AJKD
KDOQI Commentary

KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD

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The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for Anemia in Chronic Kidney Disease provides clinicians with comprehensive evidence-based recommendations to improve patient care. In this commentary, we review these recommendations and the underlying evidence. Most recommendations are well reasoned. For some, the evidence is unclear and recommendations require some qualification. While the KDIGO guideline stresses the potential risks of intravenous iron therapy, withholding iron might have its own risks. The recommendation to avoid hemoglobin levels falling below 9 g/dL sets a lower bound of "acceptability" that may increase blood transfusion. Given the lack of research supporting the optimal transfusion strategy for end-stage renal disease patients, it is difficult to weigh the risks and benefits of red blood cell transfusion. We find a paucity of evidence that hemoglobin concentration targeted between 11 and 11.5 g/dL is associated with a safety risk. Although the evidence that erythropoiesis-stimulating agent use improves patient quality of life is poor, it is possible that the instruments used to measure quality of life may not be well attuned to the needs of chronic kidney disease or dialysis patients. Our last section focuses specifically on the recommendations to treat anemia in children.
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The KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for anemia in chronic kidney disease (CKD) was published in 2012.[1] An international group of experts, led by John J.V. McMurray and Patrick S. Parfrey, with the assistance of an evidence review team from Tufts Medical Center in Boston, created comprehensive, evidence-based guidance for the treatment of anemia in CKD, tempered by the substantial judgment of experienced clinicians. Our NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) commentary group, selected as independent experts in this field, has reviewed these KDIGO recommendations and comments on this up-to-date and well-considered guideline.

Clinical practice is driven by many forces: best clinical evidence, patient and physician preferences, financial conditions, and regulatory requirements. For anemia management in particular, the United States has seen much recent activity that has impacted on anemia treatment: the US Food and Drug Administration (FDA) has changed the labeling of erythropoiesis-stimulating agents (ESAs) to reflect the risks of targeting hemoglobin (Hb) concentrations at or close to normal levels, in light of the relatively sparse evidence that ESAs improve the quality of life (QoL) for patients with CKD. In addition, the Centers for Medicare & Medicaid Services (CMS), the major payor for CKD care in the United States, has changed the method of payment for the dialysis procedure to now include ESAs and parenteral iron in the "bundle" of care reimbursed under this capitated system, effectively removing these medications as profit centers for dialysis centers. Although these regulatory and payment changes have had a substantial effect on prescribing patterns and affect how anemia in CKD is managed, we make few comments on these forces in this commentary, focusing primarily on the evidence and clinical judgment required for best medical care.

METHODOLOGY USED TO DEVELOP GUIDELINE

The evidence-gathering strategies for the KDIGO guideline are based on studies published through March 2012 and appear to be comprehensive, systematic, and unbiased. Using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) template, guideline recommendations are codified by strength of the recommendation (Levels 1 and 2) and quality of the supportive evidence (Grades High [A], Moderate [B], Low [C], and Very Low [D]). In this scheme, a Level 1 Grade A treatment would generate a statement beginning with "We recommend" (based on a Level of

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1), most patients should receive the recommended action (also based on Level of 1), and the quality of evidence is High because raters are confident that the true and estimated effects of the studies lie in close numerical proximity. However, subjectivity is inevitable, even when individual studies provide clear and consistent results. Statements beginning with "We recommend" should be examined very carefully. For example, when treatments produce large effects on a clinically relevant primary outcome in well-designed, generalizable, randomized trials, making statements beginning with "We recommend . . ." should be straightforward and unlikely to generate controversy or debate. In contrast, it is more difficult to come to a single recommendation when study results are not as straightforward (eg, similar event rates for primary outcomes but differences in important secondary outcomes or prespecified patient subgroups).

Intuitively, one would expect that Level 1 or "We recommend" statements would usually be accompanied by Grade A or High-quality evidence. It is interesting, then, that although 40.5% of the 37 recommendations were graded as Level 1, only 5.4% had an A grade for quality of evidence. Rather, some recommendations are "not graded," suggesting that these statements are based largely on expert opinion rather than on objective evidence. Finally, there were several instances in which statements implying strength of effect were used without quantifying effect size and confidence intervals in the supporting text of the KDIGO document. This approach is inherently subjective and should lead us to scrutinize these recommendations with particular care.

In the following, numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original. Not all guideline statements are included; only those that the work group thought required comment or qualification are reproduced here. All material is reproduced with permission of KDIGO.

GUIDELINE STATEMENTS AND COMMENTARY

Testing for Anemia

Frequency of testing for anemia

1.1.1: For CKD patients without anemia (as defined . . . 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
- at least monthly in patients with CKD 5HD

[See Recommendations 3.12.1-3.12.3 for measurement of Hb concentration in patients being treated with ESA.]

Investigation of anemia

1.3: In patients with CKD 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

Commentary

KDIGO made recommendations for testing of Hb concentration for patients with CKD with and without anemia and for diagnostic studies to be used in anemic adults and children with CKD. Not unexpectedly, no randomized trials were available to inform this section of the guideline. Nevertheless, most of the recommendations were similar to previous guideline documents and unlikely to generate much controversy. One notable exception, however, was the recommendation to measure Hb concentration at least annually in all patients with CKD stage 3. In practice, one could argue about the necessity of this among patients with nonprogressive or slowly progressive early-stage CKD. For example, the case for annual Hb measurement in an adult without anemia, with a stable glomerular filtration rate of 59 mL/min/1.73 m^2 but no albuminuria, is hardly compelling.

KDIGO continued to recommend the use of serum ferritin concentration and transferrin saturation (TSAT) to define iron stores and iron availability. For all their imperfections, these metrics remain our best routinely-available tools to assess iron status and manage iron supplementation. In the absence of superior, cost-effective, and easily applicable alternatives, this approach seems reasonable.

Use of Iron Agents for Anemia Treatment (Recommendations 2.1.1-2.1.3)

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 risk 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
- 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.

Commentary

Among patients with CKD, iron therapy has the potential to increase Hb concentration or decrease ESA dose when TSAT is ≤30% and should be considered. However, the guideline recommendation for iron therapy is more complex when TSAT and serum ferritin are high, but Hb is low. The KDIGO guideline recommendations point out that in most patients with TSAT >30% or serum ferritin >500 ng/mL, any erythropoietic response to iron supplementation alone will be small, and the safety of giving additional iron has been assessed in very few patients: "It is the consensus of the Work Group that additional IV iron should not routinely be administered in patients with serum ferritin levels that are consistently >500 ng/ml." The DRIVE (Dialysis Patients' Response to Intravenous Iron With Elevated Ferritin) Study[2] showed that intravenous (IV) iron administered to patients with ferritin concentrations >500 ng/mL reduced ESA doses and subsequent health care costs. While the limited power afforded by the sample size of the DRIVE trial should be acknowledged, we believe that it still merits consideration when balancing potential risks of IV iron administration against ESA dose, transfusions, and costs. KDIGO suggests that, for selected patients, "a therapeutic trial of additional iron (i.e., a single course of up to 1,000 mg of iron over a period of several weeks which can be repeated as needed) may be undertaken in patients with serum ferritin > 500 ng/ml after due consideration of potential acute toxicities and long-term risks."

The KDIGO guideline recommendations repeatedly express concern about the risks of IV iron administration. They state, for example, that "It is important that the short and long-term safety of oral and intravenous (IV) iron agents, when known, be carefully considered when iron therapy is prescribed, and that the potential for as yet undiscovered toxicities also be taken into account." Although we understand that concern about possible long-term risks has not been eliminated by adequately powered studies, we also underscore that there are currently no data available that suggest long-term IV iron administration in moderate doses causes worse outcomes. Furthermore, withholding IV iron could have unintended consequences. In focusing exclusively on caution related to potential risks associated with iron administration, the KDIGO guideline statements do not adequately emphasize that withholding IV iron might have its own risks. We encourage research to evaluate the long-term safety of iron administration. We believe that the degree of caution expressed by KDIGO is not supported by the available evidence and could have negative effects, such as sustained iron deficiency anemia, higher ESA dose requirements, and increased blood transfusions.

The guideline repeatedly includes cost as a variable influencing the choices made by treating physicians regarding treatment of anemia. However, we note that no formal assessments of the literature analyzing costs have been reviewed in the guideline. Whether physicians are practicing in the "bundled" payment environment of the US End-Stage Renal Disease (ESRD) Program or in similar or dissimilar payor environments, we agree that cost is an important determinant of treatment decisions, particularly when relative risks and benefits of different strategies are equivalent or unclear. Although no formal cost assessment has been done, Pizzi and colleagues[3] showed that IV iron administration in patients with high ferritin and low TSAT yielded cost savings. More iron may be less expensive than more ESAs and safer than higher doses of ESAs. We therefore believe that a therapeutic trial of IV iron (or in non–dialysis-dependent CKD patients [denoted as CKD ND in the guideline], a trial of oral iron therapy) could be considered when TSAT is low (≤30%), even if ferritin concentration is above 500 ng/mL. There is insufficient evidence upon which to base a recommendation for an upper ferritin limit above which IV iron must be withheld. A decision to administer iron in the setting of high ferritin would require weighing potential risks and benefits of persistent anemia, ESA dosage, comorbid conditions, and health-related QoL. In accordance with KDIGO recommendations, Hb response to iron therapy, TSAT, and ferritin should be monitored closely and further iron therapy titrated accordingly.

Use of Iron Agents for Anemia Treatment (Recommendations 2.1.4-2.1.5)

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 test (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*)

Commentary

The KDIGO guideline says, "The consensus of the Work Group is that a clearly defined advantage or preference for IV compared to oral iron was not supported by available evidence in CKD ND patients." Although we agree with this statement, we note that the guidelines issued by the European Renal Association and European Dialysis and Transplant Association recommend IV iron for non–dialysis-dependent CKD patients. A recent review of the randomized controlled trials performed to investigate this question noted that relevant studies reported inconsistent results and were too short to conclude whether the duration of oral iron administration was sufficient to answer the question definitively.[4] However, IV iron consistently achieved higher TSAT and ferritin values than oral iron. It is possible, then, that in the long run, IV iron may be superior to oral iron as a route of administration. The economic implications of choosing oral versus IV iron are complex and not easily resolved without a prospective and interventional study design.

Evaluating Iron Status and Cautions Regarding Therapy

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 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

We note that the guideline statements do not discriminate among different IV iron preparations, instead referring only to iron dextran and nondextran iron. Although head-to-head comparisons of the safety and short-term side effects related to the administration of these different preparations do not exist, there is evidence that high-molecular-weight preparations, ie, high-molecular-weight iron dextran, are associated with more adverse effects, specifically more acute reactions.[5] We therefore suggest that high-molecular-weight iron dextran should be avoided. We also note that product labeling for all IV iron preparations recommends having personnel and therapies immediately available for treatment of anaphylaxis and other hypersensitivity reactions. We believe this recommendation is consistent with the possibility of significant reactions with any nondextran irons, and therefore we also recommend resuscitative facilities be available when administering any formulation of IV iron.

Cautions Regarding Iron Therapy: Iron During Infection

2.4: Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

Commentary

Although there is theoretical evidence that iron overload stimulates bacterial growth,[6] definitive evidence from randomized controlled trials showing that IV iron administration exacerbates infection is lacking. Therefore, while we agree with the statement in the KDIGO guideline that "current evidence cannot provide a clear answer" about whether IV iron increases the risk for infection or for having a worse outcome with infection, we believe the potential risk of iron-induced worsening of infection outcomes must be weighed against the theoretical evidence that iron deficiency may itself impair response to infection.[7,8] We agree with the KDIGO statement: "Clinical judgment is necessary in each individual patient to assess whether there is an immediate need for IV iron (as opposed to delaying treatment until resolution of an infection), likelihood of achieving benefit from a dose of IV iron in the setting of an active infection, and the severity of an infection." In addition, although the association of transfusion with infection has not been specifically studied among patients with CKD, transfusion has been clearly associated with increased risk of infection in hospitalized surgical and nonsurgical patients.[9] Therefore we make no recommendation about the use or avoidance of IV iron in the setting of infection.

Initiating and Maintaining ESA Therapy

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*).

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*)

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*)

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*)

Commentary

KDIGO recommendations on the Hb target for ESA treatment in dialysis-dependent and non–dialysis-dependent CKD patients follow the change to the class ESA product labeling made by the FDA on June 24, 2011. The FDA emphasized that the Hb target range of 10 to 12 g/dL (100-120 g/L) should be replaced by the practice of using the lowest possible dose of ESA to prevent blood transfusions. The FDA now specifies that ESA dosing should be reduced or interrupted if the Hb level exceeds 11 g/dL (110 g/L), but that treatment of anemia in CKD with ESA therapy should be individualized. This means that an Hb target level or ESA dosing strategy should be informed by considering the risks and benefits for the individual patient. The KDIGO anemia guideline endorsed this cautious approach. Taken together, these are very welcome changes.

Notably, KDIGO recommends the initiation of ESA therapy for patients with CKD 5D (CKD stage 5 on dialysis) at the same threshold of less than 10 g/dL, as does the FDA, but adds the additional goal to avoid Hb falling below 9 g/dL. This recommendation was based on results from the Normal Hematocrit Study,[10] which reported that dialysis patients randomized to target Hb of 13 to 15 g/dL had worse outcomes than patients randomized to the 9- to 11-g/dL target. However, the KDIGO guideline draws attention to the lower boundary of 9 g/dL Hb in patients with non–dialysis-dependent CKD, even though TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy)[11] used this same lower boundary for rescue therapy in the placebo arm. We are concerned that the novel identification of a lower bound of "acceptability" may increase use of blood transfusion and expose patients eligible for kidney transplantation to the allosensitizing effects of such transfusions. In addition, although we agree with reducing the Hb level at which ESAs should be reduced or discontinued to 11 g/dL, we recognize that there is a paucity of evidence that an Hb concentration targeted between 11 and 11.5 g/dL is associated with a safety risk.

KDIGO took a slightly different approach than the FDA with respect to its consideration of health-related QoL benefits of anemia treatment. In its latest (June 24, 2011) iteration of the class ESA product label, the FDA removed the QoL benefits of ESA treatment as an indication for use of these drugs. KDIGO, in contrast, did not provide definitive guidance. It suggested that individualization of therapy may be reasonable in some patients, as "improvements in QoL at higher Hb concentration" are possible, leaving open the option that "ESA therapy may be started above 10.0 g/dl in some patients." Clearly, this disagreement reflects the difficulty in interpreting QoL evidence in this area. To make a reasonable judgment in an arena in which one is attempting to apply methods objectively to phenomena that are subjective within study participants, it would be desirable to have complete masking or "blinding" of patients and study-site investigators to treatment assignments, similar QoL instruments applied at similar intervals in all studies, and methods to weigh QoL changes against clinical events such as death, cardiovascular disease, and cancer. The quality of the evidence available to the KDIGO group to date falls far below these ideals. The double-blind Canadian normalization of hemoglobin trial in hemodialysis patients without overt cardiac disease demonstrated that treatment with erythropoietin improves many QoL scores (comparing placebo with mean Hb of 7.4 g/dL to the 2 target arms of 9.5-11.0 and 11.5-13.0 g/dL).[12] Subsequently, a Canadian/European trial of hemodialysis patients without overt cardiac disease reported that higher as compared to lower Hb concentration targets did not result in further positive QoL changes.[13] Few published studies have

demonstrated consistent QoL benefits. In the largest trial with sequential QoL instruments, the placebo rescue−controlled TREAT,[11] minimal improvement was seen with the fatigue-specific FACT (Functional Assessment of Cancer Therapy) instrument, but not the non–disease-specific and widely validated SF-36 (36-Item Short Form Health Survey) instrument. In the open-label CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency)[14] Study, no treatment-related difference was seen in any of the QoL domains. While the Normal Hematocrit Trial did not formally report QoL by treatment assignment in a tabular form, it did report that in the primary manuscript published in 1998, "The physical-function score on the quality-of-life questionnaire at 12 months increased by 0.6 point for each percentage-point increase in the hematocrit ($P = 0.03$)."[10] While this posttreatment assessment provides insight into the association between achieved Hb concentration and QoL changes, the intention-to-treat analysis comparing treatment groups in this study also failed to find any significant differences between target arms ($P = 0.97$).[15] Thus, it may be appropriate to conclude that reports of health-related QoL benefit are minimal or only modest when considered over all studies. Of course, it is possible that a subset of patients whose QoL improves with anemia treatment is unidentified in the larger group with little change in Qol scores. An alternative possibility is that the instruments currently used to measure QoL may not be well attuned to the needs of CKD or dialysis patients, especially for making the determination of clinically meaningful difference in QoL. The lack of a degree of exactness to this science has resulted in the removal of QoL from the class ESA product label and a "Not Graded" KDIGO recommendation to individualize anemia treatment when it comes to improving QoL. In light of this, we recommend that further studies be performed to evaluate more systematically whether there is a QoL benefit with partial anemia correction.

Reducing the Hb concentration threshold for ESA initiation raises concerns about the increased risk of blood transfusions. Since the ESA label was revised by the FDA in 2011, and the payment for "bundled" services in the United States was changed to include ESAs, the rate of blood transfusions has increased.[16] In contrast to the FDA product label for ESAs, the KDIGO guideline did not say that blood transfusions should be avoided. Rather, guideline 4.1.3 states "When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (grade *2C*): ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance) and/or the risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)." While we know about the risks of blood transfusion (eg, allosensitization of potential kidney transplant recipients, transfusion-related infections), we know less about the risks of modest anemia (Hb, 8-10 g/dL). It is therefore difficult to weigh the risks and benefits of red blood cell transfusion.

With respect to patients eligible for organ transplantation, the KDIGO guideline does specifically recommend avoidance of red blood cell transfusions when possible to minimize the risk of allosensitization (grade *1C*). It is important to emphasize that transplant candidacy is frequently determined in the first few years after initiating maintenance dialysis, particularly among minorities in whom disparities in access to transplantation have been reported. Therefore, we endorse the KDIGO emphasis to avoid blood transfusion in all patients eligible for transplantation, whether or not they are currently on the transplant waiting list.

The KDIGO guideline counsels caution in treating CKD patients with a history of prior stroke or cancer (guideline recommendation 3.3, grade *1B* and grade *2C*, respectively). In TREAT, there was an increased risk of stroke in patients treated with darbepoetin and an even greater risk in patients who had previously had a stroke.[11] In addition, TREAT reported an increased risk of cancer-related death in patients who had a history of cancer. However, the KDIGO guideline does not differentiate dialysis-dependent from non–dialysis-dependent CKD patients with respect to either the risk of stroke or cancer. It is useful to point out that the KDIGO guideline generalizes these findings in non–dialysis-dependent CKD patients to the dialysis-dependent CKD population, where these outcomes have not been demonstrated. On the other hand, since the CHOIR,[14] CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta),[17] and the Normal Hematocrit[10] Study were not placebo-controlled, and in TREAT,[11] the absolute risk of cancer-related death was relatively small, it could be argued that the effect of ESA on stroke and cancer has not been assessed adequately in patients on dialysis. Lastly, the consistency of results at least with respect to stroke should also be noted. In addition to the signal seen in TREAT, the Canadian/European trial conducted in early-vintage hemodialysis patients without overt cardiovascular disease also showed an increased risk of stroke with higher Hb concentration targets.[13] Taking all these points together, we agree with KDIGO about using caution when prescribing ESAs in patients with a prior history of stroke or cancer and point out that the evidence is stronger in the non–dialysis-dependent CKD compared to the dialysis-dependent CKD setting.

The KDIGO Anemia Work Group did provide a cutoff for the upper level for targeting Hb concentration. In contrast to the FDA's choice of 11 g/dL, the KDIGO recommendation was 11.5 g/dL. The panel reasoned: "The present suggestion not to exceed in general a Hb concentration limit of 11.5 g/dL (115 g/l) has been influenced by the fact that the upper boundary of the Hb concentration in the control group of the major ESA [randomized controlled trials] usually did not exceed 11.5 g/dL (115 g/l)." The choice of 11.5 g/dL as the top Hb cutoff adds confusion that is not strongly supported by evidence for either a benefit or a lack of a safety risk. Indeed, there may be a stronger rationale for 11 g/dL than 11.5 g/dL as a cutoff in dialysis-dependent CKD patients, as the control arm in the Normal Hematocrit Trial had a target of 9-11 g/dL (90-110 g/L). These considerations are likely to be moot in the United States because the FDA has selected 11 g/dL as the Hb cutoff at which they recommend clinicians should either interrupt or hold ESA treatment. We therefore continue to endorse the FDA-recommended upper cutoff of 11 g/dL (110 g/L).

Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hemoglobin Concentration: Frequency 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*)

Commentary

We generally agree with these guideline recommendations since they will allow for prompt dose adjustments in situations where the Hb concentration is increasing more rapidly or more slowly than is clinically desirable. However, it should be noted that Hb concentrations were measured weekly in the larger trials that provide most of the evidence for the KDIGO guideline statements. As noted in the KDIGO rationale statements for this section, response to ESA therapy is unlikely before 2 weeks, so we recommend measuring Hb concentration no more frequently than 2-week intervals for Recommendations 3.12.1 and 3.12.3.

Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hemoglobin Concentration: 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*)

Commentary

Initial ESA hyporesponsiveness as defined in these guideline recommendations appears to be predominantly based on a post hoc analysis study of darbepoetin responses in TREAT.[11] The goals of these 2 guideline recommendations are to minimize ESA dose escalations that are ineffective in increasing Hb concentration and that lead to an increase in cost, as well as the concern that "high ESA doses used in hyporesponsive patients may be toxic." Indeed, study participants who did not respond well to darbepoietin in TREAT (defined as a $<2\%$ relative change in Hb after 1 month) had a higher cardiovascular event rate than those who did respond.[11] We disagree with these recommendations. One month may not be a sufficient interval to determine ESA hyporesponsiveness in newly diagnosed anemia of CKD, especially if patients have ESA resistance from a number of causes. We also note that since TREAT studied non–dialysis-dependent patients, the results cannot easily be applied to patients initiating maintenance dialysis, a group that might be expected to have a greater burden of comorbid illness and a greater ESA requirement, even in the absence of nonrenal comorbidity. As the Work Group noted, this analysis of TREAT did not directly address the question of ESA "toxicity," and we believe strongly that the diagnosis of hyporesponsiveness should not rely on this speculation. Taken together, these 2 guideline statements limit dose titration to a short time period which could lead to persistent anemia. We suggest that, at a minimum, a 2-month period is more appropriate to determine if ESA hyporesponsiveness is present, during which time the potential causes of hyporesponsiveness can be identified and addressed (as recommended in Section 3.15.1).

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*)

Commentary

We agree with these statements. We understand that the statement about not using vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxyfylline was put forth as a suggestion because of the low

quality of the evidence. However, because these agents are rarely used for this indication, there are inadequate safety data in this context. Therefore, we believe that the balance between potential risks and benefits clearly favors avoiding use of these adjuvants until and unless new evidence becomes available. Recommending against their use poses no risk of withholding standard or clearly effective therapy at this time.

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*
- Absolute reticulocyte count less than 10,000/μl

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*)

Commentary

We agree that patients on stable ESA therapy who experience a sudden rapid decrease in Hb should be evaluated for pure red cell aplasia, although we recommend that they first be evaluated for new onset of blood loss. We note that the statement about peginesatide was formulated as a recommendation even though it was based on retrospective clinical data from a small number of patients.[18] Until recently, we agreed with suggesting this strategy (based on low-quality evidence), but recent safety concerns have led to the recall of all peginesatide drug within the United States and we now recommend against its use. There are data from nonrandomized[19,20] and randomized[21,22] trials to suggest that nandrolone decanoate can increase Hb levels in selected patients, and we suggest that clinicians consider the risks and benefits of using nandrolone to avoid transfusion among patients who cannot tolerate ESAs (although we agree with the recommendation against its routine use as an adjuvant to ESA for the general CKD population).

Red Cell Transfusion to Treat Anemia in CKD

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 an 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

Commentary

KDIGO's recommendations on transfusion are complete, well-balanced, and appropriately call attention to 2 major issues. First is the risk of blood transfusion–induced allosensitization, which affects the ability of an individual to receive a subsequent kidney transplant. The second is the lack of research examining whether important outcomes are affected by blood transfusions. The KDIGO guideline suggests that the decision to transfuse a patient with chronic anemia should be individualized rather than based on a single Hb threshold for all patients. Until research evidence is generated to the contrary, we support this suggestion.

Given the safety signal seen with ESAs, the product labeling for ESAs removed a lower limit of the goal Hb concentration range to avoid an increased risk of cardiovascular events. The mechanism whereby ESAs cause this higher risk of cardiovascular events has yet to be defined. With this change in labeling, the Quality Incentive Program for ESRD patients also removed the lower limit of the goal. Subsequently, Hb levels have fallen,[16] and the proportion of patients receiving blood transfusions has increased from approximately 9% to 22% from 2011 to 2012.[23] Although it is not clear if the increase was seen in the acute setting (ie, a smaller gastrointestinal bleed is now required to trigger a transfusion) or the chronic setting (ie, providers are responding to fluctuations in Hb level around a lower baseline), one could suggest that the increase in transfusions is related to providers maintaining the same Hb concentration thresholds for transfusion in this era of change in ESA thresholds. Unfortunately,

current research has not addressed the question of whether this higher rate of transfusion is appropriate.

Looking to transfusion guideline recommendations, it is noteworthy that there is some agreement between the recommendations put forth by the American Red Cross and the New York State Health Department.[24,25] Statements from both of these organizations conceptually agree that the treatment for chronic anemia should focus on the cause or mechanism and that the threshold for transfusion in chronic anemia in the absence of symptoms is approximately 7 g/dL. This is a threshold that is arguably much lower than traditionally entertained by nephrologists. Therein lies a tremendous dilemma that may not be clarified with additional research but rather may only be addressed through the individualization of therapy. As acknowledged in the KDIGO guideline, many symptoms experienced by people requiring dialysis may be consistent with anemia. This observation has provided the hypotheses that fuel our research to examine if better anemia management leads to improved QoL scores. However, the intention-to-treat analyses have not provided strong support for the conclusion that treating anemia improves these symptoms.[3,5] Speculation continues that QoL improvement may vary among individuals, and that perhaps individual Hb thresholds for transfusion may be best determined clinically by physician and patient.

In summary, this guideline appropriately recognizes the tremendous lack of research supporting a best transfusion strategy for patients with ESRD. The recent decrease in population Hb concentration combined with the increase in transfusions supports relatively constant thresholds for transfusion in the clinical community. Other current guidelines not tailored to patients with CKD suggest a much lower threshold than the clinical triggers the nephrology community has used, which may be a "hold-over" from previous clinical practice guidelines when Hb concentration targets were greater than 10.0 or 11.0 g/dL. As we are still focused on avoiding transfusions and enhancing QoL, a careful within-patient assessment of symptoms before and after transfusion may be the best strategy to determine a patient-specific threshold until better evidence is available.

PEDIATRIC-SPECIFIC GUIDELINE STATEMENTS AND COMMENTARY

Diagnosis of Anemia

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*)

Commentary

We agree that the lower threshold to diagnose anemia in children is age- and sex-dependent. The KDIGO guideline uses both World Health Organization and US National Health Examination Survey III data to identify a less than 5 percentile ± 2 SD Hb concentration target to set the threshold for anemia diagnosis based on patient age, but do not differentiate between boys and girls, since Hb concentration differences between the sexes before girls reach menarche is minimal. From these data, the work group identified an Hb level of approximately 0.5 g/dL (5 g/L) below the fifth percentile or −2 SD to diagnose anemia. We agree with these thresholds.

Treatment With Iron Agents

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*)

Commentary

We generally agree with the recommendations for iron therapy for all pediatric CKD patients with anemia, and with the initial route of oral iron for all patients, with consideration of IV iron preparations for patients receiving maintenance hemodialysis. Although neither dosing nor oral iron trial response time recommendations are provided, we would generally advocate for oral iron preparations to provide 3-6 mg of elemental iron per kilogram of target dry weight once daily for 3 months. If TSAT and/or ferritin levels fail to improve, IV iron repletion regimens have been studied in children with CKD receiving[26,27] or not receiving[28] hemodialysis. In addition, pediatric studies have reported effective IV iron maintenance strategies.[29,30]

ESA Initiation

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*)

Commentary

While we agree with a personalized approach to Hb concentration–directed ESA initiation based on individual patient need, this statement could lead to unin-

tended negative consequences depending on its interpretation. We suggest, in keeping with the adult guideline recommendations, that ESA initiation occur in all children with Hb concentration of 9-10 g/dL. In addition, since benefits may accrue to children in terms of exercise tolerance at hematocrit of 33%[31] and transfusion avoidance,[32] we support a lower limit of the goal Hb concentration of 11 g/dL, which is in keeping with the target lower limit in guideline statement 3.7.

ESA Maintenance Therapy

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*)

Commentary

As noted above, we support the lower limit of the goal Hb concentration of 11 g/dL. The range suggested by the KDIGO work group is quite narrow and may not be optimal. For instance, the Chronic Kidney Disease in Children (CKiD) cohort data demonstrate median Hb values ranging from 11.6 to 13.1 g/dL for children with CKD stage 4 to 2, respectively.[33] Data from the CMS' Clinical Performance Measures Project demonstrate mean Hb concentrations of 11.5 $\pm$ 1.6 (SD) g/dL in children receiving maintenance dialysis.[34] Thus, the narrow window recommended by the KDIGO group is exceeded by the interquartile range and standard deviations of these 2 large pediatric studies. We recommend a range of 11-13 g/dL to avoid the need for multiple dosing adjustments.

CONCLUSION

The KDIGO clinical practice guideline for anemia in CKD helps clinicians understand the evidence determining best practice and makes comprehensive evidence-based recommendations. The most significant change in this guideline compared with previous guidance is to move away from targets for Hb concentration and to use the lowest possible dose of ESA to prevent blood transfusions. Given the lack of research supporting a best transfusion strategy for ESRD patients, it is difficult to weigh the risks and benefits of red blood cell transfusion. We find a paucity of evidence that Hb concentration targeted between 11 and 11.5 g/dL is associated with a safety risk. While IV iron is helpful in the setting of iron deficiency, IV iron may be associated with some risk. We believe that the degree of caution expressed by KDIGO is not supported by the available evidence. Although the evidence that ESA use improves patient QoL is poor, it is possible that the instruments used to measure QoL may not be well attuned to the needs of CKD or dialysis patients. For children and adults, we support individualizing therapy to treat anemia of CKD and ESRD patients.

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