dose diluted should be infused slowly, followed by an observation for approximately 1 h to confirm the absence of hypersensitive reaction.

One week or more after the final administration of iron, its status should be assessed again. If the patient is in a state of functional iron deficiency, intravenous iron should be readministered in the same manner as described above. Since serum ferritin levels temporarily increase after intravenous administration of iron, an interval of 1 week is needed between the final administration and the measurement (3) (Level B).

In PD and ND patients who are judged to be in a state of iron deficiency and have no contraindications to iron administration (see below), 100 (73) to 200 (210) mg/day is administered orally. If testing at the patient's visit reveals no improvement in the iron deficiency or Hb levels, oral iron should be switched to intravenous iron. In clinical studies including PD and ND patients, those receiving intravenous iron had higher Hb levels and lower ESA requirements compared to those receiving oral iron (81,82) (Level A). Intravenous administrations of iron should be conducted slowly at the patient's visit while monitoring iron status.

(3) Contraindications for administration of iron therapy. Consideration should be given to indications of iron administration even in patients who are judged to be indicated, since there are conditions of contraindications or those requiring careful administration. (Intravenous iron)

Administration should be discontinued if any of the following is present:

1. Hypersensitivity to iron or any of inactive iron ingredients such as a history of anaphylaxis due to iron preparations;
2. A history of diseases or symptoms suspected to be iron overload, previous massive blood transfusion, hemosiderosis (83), hemochromatosis, siderosis of the bone (84), and similar diseases;
3. Serious liver disorders (liver disorders may be aggravated) (84).

If any of the events below is present, iron administration should be conducted carefully with consideration given to the therapeutic benefits and safety.

1. Paroxysmal nocturnal hemoglobinuria
   Hemolysis may be induced.
2. Infections
   It has been reported that administration of iron preparations caused or aggravated bacterial infection, mycosis, or similar diseases (71,85).
3. Viral hepatitis
   In iron-deficient patients, improvement in liver dysfunction and reactivity to interferon and other benefits have been reported, and iron administration may cause adverse effects (86).
4. Renal disorders
   Administration of intravenous iron preparations may aggravate renal disorders. Careful attention should be paid to evaluation of residual renal function when intravenous iron preparation is administered to PD and ND patients. (Oral iron preparations)

Administration should be discontinued if any of the following is present:

1. Hypersensitivity to iron or any of inactive iron ingredients such as a history of anaphylaxis due to iron preparations;
2. A history of diseases or symptoms suspected to be iron overload, previous massive blood transfusion, hemosiderosis (83), hemochromatosis, siderosis of the bone (84), and similar diseases.

If any of the events below is present, iron administration should be conducted carefully with consideration given to the therapeutic benefits and safety.

1. Gastrointestinal diseases (e.g. gastrointestinal ulcer, chronic ulcerative colitis, and regional enteritis)
   Ulcer or inflammation may be aggravated.
2. Paroxysmal nocturnal hemoglobinuria.

CHAPTER 4

Administration of ESAs—administration route/dosage

HD patients

1. Concerning the administration route, intravenous injection is recommended via through the dialysis circuit (Moderately strong recommendation).
2. The initial dose for intravenous injection should be 1500 IU, which is administered three times a week. When anemia-improving effects are not achieved, the dose may be increased to 3000 IU.
   DA should be used in patients who have been converted from rHuEPO. The initial dose is 10 to 40 μg once a week or once every 2 weeks on the basis of the previous rHuEPO dose. If anemia-improving effects are not achieved, the dose may be increased to 180 μg (Opinion*).

3. The dose and the frequency of administration should be determined based on the type of ESAs, baseline Hb levels, target level of improvement in anemia and the predicted or targeted velocity at which this agent improves anemia, and other factors (Opinion).

PD patients

1. Concerning the administration route, subcutaneous injection is recommended (Moderately strong recommendation). DA is approved only for intravenous injection at present.
2. The initial dose for subcutaneous injection should be 6000 IU, which is administered once a week. When anemia-improving effects are achieved, the dose is administered at 6000 to 12 000 IU once every 2 weeks (Opinion*). DA should be used in patients who have been switched from rHuEPO. The initial dose is 30 to 60 μg intravenously once a week or once every 2 weeks on the basis of the previous rHuEPO dose. When anemia-improving effects are achieved, it can be administered at 60 to 180 μg once every 4 weeks (Opinion*).
3. The dose and the frequency of administration should be determined based on baseline Hb levels, target level of improvement in anemia and the predicted or targeted velocity at which this agent improves anemia, and other factors (Opinion). When rHuEPO is administered by currently approved dosage and administration in Japan, there are difficult cases to maintain the targeted anemia improvement continuously (Opinion*).

ND patients

1. Concerning the administration route, subcutaneous injection is recommended for rHuEPO (Moderately strong recommendation). (Currently, DA is not approved for ND patients in Japan.)
2. The initial dose for subcutaneous injection should be 6000 IU, which is administered once a week. When anemia-improving effects are achieved, the dose is administered at 6000 to 12 000 IU once every 2 weeks (Opinion*).
3. The dose and the frequency of administration should be determined based on baseline Hb levels, target level of improvement in anemia and the predicted or targeted velocity at which this agent improves anemia, and other factors (Opinion). When rHuEPO is administered by current approved dosage and administration in Japan, there are difficult cases to maintain the targeted anemia improvement continuously (Opinion*).

1. Administration route of ESA—intravenous injection and subcutaneous injection

1. As a rule, rHuEPO should be intravenously injected via the dialysis circuit at the end of dialysis session in patients undergoing HD (Moderately strong recommendation).
2. In PD and ND patients, subcutaneous administration is recommended for rHuEPO (Moderately strong recommendation). When intravenous iron preparations are concomitantly used, intravenous administration of an ESA is recommended (Opinion*). For DA, intravenous administration is recommended for PD patients in whom the use has been approved. (Currently, DA is not approved for ND patients.)

In Japan, under the insurance medical care system and also based on the proposal by the Science Research Group, Ministry of Health and Welfare (Director: Yoshihei Hirasawa) (21) in 1990, rHuEPO administration in HD patients is limited to intravenous injection, and subcutaneous administration is approved only for PD and ND patients. In Europe and the US, many clinical studies comparing the intravenous and subcutaneous routes support the advantages of subcutaneous administration from the viewpoints of beneficial effects of rHuEPO on anemia improvement and its maintenance and even of medical economy (87–99) (Level A).

Based on these results, the previous Europe and US clinical practice guidelines for renal anemia (100,101) recommended subcutaneous administration not only for ND and PD patients but also for HD patients. Subcutaneous administration is still recommended for ND and PD patients in Europe and the US, partly because self-injection is approved. However, onset of pure red cell aplasia (PRCA) prompted the current European and US guidelines to demonstrate a preference for the intravenous route for HD patients, which is more convenient than the subcutaneous route (3,4). From these results, the Japanese 2004 Guideline also recommended the intravenous route (5) (Level C*).

The largest advantage of subcutaneous administration of rHuEPO is that it allows lower doses to be used and therefore reduces medical costs. Disadvantages include variable rates of absorption depending on skinfold thickness and injection pain. The pharmacokinetics of subcutaneous rHuEPO is characterized by low serum EPO levels sustained at approximately 100 mIU/mL for a long period of time (high time-averaged plasma level). This contributes to the superior efficacy in anemia improvement correction to intravenous administration despite the low bioavailability (102) (Level A).

Intravenous administration of rHuEPO is intended to transfer all administered dose into the circulating blood. The pharmacokinetics is characterized by abrupt increase of serum EPO levels immediately after the administration, followed by a rapid fall, and the trough level is lower than that by subcutaneous administration. It has been pointed out that this may contribute to clinical resistance to rHuEPO. Rice et al. (103) have reported that the abrupt fall in serum EPO levels may induce the destruction of young red blood cells (neocytolysis) newly released from the bone marrow (Level C).

After the first report by Bommer et al. (87) in 1991, investigations on the usefulness of intravenous and subcutaneous rHuEPO have been conducted mainly in Europe and the US, and most have pointed out that subcutaneous administration is more beneficial. In Japan, 2 controlled studies in HD patients have been reported (104,105). In both studies, the total

dosage could be decreased by approximately 30% (104) and 38% (105) by switching from intravenous to subcutaneous administration of rHuEPO and the efficacy of the subcutaneous route was revealed (Level A*). There has been a report, which is detailed in Chapter 7, that the incidence of PRCA with subcutaneous administration of rHuEPO was approximately 33-fold higher than that with intravenous administration of rHuEPO (73). Although the number was very low, PRCA case reports have been received with both epoetin alfa and beta marketed in Japan (106,107), indicating that caution should be exercised.

Given the circumstances described above, subcutaneous administration is recommended for rHuEPO in PD and ND patients from the viewpoint of the sustained efficacy. On the other hand, for HD patients, intravenous administration is considered appropriate from the viewpoints of pain and convenience.

DA was approved in Europe and the US for intravenous and subcutaneous administration to HD, PD, and ND patients in 2001. In Japan, intravenous administration to HD and PD patients was approved in April 2007. DA has a circulating half-life of approximately 3-fold longer than that of rHuEPO when intravenously administered, and it has been reported that the blood level is sustained longer than that of rHuEPO (108). In Japan, the use in ND patients and subcutaneous administration are not approved at present. For DA, intravenous administration is recommended for HD and PD patients in whom the use has been approved.

As clinical studies are being conducted currently on ESAs such as DA and CERA, further investigation on the appropriate administration route will be required in the future.

2. *Dosage of ESA*

1. In patients undergoing HD, rHuEPO at an initial dose of 1500–3000 IU should be intravenously injected three times a week. During administration, attention should be paid to the rate of increase in Hb levels and occurrence of events such as hypertension due to excessive erythropoiesis. When the rate of increase of the Hb level is less than 1 g/dL 4 weeks after the start of administration, intravenous injection of 3000 IU of rHuEPO should be continued at a frequency of three times a week. In PD and ND patients, the initial dose for subcutaneous injection should be 6000 IU, which is administered once a week. When anemia-improving effects are achieved, the dose is administered at 6000 to 12 000 IU once every 2 weeks (Opinion*). When rHuEPO is administered by currently approved dosage and administration, there are difficult cases to maintain the targeted anemia improvement continuously (Opinion*).
2. DA should be used in HD and PD patients who have been switched from rHuEPO. In HD patients, DA should be used in patients who have been converted from rHuEPO. The initial dose is 10 to 40 μg once a week or once every 2 weeks on the basis of the previous rHuEPO dose (Opinion*). In PD patients, the initial dose is 30 to 60 μg/dose once a week or once every 2 weeks, and when anemia-improving effects are achieved, it is administered at 60 to 180 μg once every 4 weeks. In both cases, if anemia-improving effects are not achieved, the dose may be increased to 180 μg (Opinion*).
3. When the desired effect is not obtained, etiological factors should be investigated, considering ESA hyporesponsiveness (Opinion*).

With respect to rHuEPO dosage for HD patients, the Science Research Group, Ministry of Health and Welfare (21) mentioned above provided the following therapeutic guidance: in HD patients with Ht levels less than 25%, the initial dose of rHuEPO is 1500 IU intravenously 3 times a week with the target Ht level set at 30%; if the rate of increase in Ht levels is less than 3% after 4-week treatment in this dosing schedule, the dose is increased to 3000 IU intravenously 3 times a week; if the rate of increase is still less than 3% after observation of an additional 4 weeks, the dose is further increased to 6000 IU intravenously 3 times a week. The committee also proposed that, if the target has not been achieved despite the intravenous administration of 6000 IU/dose 3 times a week, the patient should be considered resistant to rHuEPO, and the cause should be searched for. However, intravenous administration of 6000 IU/dose 3 times a week exceeds the range of the currently approved dosage and administration and is difficult to apply to clinical practice.

At any stage, once the target value is achieved, the subsequent therapy should be conducted at a maintenance dose of one-third to one-half of the previous dose. In Japan, although the package insert for rHuEPO specifies that it should be started at 3000 IU (150 to 180 IU/kg/week) intravenously at the end of the dialysis session 3 times a week, the initial dosage of 1500 IU/dose is often applied, which is provided in the guideline by the Science Research Group, Ministry of Health and Welfare. Generally, treatment is started at a low dose while monitoring the rate of anemia improvement, and if the efficacy is judged to be insufficient, the dose is increased gradually. In Japan, the incidence of serious adverse reactions such as hypertensive encephalopathy-like convulsive seizure was lower from the beginning of the clinical application than that in Europe and the US. This may have been attributed to the "treatment should be started at a low dose" proposal by the Health Sciences Research Committee.

The package insert of rHuEPO specifies the dosage for PD and ND patients based on clinical study results as follows: the administration should be started at 6000 IU/dose subcutaneously once a week, and once the anemia improvement is achieved, 6000 to 12 000 IU/dose should be administered once every 2 weeks. Discussions about the target values for anemia improvement were insufficient at the time, and the dosage was set based on the changes in Hb levels. The target values for anemia improvement provided in the current guideline may be difficult to maintain by the method described in the package insert (55,109). In addition, it has to be concluded that maintaining the targeted anemia improvement in PD and ND patients is even more difficult in Japan where self-injection has not been approved.

The package insert of DA states that it should be used in patients who have been switched from rHuEPO. The starting dose when switched should be set on the basis of the previous rHuEPO dose within the range of 10 to 40 μg for HD patients and 30 to 60 μg for PD patients. The approved dosing interval is administration once a week or once every 2 weeks for HD patients (25), and administration once a week, once every 2 weeks, or once every 4 weeks for PD patients. An appropriate dosing interval may be selected according to a testing schedule, visit frequency, and others. The dose per administration varies depending on the interval, but the mean dose per week is approximately 20 to 30 μg regardless of the dosing interval.

In order to determine the ESA dose, the target value and rate for anemia improvement should be set according to the patient's condition. At the beginning of the clinical use of rHuEPO, the Science Research Group of the Ministry of Health and Welfare in 1990 reported that in improving anemia, a rate of anemia improvement not exceeding Hb levels of 0.3 to 0.4 g/dL (Ht level 1%) per week is important from the viewpoint of prevention against adverse drug reactions, since a continuous rate of increase in Ht levels per week of 1% or greater causes aggravation of hypertension and new onset of elevation in blood pressure and often requires initiation or dose increase of antihypertensive drugs (21) (Level C*). The European and US guidelines recommend that, during anemia improvement, the rate of increase in Hb levels be 1 to 2 g/dL/month (3,4). The overseas package insert for ESAs also provides instructions that in case of an increase in Hb levels of >1 g/dL over 2 weeks, the dose should be decreased. Similar reports were submitted in a review of the method of use for ESAs held by the US FDA in September 2007. In the NHCT study in HD patients with concomitant cardiovascular diseases, it was reported that the risk for new onset of concomitant cardiovascular disease remains unchanged if the increase in Hb levels does not exceed 0.55 g/dL/week (44) (Fig. 2-2) (Level B). In the CHOIR study in ND patients, it was reported that the rate of increase per week is not a risk factor but a greater rate of decrease is associated with a higher risk (44) (Fig. 2-2) (Level B). In addition, it is understood that elevation of blood pressure associated with erythropoiesis induced by ESAs is more a symptom accompanied by increased blood viscosity, rather than an adverse drug reaction. For this reason, preventive actions against hypertension were taken at the early stage thereafter and complications associated with abrupt erythropoiesis such as hypertensive encephalopathy have rarely been reported in Japan since 2000. It is suggested that there are no problems when Hb level increase is lower than 0.5 g/dL/week. Another major contributing factor is the baseline Hb levels, and if the baseline is low, more rapid Hb improvement may be needed to avoid transfusion whenever possible.

During the administration of ESA, it is important to prevent adverse events such as symptoms of headache, elevation of blood pressure or hypertension, and vascular access occlusion in HD patients.

The FDA review revealed that the abrupt fall in Hb levels causes a higher risk for adverse events than the abrupt increase, and Hb cycling (variability) is identified as a large problem (44,193) (Level B). In order to prevent this event, dose reduction should be conducted rather than interruption of the treatment (103), and once the response to an ESA decreases, an increase of the dose should be considered before Hb levels decrease.

CHAPTER 5

Hyporesponsiveness (resistance) to ESAs

1. In Japan, by incorporating the information in the package inserts of ESAs for support, under the condition that there is no iron deficiency, hyporesponsiveness (resistance) to ESA therapy is defined as follows.

HD patients

Hyporesponsiveness to ESA therapy is defined as a failure to achieve anemia correction and the target Hb level despite the use of 3000 IU/dose of intravenous rHuEPO 3 times a week (9000 IU/week) or 60 μg of intravenous DA once a week (Opinion*).

PD patients

Hyporesponsiveness to ESA therapy is defined as a failure to achieve anemia correction and the target Hb level despite the use of 6000 IU/dose of subcutaneous rHuEPO once a week (6000 IU/week) or 60 μg of intravenous DA once a week (Opinion*).

ND patients
For ND patients, hyporesponsiveness to rHuEPO therapy is defined as a failure to achieve anemia correction and the target Hb level despite the use of 6000 IU/dose of subcutaneous rHuEPO once a week (6000 IU/week) (Opinion*). However, it should be considered difficult to define hyporesponsiveness to rHuEPO at present since achieving the target Hb level may be difficult by the currently available dosage of rHuEPO (DA can not be used in ND patients at present).

2. Iron deficiency is the most frequent cause of hyporesponsiveness in the clinical practice, and other causes should be evaluated in its absence. (Moderately strong recommendation).

1. Definition of hyporesponsiveness

Generally, resistance to ESA therapy is not absolute, but relative. Therefore, the expression of "hyporesponsiveness to ESA therapy" should be used instead of "resistance to ESA therapy" (Moderately strong recommendation*).

There is no accurate definition of hyporesponsiveness to ESA therapy.

The K/DOQI Guideline explains that hyporesponse to ESA therapy and iron replacement therapy includes a significant increase in the ESA dose requirement to maintain a certain Hb level or a significant decrease in Hb level at a constant ESA dose, and a failure to increase the Hb level to greater than 11 g/dL despite an ESA dose equivalent to rHuEPO greater than 500 IU/kg/week, and in these cases, the patient should undergo evaluation for specific causes of hyporesponse (4) (Level C). The guideline also states that among the US patients with Hb levels less than 11 g/dL and administered 30 000 IU/week (428 IU/kg/week for a 70-kg patient), those who do not achieve target Hb level for 6 months is less than 1% (4) (Level C).

The EBPG defines so-called ESA resistance as a failure to attain the target Hb level during treatment with more than 300 IU/kg/week (approximately 20 000 IU/week) of rHuEPO or 1.5 μg/kg (approximately 100 μg/week) of DA or a need for high dosages to maintain the target Hb level (Ht level) (3) (Level B). The EBPG also states that resistance is usually relative rather than absolute, so the term "hyporesponsiveness to ESA therapy" is more appropriate and that hyporesponsiveness is dependent on uncertainties and initial doses of individual patients.

None of the European or US clinical practice guidelines for renal anemia makes a distinction between criteria for ESA hyporesponsiveness in PD or ND patients and those in HD patients.

In Japan, by incorporating the package inserts of ESAs for support, hyporesponsiveness to ESA therapy is generally defined as a failure to achieve anemia correction. That is to say, an HD patient should be considered hyporesponsive to ESA therapy if he/she fails to achieve anemia correction and the target Hb level despite using 3000 IU/dose of intravenous rHuEPO 3 times a week (9000 IU/week) or 60 μg of intravenous DA once a week (60 μg/week).

A PD patient should be considered ESA hyporesponsive if he/she fails to achieve anemia correction and the target Hb level despite using 6000 IU of subcutaneous rHuEPO once a week or 60 μg/week of intravenous DA. An ND patient should be considered ESA hyporesponsive if he/she fails to achieve anemia correction despite using 6000 IU of subcutaneous rHuEPO once a week. However, it has been reported that in PD patients, maintaining the target Hb level at 11 g/dL or higher is difficult by the current dosage range covered by the national health insurance. There has also been a report that the rate of achievement of 11 g/dL or higher was approximately 30% (55) (Level B*) and in ND patients, the rate was approximately 50% even under the condition of satisfactory iron status (109) (Level C*).

The definition of ESA hyporesponsiveness described above is not based on scientific evidence, but on the Japanese package inserts of ESAs, which set the maximum dose of rHuEPO per week at 9000 IU and the maintenance dose of DA per week at 60 μg for HD patients. In a patient who weighs 50 to 60 kg, these doses correspond to 150 to 180 IU/kg/week of intravenous rHuEPO and 1 to 1.2 μg/kg/week of intravenous DA, which are much lower than those in the Europe and US guidelines. In addition, the maximum dose of DA in the package insert is 180 μg.

The definition of ESA hyporesponsiveness should be considered by taking future expansion of indications for ESA therapy, ESA dosages, achievement rates of the target Hb level, and other factors into account and this should also be reflected in the dosages covered by the national health insurance system.

2. Etiological factors for hyporesponsiveness to EPO

The most important factor for hyporesponsiveness to ESAs is absolute or functional iron deficiency. Many other contributing factors are also known. (Moderately strong recommendation).

When a sufficient amount of iron is supplied, hematopoiesis is expected to occur in 90% of patients with ESA doses much lower than those specified in the criteria for hyporesponse (110) (Level B). This finding indicates that the major cause of hyporesponsiveness to ESA therapy is absolute or functional iron deficiency. If ESA hyporesponsiveness is suspected, the patient should first undergo iron evalua-

TABLE 5-1. *Major etiological factors for low responsiveness to Erythropoiesis Stimulating Agent (ESA)*

- Loss of blood
  Chronic blood loss from digestive tract/genital organs (111) and remaining of blood in dialyzer
- Hemopoiesis inhibition and deficiency of hematopoietic system
  Infectious disease (blood access/peritoneum access infection), inflammation, surgical infection disease, tuberculosis, acquired immune deficiency syndrome (AIDS), and autoimmune disease (112–114)
  Chronic rejection from renal transplantation (115)
  Severe hyperparathyroidism (fibrous osteitis) (116)
  Aluminum toxication (117–120)
  Folic acid and vitaminB12 deficiency (121,122)
- Hematopoietic tumor and blood dyscrasia
  Multiple myeloma (123,124)
  Other malignant tumor (125)
  Hemolysis (126) and hemoglobinopathy (α,β thalassemia (127,128), sickle cell anemia (129))
- Hypersplenism (130)
- Appearance of anti-EPO antibody (131)

tion to verify the presence of iron deficiency. When iron deficiency is ruled out, other causes should be investigated. In patients with a poor response to ESAs despite the absence of iron deficiency, causes as indicated in Table 5-1 and 5-2 should be searched for.

Major factors. (1) Blood loss or hemorrhage. Persistent blood loss induces iron deficiency. Gastrointestinal and genital hemorrhages are frequent causes of blood loss, and it is important to verify the presence of hemorrhage. In HD patients, residual blood in the dialyzer should also be considered.

(2) Inhibited or impaired hematopoiesis and deficiency of hematopoietic substrates. Inflammation due to acute or chronic infection, chronic rejection of the organ transplantation, and malignant tumor causes anemia of chronic disease (ACD), which is considered to result in hyporesponse. In addition to impaired iron utilization, ACD is known to cause an increase in pro-inflammatory cytokines inhibiting hematopoiesis such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 (141), which inhibit the early developmental precursors of red blood cells.

In patients with secondary hyperparathyroidism, hyporesponse is frequently observed, and improvement in responsiveness by parathyroidectomy has been shown in case reports. Parathyroid hormones have inhibitory effects on hematopoiesis, and osteitis fibrosis that occupies the bone marrow encroaches on the space for hematopoiesis. In the international observational study in HD patients known as DOPPS, the rHuEPO requirement was 1700 units/week higher in patients with high parathyroid hormone (PTH) levels >600 pg/mL compared with patients with PTH levels of 150 to 300 pg/mL (142).

Aluminum inhibits Hb synthesis and causes microcytic hypochromic anemia. Folic acid and vitamin B12 are essential for production of red blood cells, and if they are lacking, responsiveness may decrease. In patients with hypersplenism, in which red blood cells are trapped in the spleen and the life span is shortened, anemia correction may not be achieved despite the increase in reticulocyte count.

(3) Blood dyscrasia and hematopoietic tumor. Patients with multiple myeloma are not completely unresponsive to ESAs. However, the hyporesponsiveness varies greatly from individual to individual, and the reason is unknown. In patients with other malignant tumors, ESA requirements are larger than in those with anemia in ordinary renal failure. Also in this case, involvement of cytokines such as TNF-α is presumed.

Hemolysis occurs both mechanically and immunologically, and induces hyporesponse to ESA therapy. Hemoglobinopathy requires long-term, high-dose ESA therapy.

TABLE 5-2. *Suspected etiological factors for low responsiveness to Erythropoiesis Stimulating Agent (ESA)*

Insufficient dialysis (132), non-purification of the dialysate (133), and retention of uremic toxins
Undernutrition (134)
Carnitine deficiency (135)
Vitamin C deficiency (136)
Vitamin E deficiency (137)
Zinc deficiency (138)and copper deficiency (139)
Administration of angiotensin converting enzyme (ACE) inhibitors (140)

PRCA with the development of anti-ESA antibodies has been reported on rare occasions. Cases of this event have been reported for rHuEPO and DA in foreign countries, and for rHuEPO in Japan (106,107,143).

In the K/DOQI Guidelines (4), the following diagnostic criteria for PRCA are presented: a sudden rapid decrease in Hb level at the rate of approximately 0.5 to 1 g/dL/week, or requirement of transfusions; normal platelet and white blood cell counts; absolute reticulocyte count less than 10 000/μL. In order to reach a definite diagnosis, detection of anti-ESA antibodies is required.

Suspected factors. (1) Accumulation of uremia or inadequate dialysis and non-purification of the dialysate. It is evident that inadequate dialysis directly causes hyporesponse to ESA therapy (3). In contrast, long, slow dialysis and long nocturnal dialysis for consecutive days are known to be effective in anemia correction. There has been a report that, in HD patients, an increase in dialysis dose improves resistance to therapy. In addition, purification of the dialysate (3) and use of HDF (3) have been reported to improve responsiveness.

In PD patients, hyporesponsiveness occurs with decreasing residual renal function. It may be improved with concomitant use of HD.

In ND patients, ESA hyporesponsiveness occurs with progression of impaired renal function and aggravation of uremia.

(2) Nutritional deficiency. Malnutrition is often observed in dialysis patients (3) and Alb levels correlate well with Hb levels. Hypoalbuminemia is related to inflammation. Furthermore, in a state of malnutrition, a strong relationship to insufficient intake of carnitine and vitamins, zinc deficiency, and other conditions is observed.

Carnitine is involved in synthesis of fatty acids, which is a membrane component of red blood cells. In many dialysis patients, carnitine deficiency is present, resulting in increased ESA requirements.

Vitamin C is presumed to mobilize iron stores, and has been reported to enhance efficacy of ESAs (144). Vitamin E possibly enhances efficacy of ESAs through the antioxidant action. Zinc deficient patients are known to develop anemia. In dialysis patients, decreased serum zinc levels are also often observed, and there has been a report that zinc administration decreased ESA doses. In renal failure patients receiving total parenteral nutrition, copper deficiency has been reported as a cause as well.

(3) Drugs. Many reports have indicated that angiotensin-converting enzyme (ACE) inhibitors caused a hyporesponse to ESA therapy. A similar report on PD patients has also been presented (145).

CHAPTER 6

Blood transfusion in patients with chronic kidney disease

The use of ESAs and iron preparations has decreased the frequency of blood transfusions in patients with chronic kidney disease. However, red blood cell transfusion is still needed under certain conditions.

1. Indication for blood transfusion

The indications for red blood cell transfusion should be limited to severe anemia, extreme hyporesponse to ESAs, abrupt progression of anemia due to hemorrhage and hemolysis, surgery, and similar conditions.

Management of renal anemia has markedly improved, and frequency of transfusions in renal failure patients has decreased. This could be explained by the improvement in dialysis efficiency, advances in dialysis technology, deceased blood loss during dialysis sessions, use of ESAs, proper use of iron preparations and other reasons. However, red blood cell transfusion is still required under certain conditions, and the need will never be eliminated in the future. Careful evaluation is essential prior to blood transfusion in that it can reliably improve clinical symptoms (146). Generally in many patients with chronic anemia, clinical symptoms due to anemia do not appear when Hb levels are at least 7 g/dL. However, manifestations due to anemia vary from patient to patient depending on factors such as the presence of complications, life style, and social activity status. This indicates that, in conducting anemia treatment with transfusion, careful monitoring of the patient's condition, tailoring of target Hb levels in individual patients, and use of only the minimum required amount of blood for transfusion are important. Before blood transfusion, it is mandatory to inform patients well about the benefits and risks of transfusion and obtain their consent.

Indications of red blood cell transfusion are summarized as below (Table 6-1).

TABLE 6-1. *Representative patients that require red blood cell transfusion*

Severe anemia patients with signs/symptoms specific to anemia.
Patients with acute blood loss associated with unstable hemodynamics
Patients with severe angina pectoris
Intraoperative patients with a large volume of blood loss
Patients with extremely low-response to ESA

2. Cautions for blood transfusion

Attention should be paid to the onset of adverse reactions to blood transfusion.

The major reasons to avoid blood transfusion are the following: (i) sensitization by major histocompatibility complex (MHC) antigen; (ii) hemolytic adverse reactions; (iii) non-hemolytic adverse reactions (e.g. allergic reaction, anaphylaxis, transfusion-related acute lung injury, infection, iron overload); and (iv) short-term effect of anemia correction.

Since January 16, 2007, the Japanese Red Cross Society supplies red blood cell concentrates after treatment with leukocyte removal filters. However, this treatment cannot completely eliminate the sensitization by MHC antigens that result from a trace amount of white blood cells remaining in the concentrates. For this reason, transfusion should be conducted with care in patients who may undergo organ transplantation in the future. For scheduled surgery in which transfusion is expected, administration of rHuEPO for blood collection and storage are conducted in advance to enable autologous blood transfusion during the surgery.

CHAPTER 7

Side effects and concomitant symptoms of ESAs

The side effects of ESAs include hypertension, thrombosis/embolism, and PRCA. These side effects should be considered. (Strong recommendation)

Since practical use of rHuEPO was started in Japan in 1990, many side effects and concomitant symptoms have been reported. In this chapter we discuss those with important side effects supported by clinically high-level literature evidence. In Japan DA was approved for treatment of "renal anemia in patients on dialysis" in April 2007, and its side effects and concomitant symptoms is almost the same as those of rHuEPO (Table 7-1) (25,147–150) (Level A*).

TABLE 7-1. *Side effects of Erythropoiesis Stimulating Agent (ESA)*

Side effects demonstrated in the literature at the high evidence level
Hypertension
Thrombosis/embolism
Pure red cell aplasia related to the appearance of an anti-EPO antibody
Other side effects reported
Convulsive attacks
Reduction of dialysis efficiency
An increase in residual blood/blood clotting in the extracorporeal circulation circuit
An increase in anticoagulant requirement
Hyperpotassemia
Hyperphosphatemia
Cold-like symptoms
Myelofibrosis
Visual hallucination

1. Elevation of blood pressure

An abrupt increase in Hb (Ht) levels triggers hypertension in some patients.

Japanese clinical study data and postmarketing clinical results have shown that the incidence of elevation of blood pressure, including hypertension (assessed as a side effect by the physician), with rHuEPO is approximately 3 to 7%, which is lower than the 20 to 30% of foreign countries. However, the incidence has been reported to be as high as 35.6% in a limited sample size (151). On the other hand, the incidences of hypertension and elevation of blood pressure with DA have been reported to be 11.1% and 6.0%, respectively, in Japanese clinical study results (152) (Level C*). Since elevation of blood pressure is a result from anemia correction with ESAs, it should be regarded as a concomitant symptom, rather than a side effect.

The major mechanisms of elevation of blood pressure are speculated as follows: contraction of the dilated peripheral vessels related to the correction of low tissue oxygen concentration as a result of improvement in anemia, and no or insufficient reduction of cardiac output with the increase of peripheral vascular resistance as a result of enhancement of blood viscosity. Other proposed mechanisms include resetting of the relationship between body fluid volume and peripheral vascular resistance related to improvement in anemia, involvement of vasopressor substances such as endothelin, and increased responsiveness to vasopressor substances such as angiotensin II. There has also been an opinion that patients with a family or past history of hypertension potentially have these factors and are susceptible to elevation of blood pressure (153). In addition, the relationship between a genetic predisposition and the T-allele of the angiotensinogen M235T polymorphism has been suggested (154) (Level B*).

In order to prevent serious hypertension, it has been recommended from the beginning that a slow rate of anemia correction should be maintained and that anemia should be corrected slowly with attention paid to elevation of blood pressure. The Europe and US guidelines (3,4) state that, during anemia correction, the rate of increase in Hb levels should be 1 to 2 g/dL/month. The overseas package inserts of

ESAs also provide an instruction that, in the event of an increase in Hb levels of more than 1 g/dL in 2 weeks, the dose should be decreased. Particularly in patients with a history of hypertension, cautious administration is recommended to prevent elevation of blood pressure. In HD patients, treatment should start with reduction of DW, if an increase of blood volume (fluid overload) is observed, and appropriate antihypertensive therapy needs to be conducted while monitoring the efficacy.

At the beginning of rHuEPO marketing, suspected cases of association between hypertensive encephalopathy and abrupt elevation of blood pressure were reported, but recently such events have been observed rarely because of appropriate blood pressure control.

2. Thromboembolism

An increase in Hb levels (Ht levels) causes a risk for thromboembolism.

In observational studies in large-scale populations in Japan, there have been no reports on increased risk of thromboembolism associated with rHuEPO treatment, except for those from Okinawa (155) (Level C*). Although small in number, individual cases where a causal relationship to rHuEPO cannot be ruled out have been reported. In foreign countries, increased risk for shunt occlusion (particularly artificial vascular graft), which is believed to be associated with normalization of Hb levels (Ht levels), has been reported (43) (Level A). Dialysis patients with ischemic heart disease or cardiac failure have shown increased risk for death and non-fatal myocardial infarction at normal Hb levels (Ht levels) (39) (Level A). However, there is no medical evidence that supports these results for the application to the general dialysis patient population. A Japanese study of DA has revealed no increase in thromboembolism associated with increased Hb levels (25) (Level B*). The CHOIR study with target Hb levels of 13.5 g/dL and 11.3 g/dL in ND patients has reported a significant increase in the composite endpoint of death, myocardial infarction and others in the 13.5 g/dL group (18). However, since this study population included a great many patients with a past history of cerebro- or cardiovascular diseases, it is difficult to apply this result to the Japanese patient population (22). Nevertheless, when ESAs are administered to high-risk patients with a past or current history of serious cerebro- or cardiovascular diseases, special caution should be exercised to avoid excessive hematopoiesis (see Chapter 2).

3. Pure red cell aplasia

Anti-EPO antibodies induced PRCA in some patients.

In some patients, PRCA due to development of anti-EPO antibodies (neutralizing antibodies) may occur (156).

After 1998, secondary PRCA associated with development of anti-EPO antibodies occurred primarily in European patients receiving EPREX (epoetin alfa, Johnson & Johnson Pharmaceutical Research & Development, L.L.C.) (131). Although the incidence of PRCA is extremely low for the total patient exposure to rHuEPO worldwide, the incidence of PRCA with subcutaneous rHuEPO was shown to be approximately 33-fold higher than that with the intravenous form as generally known (157). The etiology of PRCA is unknown. The incidence of new onset of PRCA thereafter decreased to the level before 1998, and subcutaneous injection of EPREX, which had been temporarily contraindicated for the use in Europe, was reapproved. Although the number is very low, PRCA case reports have also been received with both epoetin alfa and beta in Japan (106,107,143) (Level C*).

For DA, PRCA associated with anti-EPO antibodies has been reported only in foreign countries (158,159).

Considering the circumstances described above, possible occurrence of adverse events due to production of anti-ESA antibodies cannot be ruled out, and strict monitoring is needed.

4. Others

Other concomitant symptoms and side effects have been reported such as convulsive seizure, decreased dialysis efficiency, increased residual blood in the dialysis blood circuit or coagulation, increased anticoagulant requirements, hyperkalemia, hyperphosphatemia, cold-like symptoms, myelofibrosis, and visual hallucinations. However, the relationship between these events and ESAs is remote or they are unlikely to be noteworthy at present.

CHAPTER 8

Guidelines for renal anemia in children

Introduction

The need for development of clinical practice guidelines (therapy guidance) for renal anemia in children has been growing worldwide and in response to such demand, guidelines were published by the European pediatric peritoneal dialysis working group (EPPWG) (160) in 2003 and by the K/DOQI

TABLE 8-1. *Reasons for difficulties in establishment of guidelines for children*

- The small number of chronic kidney disease patients.
- The small number of patients with long-term dialysis (because of early renal transplantation)
- Difficulty to conduct large randomized controlled trials to obtain scientific evidence.
- The broad and different characteristics of subjects (infancy to puberty)
- The metabolism, growth/development and psychological factors differ greatly from adults.

(4) in 2006. Particularly, the clinical practice guidelines for renal anemia published by the K/DOQI in 2006 (4) was organized as an advanced and integrated form of the NKF-K/DOQI 2000 (40) and EBPG 2004 (3) and a section for children (Section III) was included for the first time. However, developing guidelines for children is difficult for reasons such as those indicated in Table 8-1. From these results, the following was set in the 2006 K/DOQI Guideline (4), (i) the term "Clinical Practice Recommendations" is used instead of "Clinical Practice Guidelines" because the evidence is insufficient in children; (ii) adult guideline statements that are equally appropriate for children are applied without modification (fully applicable to children) from the background of data that are abundant in adult patients, and indicated only the statements that need pediatric-specific consideration are presented (applicable to children, but needs modification). This guideline is based on the same concept as the 2006 K/DOQI guidelines (4). Therefore, the previously detailed adult guideline statements regarding the following items should be applied to children on condition of a full understanding of the contents: diagnosis and criteria of renal anemia, iron evaluation and replacement therapy, hyporesponsiveness (resistance) to ESAs, transfusion in chronic kidney disease patients, side effects of ESAs, concomitant symptoms, and others. In the process of developing these Guidelines, we made every effort to present a guideline (therapy guidance) that adapts to the current situation in Japan by consulting and reanalyzing the following; the 2006 K/DOQI guidelines (4), the guidelines by the EPPWG (160), review in 1999 (163), textbook in 2005 (164), articles and presentation in the academic meetings in and after 2006, and the data from Japanese clinical studies (165–170).

TABLE 8-3. *The hemoglobin (Hb) criteria level (g/dL) for children (soon after birth to 2 years of age)*

	Mean	–2SD
Term (cold blood)	16.5	13.5
1–3 days	18.5	14.5
1 week	17.5	13.5
2 weeks	16.5	12.5
1 month	14.0	10.0
2 months	11.5	9.0
3–6 months	11.5	9.5
6–24 months	12.0	10.5

From Hematology of Infancy and Childhood, 6th Edition (162).

1. Diagnosis and criteria of renal anemia

1. Hb levels should be used as reference values for diagnosis of anemia. A diagnosis of anemia should be made when the Hb level is at the 5th percentile or lower of the reference value when adjusted for age and sex (Opinion).
2. The main cause of renal anemia is decreased EPO producing capacity associated with renal disorder. The diagnosis of renal anemia is made for the first time when no other diseases causing anemia are found. In some ND patients, measurement of serum EPO level may be useful (Opinion*).

Previous studies have shown that children develop anemia at an earlier stage of chronic kidney disease than adults do. According to the report from the United States renal data system (USRDS), the mean eGFR at initiation of dialysis in children is 10.3 mL/min/1.73 m^2, and even at this point, 35 to 40% of children are already receiving ESA therapy. These data suggest earlier onset of renal anemia in children (171) (Level B).

TABLE 8-2. *The hemoglobin (Hb) criteria level (g/dL) for children (above 1 year of age and below 19)*

	Boy			Girl		
	Mean	SD	<5th percentile	Mean	SD	<5th percentile
1 year <	14.7	1.4	12.1	13.2	1.1	11.4
1–2 years	12.0	0.8	10.7	12.0	0.8	10.8
3–5 years	12.4	0.8	11.2	12.4	0.8	11.1
6–8 years	12.9	0.8	11.5	12.8	0.8	11.5
9–11 years	13.3	0.8	12.0	13.1	0.8	11.9
12–14 years	14.1	1.1	12.4	13.3	1.0	11.7
15–19 years	15.1	1.0	13.5	13.2	1.0	11.5

From NHANES III data, United States, 1988–94 (161).

Since systematic, large-scale epidemiological surveys such as the National Health and Nutrition Examination Survey (NHANES) in the US are limited in Japan, we indicate the Hb reference values in the US as in Table 8-2 and 8-3. The values for children older than 1 year of age have been taken from the NHANES III (161), whereas the values for children from birth to 2 years of age are taken from Nathan and Orkin's textbook of pediatric hematology (6th Edition) (162) (Level B). These reference values should be revised once new values are established based on a large-scale epidemiological study in Japanese children.

Red blood cells produced by the bone marrow migrate to peripheral blood in the form of reticulocytes and become normal red blood cells in approximately 1 day. Therefore, the absolute reticulocyte count reflects the degree of erythropoiesis in the bone marrow, and serves as a useful indicator to diagnose the cause of anemia. In children who have no sufficient increase in reticulocyte count (usually 100 000 or greater) despite the presence of anemia, renal anemia is suggested if no other causes are found (172) (Level B).

2. Target Hb level and criteria for starting ESA therapy

1. We recommended that ESA therapy should target an Hb level of 11 g/dL or higher (Opinion*).
2. When the Hb level is less than 11 g/dL at several examinations under a diagnosis of renal anemia, administration of ESA should be initiated. (Opinion*)

There have been reports that in children with Hb levels less than 11 g/dL, compared to those with Hb levels of 11 g/dL or higher, there is a significant increases in risk for death (173), probability of hospitalization within 1 year after initiation of dialysis (173), and incidence of left ventricular hypertrophy (174) as well as accelerated disease progression in ND patients (175). It has also been demonstrated in foreign countries that various QOL indices improve with anemia correction (176–178) (Level B). Furthermore, reanalysis of the previously reported domestic clinical study data (165–170) revealed that as anemia was corrected, general malaise, shortness of breath, anorexia, and decreased motivation for learning improved (Level C*).

In the US, adults with Hb levels of 12 g/dL or higher have been reported to have higher risk for death and serious cardiovascular events (18), but to apply this finding to children who have fewer underlying diseases such as arteriosclerosis and concomitant cardiovascular diseases seems inadequate. For children at the developmental stage, target Hb levels should be determined by taking the indices different from those for adults, such as metabolism, growth, psychomotor development, kindergarten or school attendance, and learning or exercise capacity as well into consideration (179). Currently, data related to determination of the upper limit of the target in particular (efficacy, risk, and cost) is scarce. At present, it would be appropriate to select the individual children's target value with consideration given to patient characteristics, with the lower limit of Hb level as 11 g/dL.

3. Evaluation of iron status and administration of iron

1. Measurement of transferrin saturation (TSAT) and serum ferritin levels should be used as standard evaluation of iron status in chronic kidney disease (CKD) patients on ESA therapy. Iron should be given to CKD patients with TSAT ≤20% and serum ferritin levels ≤100 ng/mL (Opinion*).
2. Iron status should be assessed at least every 3 months. At the start of ESA therapy and in the cases below target Hb levels, more frequent examination should be considered (Opinion).
3. Attention is needed for conditions in which intravenous iron is contraindicated or should be administered carefully.

Children on ND or PD and HD are susceptible to iron deficiency since they lose 0.9 and 1.6 g/1.73 m^2/year of iron, respectively (180). Therefore, in treating renal anemia, diagnosis for the need of iron supplementation is important. The indices used for this purpose include TSAT, serum ferritin levels, and reticulocyte Hb contents. In children, however, there has been insufficient research on reticulocyte Hb contents and TSAT and serum ferritin levels are the only indices available (4).

In principle, iron drugs should be administered orally. However, when the following circumstances occur, intravenous administration should be conducted; difficulty in oral administration, impaired absorption, and failure to reach TSAT or target serum ferritin levels. Particularly in children on HD, the need and efficacy for intravenous iron have been reported (181,182) (Level A).

For oral use, 2 to 3 mg/kg/day (up to 6 mg/kg/day) of iron should be administered in two to three divided doses (160,163). In the use of intravenous iron, attention needs to be paid to the occurrence of shock immediately after the administration; intravenous iron should be administered slowly.

It has been shown that iron supplementation in children with functional iron deficiency had a beneficial effect on psychomotor development as well as on anemia correction. On the other hand, there has been a report that the infection risk increased when iron

replacement was conducted despite sufficient iron store. This report indicates that careful assessment for the need of iron supplementation is important before iron administration (183).

4. Administration method of ESA– administration route/dosage

1. In principle, the route of administration should be subcutaneous (Opinion*).
2. The dosage at the beginning of treatment should be 50 to 100 IU/kg of body weight/dose subcutaneously once a week. When anemia correction is achieved, 100 to 200 IU/kg of body weight/dose should be administered subcutaneously once every 2 weeks as a maintenance dosage (Opinion*).

With respect to the dosage and frequency of administration to maintain Hb levels at 11 g/dL or higher, the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) (184) revealed that children on PD required lower ESA doses than those on HD and that younger children required higher doses. For the frequency of administration, HD patients received ESAs 3 times a week (intravenous administration in most children), whereas PD patients received them once to 3 times a week (subcutaneous administration in a large majority of children) (Level B). These results suggest that further investigation is needed regarding the current dosages and frequency of administration to achieve and maintain the target Hb levels.

Results (dosage, frequency of administration, side effects, etc.) of treatment with DA in the pediatric field have been reported from Europe and the US (185–188). These results have revealed that initiation of DA decreased the frequency of administration, suggesting that this drug would confer a great benefit particularly on children in whom consideration to pain, compliance, burden of the family, and other factors is required. In Japan, DA was approved in April 2007 for treatment of renal anemia in patients on dialysis, but the use in Japanese children has not been studied. Efforts to include the DA indications for children should be made as soon as possible in Japan.

As a measure against pain associated with subcutaneous administration to children on PD, an attempt to administer ESAs intraperitoneally has been made (160). However, this intraperitoneal administration is not widely adopted for the following reasons: (i) a large volume of ESAs needs to be administered; (ii) there is a risk for peritonitis; and (iii) the abdominal cavity needs to be emptied to promote absorption of ESAs (if not, dialysis efficiency is decreased).

5. Hyporesponsiveness (resistance) to ESAs

In many cases, hyporesponsiveness (resistance) to ESAs is due to absolute/functional iron deficiency. In the absence of iron deficiency, other causes should be searched (Moderately strong recommendation).

There are no pediatric-specific causes of ESA hyporesponsiveness as compared to those in adults. However, it has been reported that inflammation and hyperparathyroidism have a role in causing ESA hyporesponsiveness (189) (Level C).

6. Blood transfusion in pediatric patients with chronic kidney disease

See Chapter 6 “Blood transfusion in patients with chronic kidney disease”.

7. Side effects and concomitant symptoms of ESA

Side effects of ESAs include hypertension, thromboembolism, and PRCA. These side effects should be considered in children. (Strong recommendation)

Hypertension triggered by an abrupt increase in Hb levels has also been reported in children (190,191) (Level B*). It is recommended to correct anemia gradually with attention to blood pressure elevation while maintaining a slow rate of anemia correction. More careful administration and monitoring are preferable in children with hypertension. Although small in number, there have been PRCA cases due to anti-EPO antibodies (192) (Level C). In most of these cases, subcutaneous administration was conducted. Since ESAs are administered subcutaneously in the majority of children, sufficient information should be given at the start of treatment to the child and family members that such a side effect may occur, although rarely, and that the therapeutic benefits may significantly outweigh the possible risks.

CONCLUSION

It has been our privilege to prepare these 2008 Guidelines for Renal Anemia in Japanese CKD patients, including HD, PD, ND and pediatric CKD patients.

It took approximately 3 years, starting in 2005, to prepare these Guidelines. Many new developments occurred during this period; the cost of ESAs was included in a flat payment system of dialysis therapy in April 2006; the revision of the US K/DOQI guidelines in May 2006; the reporting of the results of the CREATE and CHOIR studies, large-scale intervention studies in ND patients, in October 2006; the issuance of the US FDA recommendations based on

these reports in November 2006; the re-revision of the US K/DOQI guidelines July 2007 to reflect these recommendations; the holding of a US FDA public hearing in September 2007 and the public release of data; the marketing of DA in Japan in July 2007; and issues such as conflicts of interest arising with committee members involved in the preparation of papers or guidelines.

Even developments such as these did not threaten the foundational concept for the preparation of the Japanese Guidelines, and the working group diligently proceeded with its work as originally planned, and finally issued the original Japanese guidelines, the "Guidelines for Renal Anemia in Chronic Kidney Disease (CKD)" (*J Jpn Soc Dial Ther* 41 (10):661–716, 2008).

These Japanese guidelines differ from the Western guidelines in the following four ways: (i) these guidelines recommend different target Hb levels for HD patients than for PD and ND patients in ESA therapy; (ii) renal anemia has been clearly defined as an endogenous EPO production disorder associated with renal disorder, without relying solely on a decrease in the GFR, so renal anemia may be diagnosed even in the presence of a high GFR, and reference to "chronic renal failure" has been abandoned in favor of "non-dialysis CKD (ND)"; (iii) when, for example, establishing target Hb levels, Japanese evidence has been emphasized wherever possible; and (iv) while consideration has been given to Western evidence regarding the use of iron preparations, the detrimental aspects of the overuse of iron preparations has been emphasized.

The reason we have emphasized Japanese evidence is that the backgrounds of the patient populations in the large-scale studies conducted in the West—and particularly the prevalence of, for example, cardiovascular complications—is markedly different than that of the patients that we see in the average clinical setting in Japan. Regarding this point, we have cited a paper that compared the patient population in the CHOIR study, which had a significant impact on the establishment of the target Hb level in ND patients, with the results of epidemiological research in patients who were newly introduced to HD that is underway in Japan.

Although we used an unorthodox method to prepare these guidelines, as described above, and as was the case with the first guidelines, we are confident that these guidelines will be accepted without serious criticism by Japanese experts, and sincerely hope that they will be actively used by general practitioners involved in treating ND patients, as well. However, since treatment plans in the actual clinical setting will be determined at the discretion of the attending physician, taking into account the patient's background and individual circumstances, and while we hope that these guidelines will be used when formulating patient treatment plans, they are not intended to circumscribe the discretion of the attending physician, nor are they intended to serve as a standard for deciding medical disputes or legal actions.

All of the members involved in preparing these Guidelines would like to thank the doctors at the Japanese Society of Hematology and JBIS for their advice, as well as all of the other doctors who took the time to give us their valuable opinions.

It is our desire that these Guidelines may serve as a foundation for the acquisition of evidence worthy of being cited in Japan, and that the results thereby obtained may in turn be used to update these Guidelines further.

RECORDS ON COMMITTEE MEETINGS AND INTERMEDIATE REPORT MEETINGS HELD

First committee meeting, December 9, 2005
Second committee meeting, March 10, 2006
Third committee meeting, June 15, 2006
Fourth committee meeting, November 24, 2006
Fifth committee meeting, February 2, 2007
Sixth committee meeting, April 4, 2007
Seventh committee meeting, May 30, 2007
Eighth committee meeting, November 14, 2007
Ninth committee meeting, January 9, 2008
Tenth committee meeting, February 7, 2008
11th committee meeting, February 16, 2008
12th committee meeting, April 21, 2008
13th committee meeting, May 26, 2008
51st Congress of the JSDT, JSDT Special Session, June 25, 2006, Japan
52nd Congress of the JSDT, JSDT Consensus Conference, June 16, 2007, Japan
The guideline draft was posted in the JSDT Home Page. January to February, 2008
Public hearing for the JSDT guidelines. February 16, 2008, Tokyo
Accepted by the administrative board in March 14, 2008
53rd Congress of the JSDT, Summarized report of the JSDT guideline, June 22, 2008, Japan

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APPENDIX I

Recommendations and definition of evidence levels

1. Recommendation level for the guideline in boxed text
   - Strong recommendation: recommend strongly to conduct
   - Moderately strong recommendation: recommend to conduct
   - Opinion: recommend as an opinion from the committee
2. Definition of the scientific evidence assessment for the references cited in the expository writing
   Level A

a. Systematic reviews and meta-analyses
b. Randomized Controlled Trials (RCT)
c. Epidemiological results obtained from the statistical researches by the Japanese Society for Dialysis Therapy
d. Equivalent to Strong recommendation in the K/DOQI guideline and evidence level A in the EBPG

Level B

a. Several prospective open trials and prospective cohort studies
b. Retrospective statistical analysis researches by The Japanese Society for Dialysis Therapy
c. Other researches and large statistical researches abroad
d. Equivalent to Moderately strong recommendation in the K/DOQI guidelines and evidence level B in the EBPG

Level C

a. Constraint accompanied with health insurance treatment, case reports, clinical trials, retrospective cohort studies, package inserts and non-clinical studies
b. Equivalent to Opinion in the K/DOQI guidelines and evidence level C in the EBPG

Clinical trial results and investigation reports that include those conducted in Japanese subjects are marked with "※" in both 1 and 2.

☆ Recommendation levels in boxed text were determined by the committee based on the references and so on cited in the expository writings and are not necessarily the same as the evidence levels of the expository writings.