AJKD
CSN Commentary

Canadian Society of Nephrology Commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD

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The KDIGO (Kidney Disease: Improving Global Outcomes) 2012 clinical practice guideline for anemia management in patients with chronic kidney disease provides the structural and evidence base for the Canadian Society of Nephrology commentary on this guideline's relevancy and application to the Canadian health care system. While in general agreement, we provide commentary on 11 of the 61 KDIGO guideline statements. Specifically, we agreed that a therapeutic trial of iron is appropriate in cases in which a reduction in erythropoiesis-stimulating agent (ESA) dosage or avoidance of ESA and transfusion is desired, transferrin saturations are >30%, and ferritin concentrations are >500 μg/L. However, we concluded that there is insufficient evidence to support an upper target or threshold for ferritin and transferrin saturation levels. We agree with the initiation of ESA treatment when hemoglobin (Hb) level is 90-100 g/L; however, we specifically state that an acceptable range for Hb level is 95-115 g/L, with a target of 100-110 g/L, and add caution to individualization above this range due to concerns regarding the safety of ESAs. We agree that ESAs should be used with considerable caution in patients with active malignancy, history of stroke, or history of malignancy, and we suggest initiating ESA therapy at Hb level of 90 g/L and to aim for a Hb level in the range of 90-105 g/L. The reader is encouraged to note the level of evidence and review the entire KDIGO anemia guideline to interpret the guideline statements and commentary appropriately.
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KDIGO (Kidney Disease: Improving Global Outcomes) was established to improve the care and outcomes of patients with chronic kidney disease (CKD) throughout the world by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. KDIGO was based on a systematic literature search conducted in 2010 and updated through March 2012.[1] KDIGO used the Grading of Recommendation Assessment Development and Evaluation (GRADE) system to rate the strength of evidence and the strength of recommendations[2] and found that the level of evidence to inform this guideline was suboptimal in several subject areas. Just 2 (5.4%) recommendations in this guideline had overall quality graded as an "A," 9 (24.3%) were graded "B," 14 (37.8%) were graded "C," and 12 (32.4%) were graded "D." Guideline statements were also evaluated on the strength of recommendation and 15 (40.5%) recommendations were grade 1 (ie, "I recommend"), meaning that most patients in the given situation would choose the recommended course of action, and 22 (59.5%) were grade 2 ("I suggest"), which implies that while a majority of patients would likely choose the recommended course of action, a significant number would not, and physicians should engage their patients in decision making.

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There were 22 (37.3%) statements that were not graded and opinion-based recommendations were provided with little or no evidence. The KDIGO Work Group emphasizes that the guideline is meant to be a starting point, not end point, for clinician inquiry, and that the guideline is intended for patient management and not for the development of policy.

The purpose of this commentary is to use the structural and evidence base of the KDIGO anemia guideline and outline how to apply and adapt it to the Canadian health care system. Our working group was diverse, consisting of pediatric and adult nephrologists, pharmacists, and a nurse practitioner. The Canadian Society of Nephrology (CSN) Anemia Work Group recognizes and applauds the excellent work of the KDIGO Work Group. Any limitations or differences in interpretation of the guideline are based on the lack of conclusive evidence and the applicability in the Canadian health environment.

The KDIGO anemia guideline and this commentary apply to patients with CKD not dependent on dialysis (designated CKD-ND in the guideline), or receiving hemodialysis (CKD-HD) or peritoneal dialysis (CKD-PD). It does not specifically address the transplantation population. Where appropriate, comments are made on the pediatric population with CKD. This commentary is relevant to Canadian nephrologists, primary care physicians, and nursing and pharmacy specialists who care for patients with CKD. The CSN Anemia Work Group acknowledges the need for efficient use of health care resources. Commentary on costs and recommendations related to cost-effective use of medications pertaining to anemia management is made where appropriate.

REVIEW AND APPROVAL PROCESS FOR CSN COMMENTARIES

The development and review of this commentary was consistent with the CSN policy set out for conduct of clinical practice guidelines.[3] This review and commentary process is similar to the CSN commentaries recently published, reviewing the KDIGO guidelines on bone and mineral disorder in CKD[4] and acute kidney injury.[5] Individual members were selected based on their interest and expertise, geographical distribution, and relevant conflicts of interest. Commentary development took place during 2012 using the KDIGO anemia guideline and the CSN 2008 anemia guidelines.[3] All guideline statements were independently reviewed and ranked as "concur," "do not concur," or "concur with comments" by each member of the Work Group. The Work Group discussed all guideline statements that indicated "do not concur" or "concur with comment." This commentary is based on this discussion, additional literature review, and final consensus by the Work Group. The commentary was reviewed by an external review committee established through the CSN Guideline Committee. The reviews were considered, with incorporation of further revisions prior to ratification by the CSN Guideline Committee and CSN Executive.

STRUCTURE OF THIS COMMENTARY

The KDIGO summary recommendation statements are provided in Tables 1-4. This commentary does not seek to discuss all KDIGO recommendations. The focus will be on the guideline statements that the working group indicated "do not concur" or "concur with comments" and where implications and context in the Canadian health care setting were more controversial or required discussion. These statements are presented as numbered text within horizontal rules, using the same numbering scheme as in the original. All recommendations, including those reproduced in the tables, are quoted directly from the KDIGO guideline, and all material is reproduced with permission of KDIGO.

The reader is encouraged to note the level of evidence and review the entire KDIGO anemia guideline to interpret the guideline statements appropriately.[1] It is important to point out that even a recommendation based on good or high-quality data may not be appropriate for a given individual. While standardization of individualized care balances the instructive approach of guideline statements with the health care assessment of individual patients,[6] not all patients will benefit to the same degree from guideline recommendations.

GUIDELINE STATEMENTS AND COMMENTARY

Frequency of Testing for Anemia

1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (*Not Graded*):
- at least every 3 months in patients with CKD 3-5ND and CKD 5PD
- at least monthly in patients with CKD 5HD

Commentary

Comparatively little information is available regarding the development and progression of anemia and the optimal frequency for hemoglobin (Hb) monitoring in patients with CKD who are not currently being treated with erythropoiesis-stimulating agents (ESAs). As stated in guideline recommendation 1.1.2, it would seem reasonable that patients with anemia and dialysis-dependent CKD (CKD-D) and CKD-ND (at any level of kidney function) should be screened for worsening anemia in any situation where the signs, symptoms, or general clinical condition made such a diagnosis ei-

Table 1. KDIGO Recommendation Statements on Diagnosis and Evaluation of Anemia in CKD

Number	Recommendation Statement	Concur
	TESTING FOR ANEMIA	
	Frequency of testing for anemia	
1.1.1:	For CKD patients without anemia (as defined below in Recommendation 1.2.1 for adults and Recommendation 1.2.2 for children), measure Hb concentration when clinically indicated and (*Not Graded*):	
	• at least annually in patients with CKD 3	✓
	• at least twice per year in patients with CKD 4-5ND	✓
	• at least every 3 months in patients with CKD 5HD and CKD 5PD	✓
1.1.2:	For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (*Not Graded*):	
	• at least every 3 months in patients with CKD 3-5ND and CKD 5PD	see comments
	• at least monthly in patients with CKD 5HD	see comments
	Diagnosis of anemia	
1.2.1:	Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)	✓
1.2.2:	Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5-5 years, <11.5 g/dl (115 g/l) in children 5-12 years, and <12.0 g/dl (120 g/l) in children 12-15 years. (*Not Graded*)	✓
	Investigation of anemia	
1.3:	In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):	
	• Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count	✓
	• Absolute reticulocyte count	✓
	• Serum ferritin level	✓
	• Serum transferrin saturation (TSAT)	✓
	• Serum vitamin B_{12} and folate levels	✓

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ther likely and/or of value/importance to their current health or medical condition.

The question remains, however, whether the intensity of Hb monitoring suggested by KDIGO for anemic ESA-naïve patients (quarterly for all CKD-ND and CKD-PD and monthly for CKD stage 5 HD) can be justified.

The frequency of monitoring should be determined by the likelihood of the Hb changing within/between the monitoring recommended. Two published articles assist in addressing this issue. The first study[7] includes a control group which provides a natural history for changes in Hb over time. The baseline values were an estimated glomerular filtration rate of 27.8 ± 9.3 mL/min/1.73 m^2 and Hb of 117.3 ± 8 g/L. The mean change in Hb over the 24 months of follow-up was only 3 ± 11.5 g/L, and only 16/74 (21.6%) of patients initiated ESA therapy (at Hb levels of about 95-100 g/L). From these data, it would appear that less frequent monitoring would be appropriate for patients with CKD stages 3 and 4 and above. Two caveats of this study are: (1) all other underlying conditions potentially causing anemia were ruled out prior to enrollment, and (2) approximately 80% of patients were receiving iron therapy. A second study examined the variability of Hb in the CKD-ND stage 3-5 population, either with or without ESA use.[8] Those who were not using ESAs, n = 3,143, had a slow rate of decline in Hb over time from a baseline of 125 ± 15.7 g/L, with a −0.1 ± 2.6 g/L change per month over the 18-month follow-up. Furthermore, if the baseline Hb was ≥110 g/L, only 23.1% demonstrated an Hb < 110 g/L within the initial 6-month assessment, with a mean Hb change of 4.52 ± 1.37, range of 3-7 g/L.

Implications Within Canadian Health Care

1. Standards for frequency of Hb monitoring should be in place in all programs caring for patients with CKD, with a defined process to review and act on the Hb measures as necessary.

2. It is reasonable to monitor Hb in ESA-naive patients who are anemic and in CKD stage 3a, 3b, and early stage 4 as infrequently as 1-2 times per year.

3. We agree with the KDIGO suggestions for the frequency of monitoring for patients with stage 5 CKD-ND, CKD-PD, and CKD-HD.

Table 2. KDIGO Recommendation Statements on Use of Iron to Treat Anemia in CKD

Number	Recommendation Statement	Concur
	TREATMENT WITH IRON AGENTS	
2.1.1:	When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (*Not Graded*)	✓
2.1.2:	For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if (*2C*):	
	• an increase in Hb concentration without starting ESA treatment is desired* and	see comments
	• TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l)	see comments
2.1.3:	For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if (*2C*):	
	• an increase in Hb concentration** or a decrease in ESA dose is desired*** and	see comments
	• TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l)	see comments
2.1.4:	For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)	✓
2.1.5:	Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)	✓
2.1.6:	For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 μg/l). (*1D*)	✓
2.1.7:	For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 μg/l). (*1D*)	✓
	IRON STATUS EVALUATION	
2.2.1:	Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (*Not Graded*)	✓
2.2.2:	Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)	✓
	CAUTIONS REGARDING IRON THERAPY	
2.3:	When the initial dose of IV iron dextran is administered, we recommend (*1B*) and when the initial dose of IV nondextran iron is administered, we suggest (*2C*) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.	see comments
	Iron during infection	
2.4:	Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)	✓

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*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

**Consistent with Recommendations #3.4.2 and 3.4.3.

***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

Treatment With Iron Agents

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration without starting ESA treatment is desired* and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l)

2.1.3 For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if (*2C*):

- an increase in Hb concentration** or a decrease in ESA dose is desired*** and
- TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

**Consistent with Recommendations #3.4.2 and 3.4.3.

***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

Table 3. KDIGO Recommendation Statements on Use of ESAs and Other Agents to Treat Anemia in CKD

Number	Guideline	Concur
	ESA INITIATION	
3.1:	Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (*Not Graded*)	✓
3.2:	In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (*1B*)	✓
3.3:	We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy (*2C*).	see comments
3.4.1:	For adult CKD ND patients with Hb concentration ≥10.0 g/dl (≥100 g/l), we suggest that ESA therapy not be initiated. (*2D*)	✓
3.4.2:	For adult CKD ND patients with Hb concentration <10.0 g/dl (<100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (*2C*)	✓
3.4.3:	For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0-10.0 g/dl (90-100 g/l). (*2B*)	✓
3.4.4:	Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (*Not Graded*)	see comments
3.4.5:	For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (*2D*)	✓
	ESA MAINTENANCE THERAPY	
3.5.1:	In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)	see comments
3.5.2:	Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)	see comments
3.6:	In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)	✓
3.7:	In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (*2D*)	✓
	ESA DOSING	
3.8.1:	We recommend determining the initial ESA dose using the patient's Hb concentration, body weight, and clinical circumstances. (*1D*)	✓
3.8.2:	We recommend that ESA dose adjustments be made based on the patient's Hb concentration, rate of change in Hb concentration, current ESA dose and clinical circumstances. (*1B*)	✓
3.8.3:	We suggest decreasing ESA dose in preference to withholding ESA when a downward adjustment of Hb concentration is needed. (*2C*)	✓
3.8.4:	Re-evaluate ESA dose if (*Not Graded*):	
	• The patient suffers an ESA-related adverse event	✓
	• The patient has an acute or progressive illness that may cause ESA hyporesponsiveness (See Recommendations 3.13.1-3.13.2)	✓
	ESA ADMINISTRATION	
3.9.1:	For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, we suggest either intravenous or subcutaneous administration of ESA. (*2C*)	see comments
3.9.2:	For CKD ND and CKD 5PD patients, we suggest subcutaneous administration of ESA. (*2C*)	✓
	Frequency of administration	
3.10:	We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (2C)	✓
	TYPE OF ESA	
3.11.1:	We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (*1D*)	✓

(Continued)

Table 3 (Cont'd). KDIGO Recommendation Statements on Use of ESAs and Other Agents to Treat Anemia in CKD

Number	Guideline	Concur
3.11.2:	We suggest using only ESAs that have been approved by an independent regulatory agency. Specifically for 'copy' versions of ESAs, true biosimilar products should be used. (*2D*)	✓
	EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HEMOGLOBIN CONCENTRATION	
	Frequence of monitoring	
3.12.1:	During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (*Not Graded*)	✓
3.12.2:	For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (*Not Graded*)	✓
3.12.3:	For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (*Not Graded*)	see comments[a]
	Initial ESA hyporesponsiveness	
3.13.1:	Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. (*Not Graded*)	✓
3.13.2:	In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (*2D*)	✓
	Subsequent ESA hyporesponsiveness	
3.14.1:	Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (*Not Graded*)	✓
3.14.2:	In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (*2D*)	✓
	Management of poor ESA responsiveness	
3.15.1:	Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (*Not Graded*)	✓
3.15.2:	For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, accounting for relative risks and benefits of (*2D*):	
	• decline in Hb concentration	✓
	• continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required, and	✓
	• blood transfusions	✓
	ADJUVANT THERAPIES	
3.16.1:	We recommend not using androgens as an adjuvant to ESA treatment. (*1B*)	✓
3.16.2:	We suggest not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (*2D*)	✓
	EVALUATION FOR PURE RED CELL APLASIA (PRCA)	
3.17.1:	Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (*Not Graded*):	
	• Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week *OR* requirement of transfusions at the rate of approximately 1 to 2 per week, *AND*	✓
	• Normal platelet and white cell counts, *AND*	✓[b]
	• Absolute reticulocyte count less than 10,000/μl	✓[b]
3.17.2:	We recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (*1A*)	✓
3.17.3:	We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (*1B*)	see comments

Note: This chapter does not discuss iron, which is covered in chapter 2 of the KDIGO guideline. Reproduced with permission of KDIGO from the *KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease*.[1]

[a]See Chapter 1 monitoring of anemia in CKD.

[b]Related to guideline 3.15.2 "blood transfusions."

Commentary

The KDIGO anemia guideline differs from the 2008 CSN anemia guideline, which recommended maintaining a ferritin $>$ 100 μg/L in CKD-ND and CKD-PD and $>$200 μg/L in CKD-HD and a transferrin saturation (TSAT) $>$ 20% in all groups.[9] The 2012 KDIGO guideline does not include an upper threshold for administration of iron therapy.

Serum ferritin and TSAT are imperfect biomarkers of iron deficiency in patients with CKD. Bone marrow examination shows little or no stainable iron with a TSAT $\leq$ 20% and ferritin $\leq$ 100 μg/L in patients with

Table 4. KDIGO Recommendation Statements on Red Cell Transfusion to Treat Anemia in CKD

Number	Guideline	Concur
	USE OF RED CELL TRANSFUSION IN CHRONIC ANEMIA	
4.1.1:	When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (*1B*)	✓
4.1.2:	In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (*1C*)	✓
4.1.3:	When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (*2C*):	
	• ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)	✓
	• The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)	✓
4.1.4:	We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (*2C*)	✓
	URGENT TREATMENT OF ANEMIA	
4.2:	In certain acute clinical situations, we suggest patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (*2C*):	
	• When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)	✓
	• When rapid pre-operative Hb correction is required	✓

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CKD-ND and CKD-PD (and in CKD-HD when ferritin is $\leq$200 μg/L).[10-12] These thresholds indicate absolute iron deficiency and are the strongest indication for iron therapy.

Studies addressing additional responsiveness to iron, or relative iron deficiency, in CKD-HD patients include an open-label randomized controlled trial of 42 patients; Hb levels were maintained on 40% lower ESA doses with the higher TSAT targets (TSAT, 30%-50%; ferritin, 738 μg/L) compared to a lower TSAT (TSAT, 20-30%; ferritin, 298 μg/L).[13,14] Studies examining a higher ferritin threshold demonstrated a 28% reduction in ESA dose in patients randomized to a ferritin target of 400 μg/L versus 200 μg/L.[16] The DRIVE (Dialysis Patients' Response to IV Iron with Elevated Ferritin) study demonstrated a greater Hb response in patients receiving 1,000 mg of intravenous (IV) iron with ferritin levels of 500-1,200 μg/L and TSAT $<$ 25%; however, all patients received a 25% increase in ESA dose.[15] Interestingly, ferritins $<$ 800 or $>$ 800 μg/L had no relationship to the magnitude or likelihood of responsiveness to IV iron.

There have been no randomized controlled trials in CKD-ND and CKD-PD patients comparing ferritin or TSAT thresholds. However, a recent diagnostic study adds valuable insight to the challenges of both diagnosing iron deficiency and its ability to predict a Hb response.[10] Iron sucrose, 1,000 mg, IV was given to 100 ESA- and iron-naïve CKD-ND patients. TSAT, ferritin, and Hb responses were of comparable (but limited) utility in identifying depletion of bone marrow iron stores. Additionally, TSAT, ferritin, and bone marrow parameters were insufficient to confidently predict Hb response to iron administration. Despite this, the ratio of responders to nonresponders was greatest using a combination of TSAT of 20% and ferritin of 100 μg/L in CKD-ND.

Based on limited studies, Hb levels increase with iron administration in both CKD-HD and CKD-ND patients, at higher TSAT and ferritin thresholds. However, the degree and variability of responsiveness will be lower when the TSAT is $>$30%.[10,16]

The use of iron to increase Hb and avoid or reduce exposure to ESAs and blood transfusions is balanced against its known and unknown toxicity. KDIGO states "there is only very limited evidence in patients with CKD that informs any decision about defining any specific upper limits for iron status targets in guiding iron treatment."[1(p23)] The proposed ferritin threshold of $\leq$500 μg/L is not based on trials addressing clinical toxicity, but on evidence of greater hepatic iron deposition at that level.[17] As a result, each clinician should weigh the likelihood of achieving an increase in Hb or reduction in ESA dose against the perceived risk to the patient they are treating.

Implications Within Canadian Health Care

1. The balance between risks and benefits of ESAs, iron, and red blood cell transfusion has changed since publication of the 2008 CSN anemia guidelines. There is good evidence (*1B*) to support the administration of iron in adult CKD patients when the TSAT and ferritin thresholds are above 20% and 200 μg/L (or 100 μg/L in CKD-ND and CKD-PD). A therapeutic trial of iron can be considered in those where an increase in Hb or reduction of ESA or avoidance of ESA and transfusion is desired, while recognizing that an increase in Hb is less likely when TSATs are $>$30% and ferritins are $>$500 μg/L.

Table 5. Timing Between Intravenous Iron Administration and Follow-up Testing

IV Iron	Dose	Timing of Ferritin and TSAT Retest
Iron dextran	25- to 125-mg maintenance dosing and 500-mg infusions	7 d postdose
	≥1 g includes 10 × 100 mg loading doses	14 d postdose
Iron sucrose (Venofer)	Not specified	48 h postdose
Sodium ferric gluconate (Ferrlecit)	125-mg maintenance dosing	7 d postdose
Ferumoxytol (Feraheme)	510 mg × 2 doses given 3 days apart	14 d after 2nd dose

Abbreviations: IV, intravenous; TSAT, transferrin saturation.
Sources:[59-62]

2. However, as opposed to the KDIGO anemia guideline, the CSN anemia work group feels the current evidence does not permit a clear delineation for an upper limit of TSAT or ferritin levels.

Iron Status Evaluation

2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)

Commentary

The KDIGO anemia guideline recommends more frequent iron status testing following a course of IV iron but details on timing of ferritin and TSAT monitoring in relation to administration of IV iron are not discussed.

IV iron complexes are cleared from the systemic circulation by reticuloendothelial cells, which have a time-limited capacity to clear IV iron. This can result in a prolonged half-life, with serum iron and ferritin values remaining significantly elevated for a period of time postinfusion. In addition, ferumoxytol and iron dextran release iron from their carbohydrate complexes more slowly than iron sucrose and sodium ferric gluconate, which contributes to the time delay in stabilization of serum iron and ferritin values postinfusion.

Implications Within Canadian Health Care

1. Iron status should be checked after IV iron administration after an appropriate time interval as outlined in Table 5.

Cautions Regarding IV Iron Therapy

2.3: When the initial dose of IV iron dextran is administered, we recommend (*1B*) and when the initial dose of IV non-dextran iron is administered, we suggest (*2C*) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

Commentary

There are 4 IV iron products available in Canada: iron dextran (Infufer [Sandoz Canada Inc], DexIron [Lutipold Pharmaceuticals Inc]), iron sucrose (Venofer [Genpharm Inc]), sodium ferric gluconate (Ferrlecit [Sanofi-Aventis Canada Inc]), and ferumoxytol (Feraheme [Takeda Canada Inc]). For the initial dose of iron dextran (Infufer, DexIron), product labeling recommends a test dose of 25 mg gradually over at least 5 minutes followed by an observation period of at least 1 hour before the remainder of the initial therapeutic dose be given.[18,19] Canadian product monographs were modified in January 2013 for iron dextran, iron sucrose, and sodium ferric gluconate to include a 30-minute postinfusion monitoring period.[18-21] Canadian labeling recommendations for the newer IV iron, ferumoxytol, also includes a 30-minute observational period following injection.[22]

Previous studies have compared rates of adverse drug events (ADEs) with the different IV iron products using data from registries or by comparing ADEs collectively from observational or clinical trials.[23-31] The absolute rates of life-threatening ADEs have been reported as 0.6, 0.9, and 3.3 per million for iron sucrose, sodium ferric gluconate complex, and low-molecular-weight iron dextran, respectively.[23] A recent analysis with ferumoxytol reported higher rates of ADEs per million units sold compared to iron sucrose or sodium ferric gluconate[26]; however, additional comparative safety information is needed. Current extrapolation of incidence rates from registry-based research has several limitations, including lack of differentiation of first versus subsequent dose and severity of the reaction.[32]

The distinction between immune-allergic and non-allergic or free iron–related ADEs is important. However, it is difficult to discern if ADEs to IV iron are related to an allergic or hypersensitivity reaction or associated with the rapid release of labile or free iron after larger doses or more rapid administration.[33-35] The nature and frequency of ADEs associated with IV iron administration is debatable.

Implications Within Canadian Health Care

1. Any type of IV iron may cause hypersensitivity or other reactions due to free iron and in rare cases life-threatening ADEs and all patients should be monitored for signs and symptoms of hypersensitivity during and after IV iron administration for at least 30 minutes and until clinically stable following completion of the infusion.

2. There is no strong evidence to extend the post-infusion observational period from 30 minutes to 60 minutes as suggested by KDIGO. IV iron should be administered when personnel and resuscitative interventions are immediately available for the treatment of serious hypersensitivity reactions.

ESA Initiation

3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy (*2C*).

Commentary

We do not have estimates of the prevalence of active malignancy (or a standard definition of active malignancy), history of stroke, or history of malignancy in the Canadian CKD-ND population, but data from the Canadian Organ Replacement Register (CORR) report that 14% of CKD-D patients have a history of stroke or transient ischemic attack, and over 12% have a history of malignancy.[36] The use of ESAs requires careful consideration in patients with CKD-ND and CKD-D and active malignancy or a history of stroke or malignancy.

These concerns arise in part from TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy).[37] In this trial, among patients with a history of malignancy, mortality related to cancer was higher among those assigned to darbepoetin alfa than among those assigned to placebo ($P = 0.002$); these findings are consistent with those in a meta-analysis.[38] It should be noted that the result was a subgroup analysis and the difference in overall deaths among the subgroup of patients with a history of malignancy was not statistically significant ($P = 0.13$). Moreover, it remains unclear if outcomes would have been better if ESAs had not been used at all in the placebo group, as opposed to rescue therapy with ESAs at Hb of 90 g/L. Given the level of evidence, it would seem reasonable to consider initiation of ESAs at lower levels of Hb (90 g/L) and to use a lower Hb range (90-105 g/L) in people with a history of malignancy (except for nonmelanoma skin cancer).

Systematic reviews of studies where ESAs have been used to target higher Hb levels in patients with active malignancy (but without CKD), especially when cure is anticipated, have noted an increased risk of death.[39] Of note, in the oncology anemia guidelines, the types of cancers for whom curative therapy is the intent have been noted to be early-stage breast cancer, Hodgkin and non-Hodgkin lymphoma, testicular cancer, and early-stage lung cancer, among others.[40]

Regarding the risk of stroke, this is based on several randomized trials noting an increased risk of stroke in the high target ESA arm[41] and a post hoc analysis of TREAT showing that the increased risk of stroke was significantly higher in people with a prior history of stroke or transient ischemic attack.[42,43] While avoiding the use of ESAs entirely in patients with a history of stroke or transient ischemic stroke may not be reasonable, we recommend a lower Hb target of 90-105 g/L, which is consistent with the control arm of the trials listed above.

Implications Within Canadian Health Care

1. The CSN workgroup agrees that ESAs should be used with caution, if ever, in patients with active malignancy.

2. In patients with a history of stroke, recent transient ischemic attack, or a history of malignancy (aside from nonmelanoma skin cancer), we suggest initiating an ESA at Hb of 90 g/L and to aim for an Hb in the range of 90-105 g/L.

3. Use of ESAs in these circumstances should occur only after discussion with patients at risk, who have been informed of the increased risk of stroke and cancer mortality associated with ESA use and the risks of transfusion therapy.

Individualization of ESA Therapy

3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/L). (*Not Graded*)

Commentary

It is important to clarify that this is opinion based and does not seem consistent with guideline statement 3.4.1, which states not to start an ESA if Hb $>$ 100 g/L. Symptoms of anemia are extremely vague and can emulate uremic symptoms, old age, deconditioning, and neuropathy, among others. The placebo response to ESA is high (ie, quality of life improves in patients in the control arms of ESA normalization trials) and quality-of-life difference across such a small difference in Hb would likely not be clinically detectable.[44]

Implications Within Canadian Health Care

1. The CSN work group agrees that initiation of ESAs in patients with CKD and Hb > 100 g/L should not generally be undertaken.

ESA Maintenance Therapy

3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)

3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)

Commentary

Given that trials comparing lower and higher Hb target strategies have shown either no difference or increased risk for the higher Hb target strategies, the US Food and Drug Administration (FDA) has mandated lower Hb targets, stressing customized therapy for individual patients, with use of the lowest possible ESA dose required to reduce the need for transfusions.[45] The revised label also recommends lowering the ESA dose when Hb exceeds 100 g/L and 110 g/L in patients with CKD-ND and CKD-D, respectively.[45] While the FDA perspective is generally consistent with the evidence from clinical trials,[37,46,47] some have expressed concerns that a lower Hb target level could increase the risk that patients may face red blood cell transfusions and diminished quality of life.[48] With respect to the risk of red blood cell transfusion, in studies comparing near-normal and low Hb targets, the risk of transfusion (among trials in which this was reported as an outcome) was 13.7% and 19.6% in the near-normal and low-Hb arms, respectively (relative risk, 0.69; 95% confidence interval, 0.57-0.82).[49] While red blood cell transfusion is associated with adverse effects (including alloimmunization), the data presented in the systematic review support the contention that the reduced risk of transfusion associated with near-normal Hb targets is outweighed by the 17% greater risk of death and 34% greater risk of access thrombosis.[49]

Another systematic review investigated the effect of Hb target on quality of life in patients whose Hb target levels were either low (90-120 g/L) or near-normal (>120 g/L).[44] The authors found poor reporting but did note statistically significant changes in 4 of 8 domains of the 36-Item Short Form Health Survey (SF-36). Of note, the changes were all well below the threshold for a minimal clinically important difference.[50] TREAT included data on quality-of-life outcomes for all domains that were measured, reporting mean changes of 4.2 and 2.8, respectively, at 6 months in the Functional Assessment of Cancer Therapy–Fatigue (FACT-Fatigue) scale for the darbepoetin and placebo groups ($P < 0.001$). As the TREAT investigators explain, this corresponds to an additional 6% of patients in the darbepoetin group experiencing a clinically detectable change in FACT-Fatigue scores ($P = 0.002$); this finding implies that 17 additional patients would need to be treated to near-normal levels with darbepoetin to have one individual achieve a clinically detectable change in FACT-Fatigue score.[37]

With respect to individualizing therapy in patients to intentionally raise the Hb above 115 g/L and improve quality of life, the above quality-of-life findings are consistent with the apparent clinical link between ESA use and better quality of life being due to a placebo or healthy patient effect and do not support increasing Hb above 115 g/L. Recent trials[37,47] support a consistent trend to increased risk with ESA use targeting near-normal Hb levels in CKD-ND and CKD-HD patients with anemia; however, they do not provide specific data on the risk of targeting Hb within the range of 115 to 130 g/L.

Implications Within Canadian Health Care

1. The CSN work group recommends that for CKD patients with anemia on ESAs, an acceptable range for Hb is 95-115 g/L with a target of 100-110 g/L.

2. The CSN work group does not support the use of ESAs to target Hb > 115 g/L, since the impact on quality of life and adverse events is uncertain.

ESA Administration

3.9.1: For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, we suggest either intravenous or subcutaneous administration of ESA. (*2C*)

Commentary

Darbepoetin alfa and epoetin alfa are the currently approved ESAs in Canada. Darbepoetin alfa dosing requirements are not different between the IV and subcutaneous routes of administration based on pharmacokinetic properties.[49] However, epoetin alfa administered by the IV route results in a significantly shorter half-life compared to the subcutaneous administration, increases dosages by 13% to 26% based on past Canadian studies, and requires more frequent dosing to achieve similar Hb targets.[51-54] The cost reduction associated with subcutaneous administration of epoetin alfa, based on an average wholesale price of $14.25/1,000 units, with an Hb target of 105 to 120 g/L, has been estimated at Can $2,817 per patient per year.[49] Accordingly, it has been stated that the merits of reimbursing only subcutaneous epoetin alfa should be explored, but to date, no provincial government has implemented this restriction.[49,55] Be-

tween 1998 and 2002, the risk of pure red cell aplasia (PRCA) associated with subcutaneous epoetin alfa can probably be attributed to leachates from uncoated rubber stoppers of prefilled syringes.[56] This risk has returned to baseline levels since coating the stoppers, but most Canadian hemodialysis centers continue to use IV epoetin alfa.[49,57]

Implications Within Canadian Health Care

1. Administration of epoetin alfa should be given by the subcutaneous route to CKD 5HD patients. Darbepoetin alfa can be given by either the subcutaneous or IV routes.

2. Patients who experience severe pain or bruising with subcutaneous injections due to cachexia, thrombocytopenia, or other underlying disorders may receive IV epoetin alfa.

Subsequent ESA Hyporesponsiveness

3.14.1: Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (*Not Graded*)

3.14.2: In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (*2D*)

Commentary

The issue of hyporesponsiveness is important in patients with CKD as their risk of cardiovascular events and mortality is extremely high, even when patient comorbidity is accounted for by adjustment.[42] Since ~15% of patients with CKD-D have ESA resistance,[58] there is an immediate need for studies to discern optimal anemia management in this population. There has been uncertainty in the definition of ESA hyporesponsiveness, though the definition provided by KDIGO seems reasonable. Given the absence of definitive clinical trials of hyporesponders and the safety concerns with higher Hb targets (which often require higher ESA doses), monitoring of patients using higher ESA dosing seems prudent.

Below, we provide some recommended dosing regimens for epoetin alfa and darbepoetin alfa. Given that the suggested starting dose for epoetin alfa is 20-50 U/kg/wk and darbepoetin alfa is 0.45 μg/kg/wk; for an 80-kg person, this would equate to 1,600 to 4,000 units thrice weekly of epoetin alfa or 40 μg/wk of darbepoietin alfa. The recommended maximal dose would be in the range of epoetin alfa, 3,200-8,000 U thrice weekly, or darbepoetin, 80 μg/wk.

Implications Within Canadian Health Care

1. The CSN working group recommends systems/protocols be implemented to identify and review patients receiving high-dose ESAs.

Evaluation for PRCA

3.17.3: We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (*1B*)

Commentary

Peginesatide does not currently have Health Canada approval and was recently withdrawn from the US market in February 2012 based on reports of anaphylaxis.

Implications Within Canadian Health Care

1. The CSN work group does not recommend using peginesatide. However, if and when available and approved by Health Canada, it could be considered for use in patients with antibody-mediated PRCA.

TRANSLATING THIS COMMENTARY INTO PRACTICE CHANGE IN CANADA

The Canadian Kidney Knowledge Translation and Generation Network (www.CANN-NET.ca) is working with the CSN guidelines group to implement priority recommendations identified by medical leads of Canadian kidney programs. The prioritization exercise identified the following statements from the KDIGO anemia guideline[1] as priority areas for knowledge translation:

3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, and hypertension). (*1B*)

3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy (*2C*).

3.15.2: For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, accounting for relative risks and benefits of (*2D*):

- decline in Hb concentration
- continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required, and
- blood transfusions

4.1.4: We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (*2C*)

It is the expectation that the CANN-NET knowledge translation group will develop the tool and measures necessary to assist with dissemination of the updated KDIGO anemia guideline with the Canadian context as provided in this document.

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APPENDIX

Conflict of Interest Information for Work Group Members

Member	Type of Conflict of Interest	Role	Period	Sponsor
Louise M. Moist	None			
Stéphan Troyanov	None			
Colin T. White	None			
Lori D. Wazny	None			
Jo-Anne Wilson	Advisory board	Member	1 year	Takeda
Phil McFarlane	Advisory board	Speaker		Amgen
	Unrestricted grant	—		Takeda
	Research grants	—		Janssen
Lori Harwood	None			

(Continued)

Appendix (Cont'd). Conflict of Interest Information for Work Group Members

Member	Type of Conflict of Interest	Role	Period	Sponsor
Manish M. Sood	Speaker fees	Visiting speaker	Fall 2012	Janssen
	Advisory board	Member	2011-present	Roche
	Speaker	Speaker	2011	Amgen
	Speaker	Speaker	2010	Sanofi
Steven D. Soroka	Advisory board	Chair	2010-2013	Amgen
	Advisory board	Chair	2012-2013	Takeda
Adam Bass	None			
Braden J. Manns	Unrestricted grant	Co-Investigator	2010-2014	Roche

Note: Information provided concerns the past 3 years and is restricted to companies that make products related to the diagnosis or management of anemia in CKD.