

## Responses to comments from CSN members on Anemia guidelines (June 15, 2007)

Comments (categorized by Issue)	Response
<p><b>Issue of Guidelines vs Recommendations:</b></p> <p>1) I think the KDOQI guidelines/recommendations distinction is useful, and for CSN to buck the trend and go with only recommendations (despite the strong evidence for a few of them) will be confusing. Unless you mean that there is not enough evidence to call any of this a guideline? If that is meant, then anemia is our best studied topic, all else are worse, so then CSN should not have a "guidelines committee" and should issue only recommendations, position statements and consensus statements. All this needs to be made consistent or it will be confusing to Canadian and non Canadian nephrologists alike.</p>	<p>This was discussed at CSN amongst the CSN Guideline Groups and it was decided that the CSN Guidelines Committees would continue to use "Guidelines only", as per the existing CSN Guidelines policy.</p> <p>See below for relevant changes to the introduction:          "The CSN Anemia Guidelines that follow are intended to rely on evidence and avoid opinion-based statements, where possible. Other similar workgroups have made a distinction between Clinical Practice Guidelines and Clinical Practice Recommendations, with Guidelines being provided when the Workgroup felt the evidence was sufficiently strong to make definitive statements about the appropriateness of clinical practice (6). Alternatively, Clinical Practice Recommendations were provided for statements based upon a lesser grade of evidence. The main reason for making this distinction was to highlight areas where adherence to a Guideline would be particularly likely to improve outcomes. While this is a reasonable goal, it is unclear whether it was achieved, and distinguishing between Guidelines and Recommendations is very subjective.</p> <p>Given the potentially arbitrary nature of the distinction between guidelines and recommendations, and to be consistent with previous CSN guidelines, we present only Clinical Practice Guidelines. In all cases, Guidelines are only made if the Workgroup is confident that adherence would do more good than harm."</p> <p>As such, within the amended document, CPGs are presented, rather than CPR's, as had been presented in the initial draft.</p>

<p><b>Consideration of costs within Guideline process:</b></p> <ol style="list-style-type: none"> <li>1) I continue to believe that recommendations from professional societies should not consider costs.</li> <li>2) In my opinion, clinical practice guidelines first and foremost must describe the risks and benefits of therapy and make recommendations on the use of a particular test/treatment in that regard. Most arguments against unnecessary treatment can be made on the grounds of either lack of evidence to show clinical benefit or the possibility of harm. In writing clinical guidelines we are surrogate advocates for the best care of patients, even if it is expensive. I would agree that when there is equivalence, we ought to choose those therapies which cost the least. We can inform the policy makers and the public/patients on what the costs are, and they may make decisions with our input on whether the financial cost is worth the medical risks/benefits that we can describe. If a test or treatment has benefit to the patient, we should be recommending it, notwithstanding that it may be expensive.</li> </ol>	<p>It is acknowledged that the most important first step in creating clinical practice guidelines is to understand the risks and benefits of therapy, or test. Cost is clearly not the first consideration. It should be noted that, in the majority of guidelines where cost was a significant consideration, in the end, cost did not figure into the decisions as extensively since there were also significant concerns around the safety of excessive amounts of iron, and higher doses of ESAs (required for higher hemoglobin targets).</p> <p>However, I would reiterate that if our goal is for these clinical practice guidelines to influence practice and policy, then if we do not take costs into account at all, we should not be surprised if our guidelines do not influence policy.</p>
<p><b>Appropriate hemoglobin target:</b></p> <ol style="list-style-type: none"> <li>1) I think you need a paragraph to discuss the gray zone of Hb 120 - 130 where there is just no data. I think recent statements might also be considered. Hb 120 -130 may or may not be OK, and transient elevations above 130 as is common in clinical practice may be OK too, as compared to sustained Hb &gt; 130 as is done in RCTs.</li> <li>2) I wonder if guideline 3.1.2 is a little too soft regarding the upper limit of the Hgb target. I mean, the recommendation does not state anything about making sure that the upper limit of 120 is not exceeded, given strong evidence for increased harm with target Hgbs of 130. Should there not be a statement saying that exceeding Hgb of 120 is not recommended (similar to statement about androgens in chapter 4)?</li> </ol>	<ol style="list-style-type: none"> <li>1. It is acknowledged that the majority of studies which compared high and intermediate hemoglobin targets used &gt; 130g/l as the high hemoglobin target range. Given the lack of studies using a target in the 120-130 range, it is correct that the safety and effectiveness is uncertain in this area. However, a presumption that safety concerns only begin above a hemoglobin of 130g/l may be incorrect. Given the lack of studies testing the 120 to 130g/l range, it is uncertain whether safety concerns (cardiovascular safety / vascular access failure) rise in a “linear fashion”, or whether there is an upper threshold. However, given that there are relatively small and uncertain quality of life benefits associated with targeting hemoglobin &gt; 130g/l, it does not appear that there would be any reason to target hemoglobin to above 120g/l, particularly given a recent Health Canada warning advising that hemoglobin should not be targeted above 120g/l.</li> </ol>

3) I do have a major concern with the section 3.1.2 on the target for ESA therapy. Central to my concern is the responsibility of physicians and policy-makers regarding harm. As physicians we have a fundamental responsibility to our patients to avoid harming them -- even when the harm results from well-intentioned actions (like raising their Hb). From a policy standpoint, the burden of proof for harm is not the same as for efficacy. The problem is exemplified by the way in which the unwanted results in CHOIR and CREATE have been discounted by some observers. These methodological caveats would be quite appropriate if they concerned efficacy. But almost all authorities acknowledge that a less stringent standard is required to demonstrate harm (for example,  $<0.10$  is often considered statistical evidence of harm). In part, this is because of the highly select nature of trial participants -- event rates and the risk of harm are always higher in the real world. Insisting that evidence of harm from a randomized trial is only valid if it is robust to multivariate adjustment, or that an increased risk of a hard clinical outcome (kidney failure) should be supported by an increased risk of an unvalidated surrogate outcome (rate of change in eGFR) misses the point. Again, these critiques are valid if the goal is to be conservative about the potential benefits of therapy...but we should not be overly conservative about concluding that a medication may cause harm. As recent events concerning other drug classes have clearly shown, it often takes years after a drug is marketed to demonstrate that it is actually harmful (or can be harmful under some circumstances, as I believe is the case for ESA). Therefore, policy-makers have a special duty to be cautious and respond appropriately to protect patients when there is reason to suspect that a drug MAY cause harm.

Below I outline why I strongly feel that the target should be lowered to a range of 100-110 g/l.

a) First, there is little or no good quality evidence that a Hb target of 120 is superior to 110 g/l. As you note, the evidence for QoL improvements is inconsistent and often clinically small even for the large differences in Hb between high- and intermediate-dose strategies. Therefore, it seems implausible that there would be a major difference between 110 and 120 g/l. As you know, the target range of 110-120 g/l was chosen somewhat arbitrarily at a time when there was an overwhelming belief that ESA would have a dramatic effect on QoL and improve hard outcomes for our patients. There was little evidence for this target then and no good quality data have

2-4. The major comments from these 3 members appear to raise concern with the upper limit of the hemoglobin target (120g/l) and whether the upper target should be lowered.

When considering such a change, the major considerations would appear to be the concern that the proposed target 100-120g/l would result in some patients having a hemoglobin  $>120$ g/l and that this would present a safety concern, as outlined in the recent Dear Health Care Professional Letter jointly authored by Health Canada and the makers of Eprex and Aranesp. Moreover, aiming for the higher target could be seen to be an inefficient therapy given that there is no evidence that clinical benefits will result from this slightly higher target. Alternatively, concerns with a slightly lower target (i.e. 105g/l or 100-110g/l) would potentially be a reduction in quality of life and possible a higher need for transfusions. With respect to quality of life, the only randomized study that has compared a low (95-110g/l) and intermediate (115-130g/l) target hemoglobin (the CANEPO study) did not show any difference in quality of life between these two targets. Moreover, it must be remembered that there were only small and inconsistent benefits to quality of life noted in the larger RCTs testing intermediate and high hemoglobin targets (many of these studies were negative for QOL). As such, it is unlikely that significant quality of life differences would exist between the proposed target and a slightly lower target. With respect to a higher risk of transfusion for a "slightly" lower hemoglobin target, interestingly, only a minority of the larger RCTs testing intermediate vs higher hemoglobin targets report the proportion of patients requiring a transfusion, suggesting that the risk did not differ in the majority of studies. The largest study which did report a difference in transfusion risk was the Besarab study, which reported that 31% of patients targeted to a hemoglobin of 100g/l required a transfusion, vs 21% of patients targeted to a normal hemoglobin. While this does not directly address the question under consideration, if a slightly lower

been published to support it since.

- b) Second (as you acknowledge), there is clear potential for harm with higher hemoglobin targets. Given this, if we also accept that low targets are not harmful (and perhaps even beneficial), then there may be a threshold Hb target (or dose, which will be highly correlated with target) above which harm occurs. We do not know the maximum safe Hb level -- but we do know that the mean achieved Hb in the treatment arm CHOIR was 12.6 g/l. Allowing the target range to include 12.0 g/l inevitably means that a substantial number of patients will have Hb between 12.0-13.0 g/l. How will these patients benefit from Hb in this range (as compared with patients who overshoot a range of 10.0-11.0 g/l and have Hb of 11.0-12.0?). Can we be sure that some patients who overshoot the 12.0 g/l limit will not experience harm as a result?
- c) Third, setting the target range at 100-120 g/l will almost certainly incur substantially higher medication costs than a range of 100-110 g/l. The well known exponential relation between ESA dose and target Hb suggests that the magnitude of these costs will be substantial. Why spend more money for uncertain benefit and the potential of harm?

I acknowledge that the range of 110-120 g/l is familiar and that it may seem safer or less radical to simply lower the lower limits of the target. However, I believe that this change is not sufficient. For the reasons above, I believe that a target of 100-110 g/l is better supported by evidence, better reflects the duty of policy-makers to protect patients from potential drug-induced harm, and constitutes a more prudent use of resources. I hope that you will reconsider and will change the target range for Hb to 100-110 g/l.

4) I would suggest that the target hemoglobin be changed to 100-110, rather than 100-120, for the following reasons:

- a) Having a target between 100-120 would result in a substantial number of patients having Hb>120 and all of the risks involved with that. Most people who are used to the idea that higher Hb is better would aim between 110-120 rather than 100-120. Lowering the target to 110 will prevent that.

hemoglobin target (i.e. 105g/l or 100-110g/l) results in a higher risk of transfusion, compared with a strategy of 100-120g/l, the increase in risk would likely be very small.

A teleconference was undertaken to discuss this change and a vote was taken as to whether to maintain the current proposed target hemoglobin (110g/l), or to lower the proposed target to 105g/l. The motion to lower the target hemoglobin was defeated (4 votes to 2) and the current target hemoglobin is thus maintained. It was agreed that the debate around the concerns related to a hemoglobin > 120g/l should be addressed more clearly in the guidelines and a section on this was added. Moreover, in section 3.8 (anemia protocol section), a way to operationalize the target hemoglobin guideline, with specific suggestions as to how best to avoid hemoglobins > 120g/l was added.

b) As you know, the only benefit of management of anemia with EPO is quality of life, and there is no significant evidence of benefit of QOL above a target Hb of 110.

c) The only blinded RCT comparing 2 levels of Hb was the CANEPO study, and it showed very marginal benefit for QOL in the higher Hb target, but statistically significant harm in terms of both higher BP and increased AV access clotting.

d) More importantly, targeting the Hb to 120 would result in substantially increased doses of erythropoietin since the EPO dose increases significantly more in patients who are relatively resistant to EPO; that is partly the reason that the dose requirements are algorithmically higher for higher targets.

I can not see even a single reason to have a target Hb above 110 in CKD with most of the benefit at that level and significant evidence of harm at higher targets. This would result in some patients having Hb<100. However, in the CANEPO study, there were patients whose hemoglobins were between 90-105 and they still achieved all of the benefits in terms of QOL and exercise capacity.

**Erythropoietin resistance**

1. Under EPO resistance, perhaps some (opinion-based) recommendations could be made regarding when to investigate a drop in Hgb in pts who were previously within target on a stable dose of ESA (eg. patient who drifts from Hgb of 112 to 108 to 102 to 95 with increasing doses of ESA, or pt who drops suddenly from 112 to 95).
2. The definition of resistance is stated as being >300IU/kg/week or 20,000U/week of epo alpha or 1.5mcg/kg/week or 100mcg\week darbepoetin - is this IV or Sub-Q? Please clarify the route of administration.
3. I question the resistance cutoffs - they seem low. In EPREX terms, clinically we have used 25-30,000U per week as a max dose (and the equivalent dose of NESP). If you investigate resistance at 20,000U/wk, what are you likely to find?

1. All of these comments highlight the considerable lack of data to guide specific investigation and management. All of the CPG's in this section were opinion-based and to some extent vague. After further discussion among the committee, we have removed all CPGs within this section. Rather, they are now discussed within the background section.
2. Regarding comment 2, these are based on populations of patients receiving both iv and sc administration, and as such, we feel they are applicable to both populations.
3. As discussed in the text, there is a large range of resistance cited (9000 to 35000 IU/wk). A moderate value was chosen, in the context of Canadian data indicating that this would include a relatively small fraction of the ESRD population. As described in the background it is unclear if anything of significance would be found at any threshold.

	<p>To reflect each of these uncertainties, the following sentence has been added: “The decision to investigate and the scope of the investigation is at the discretion of the clinician”.</p>
<p><b>Oral vs iv iron in hemodialysis patients:</b></p> <p>My comment pertains to your recommendation of IV iron for treatment of chronic hemodialysis patients. If IV Fe were innocuous and cheap, there would be less of an issue, but that is not necessarily the case. I think its clear that there is a role for oral Fe in the chronic hemodialysis population and that one does not pay the price of increased ESAs with oral iron supplementation. (A study, recently accepted for publication, was appended to support this statement).</p>	<p>A recent non-randomized study by a Canadian group suggested that a large proportion of HD-CKD patients tolerate oral iron and maintain hemoglobin in the target range, without apparently requiring excessive doses of erythropoietin. Given that several RCTs suggest that patients require lower doses of ESA, when given iv iron, rather than oral iron, we have not changed our guidelines. However, we have added a paragraph in the text of the “route of administration of iron section” discussing this study.</p> <p>“A recent nonrandomized study suggests that a large proportion of HD-CKD patients tolerate oral iron and can maintain an adequate hemoglobin without the use of significant intravenous iron. As such, some HD patients may be capable of achieving target hemoglobin while receiving oral iron (particularly if they are compliant), though the randomized trials noted above suggest that a higher amount of erythropoietin would be required on average. The risks and benefits of minimizing the use of intravenous iron (and using oral iron instead), but possibly increasing the use of erythropoietin, are unknown.”</p>
<p><b>Whether to hold Erythropoietin or not when above target hemoglobin:</b></p> <p>1) The guidelines do not elaborate on a "safe" duration of time above 120g/l before decreasing ESA doses further. Given the long half-life of RBCs, how long can we wait until adjusting ESA doses? I refer to the statement from the K/DOQI 2006 guidelines:</p> <p>ESA doses should be decreased, but not necessarily held, when a downward adjustment of Hb level is needed. Withholding ESA doses, particularly for long periods, may lead to a delayed</p>	<p>As noted, K/DOQI guidelines do not recommend holding ESA when hemoglobin is above the target level. This is based on the physiology of ESAs and a concern about the hemoglobin dropping below target if the ESA is held for a prolonged period. While this seems very reasonable when the hemoglobin has risen slightly above target, it is unclear what the best course of action would be if the hemoglobin goes significantly above target (i.e. &gt;140g/l for example). Clinicians have managed such patients in the past by</p>

decrease in Hb levels to less than target range. Such a decrease may initiate periodic cycling of Hb levels at greater than and less than the target Hb range. This finding is in keeping with the mechanism of action of ESA in preventing apoptotic death of CFU-Es and early erythroblasts. Should ESA doses be withheld in an ESA-dependent patient, a prolonged loss of erythropoietic precursors may result. Accordingly, the Work Group recommends that ESA doses not be withheld routinely for Hb levels greater than target range, hospitalization, poorly controlled hypertension, or vascular access occlusion.

discarding blood after dialysis, by holding ESAs, or by simply reducing the dose of ESA. The safety of each of these strategies is unknown and which to choose is based almost solely on opinion.

A statement to this effect has been added to the “Protocol-based administration” section of the guidelines.

**Frequency of ESA administration:**

We think evidence from the PROMPT study should be included in the CSN guidelines for ND CKD patients receiving ESAs. Clin Nephrol. 2005 Aug;64(2):113-23

**Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: the PROMPT study.**

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AIM: To determine whether extended epoetin alfa dosing schedules of up to once every four weeks are as effective as weekly dosing in maintaining hemoglobin (Hb) levels in patients with anemia of chronic kidney disease (CKD). METHODS: This randomized, open-label trial enrolled patients with anemia of CKD not on dialysis. Patients were required to have a stable Hb level (> or = 11.0 g/dl) and to have been previously receiving epoetin alfa for two or more months. Patients were randomized to one of four subcutaneously administered epoetin alfa dosing regimens: 10,000 units (U) once weekly (QW), 20,000 U every two weeks (Q2W), 30,000 U every three weeks (Q3W) or 40,000 U every four weeks (Q4W). Dose reductions, but not escalations, were permitted. Patients received treatment for a total

The abstract of the prompt study is appended below the members’ comment. The full text of this study shows small reductions in hemoglobin (on average for q3wk and q4wk compared with q1 week (only statistically significantly different for q4wk vs q1wk) and that you need ~600more units of erythropoietin per week for the q4week, vs q1 week. There were small differences in the proportion of patients meeting “target Hemoglobin”, particularly when erythropoietin was administered q3 and q4 week, compared with q1 week.

With regards frequency, we do note the following:

“Regarding subcutaneous administration, a recent Cochrane Collaboration review reported a non-significant 12 U/kg/wk increase in dose of epoetin alpha when administered once weekly compared to thrice weekly. The cost of this additional epoetin alfa needs to assessed, in particular with regard to patient preference and compliance.”

The following has been added, referring to the PROMPT study.

“A recent randomized, open-label trial of patients with stage 3 CKD and a

of 16 weeks. The primary endpoint for the trial was the mean final Hb measurements of the QW, Q2W, Q3W, and Q4W groups. The primary efficacy analyses were non-inferiority assessments of the mean final Hb measurements of the Q2W, Q3W, and Q4W groups, compared with the QW group. The primary efficacy analyses were performed using a modified intent-to-treat (MITT) population, defined as all patients meeting all inclusion/exclusion criteria (or, if not satisfying all criteria, were granted an exemption at study entry), and who were randomized and received at least one dose of study medication. A per-protocol population, based on all patients who met the MITT criteria and completed the entire study, was used to evaluate the robustness of the MITT results. Quality of life was assessed for all dosing groups throughout the study. Safety was based on all patients randomized who received at least one dose of study medication. RESULTS: A total of 519 patients were enrolled; 445 were included in the MITT population. The four treatment groups were comparable with respect to baseline characteristics. The primary etiologies of CKD were diabetes (45.7%) and hypertension (29.9%). The mean baseline Hb, serum creatinine and glomerular filtration rate for all patients were 11.9 +/- 0.8 g/dl, 3.1 mg/dl, and 21.1 ml/min/1.73 m<sup>2</sup>, respectively. The mean baseline transferrin saturation was 25.2% and the mean ferritin was 201.9 ng/ml for all patients. All groups had a mean final Hb of > 11.0 g/dl. The mean final Hb levels of the Q2W and Q4W groups were statistically non-inferior to the QW group. The results of the per-protocol analysis were consistent with the MITT results. In addition, 93.5%, 89.5%, 77.2%, and 76.0% of patients maintained a mean Hb > or = 11.0 g/dl throughout the course of the study in the QW, Q2W, Q3W, and Q4W groups, respectively. Quality of life was maintained or improved from baseline to final within each dosing group. There were no significant differences in the mean final quality of life scores between the QW group and the Q2W, Q3W, and Q4W groups. Among the 513 patients evaluated for safety, epoetin alfa was well tolerated with no differences in adverse events between groups. The incidence of thrombotic adverse events was low (2.5% of patients), as was mortality (1.4% of patients). CONCLUSIONS: Approximately 90% of patients dosed once every two weeks and over 75% of patients dosed once every three or four weeks maintained mean Hb levels > or = 11.0 g/dl, consistent with the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. This study suggests that extended epoetin alfa dosing schedules are effective and safe for maintaining Hb, and may offer the possibility of

stable hemoglobin ( $\geq 110$ g/l) randomized patients to one of four subcutaneously administered epoetin alfa dosing regimens: 10,000 units (U) once weekly (QW), 20,000 U every two weeks (Q2W), 30,000 U every three weeks (Q3W) or 40,000 U every four weeks (Q4W). Compared with QW, patients treated with Q4W regimens had non-statistically significantly lower hemoglobin (-8g/l), despite using 513 more units of epoetin alfa per week. The proportion of patients with hemoglobin > 110g/l was 93% for QW and 76% for Q4W at study end. Given this, and the fact that this was a short-term study (i.e. 16 weeks), there is insufficient evidence to recommend dosing intervals for subcutaneous epoetin alfa of > 1 week.”

<p>increased flexibility and convenience for the majority of patients with the anemia of CKD.</p>	
<p><b>Adverse effects from ESAs</b></p> <p>Please clarify risk of seizures in the guidelines. Is the risk is increased significantly by ESAs</p>	<p>The following has been added to the “adverse events” section:</p> <p>"Seizures have been reported in association with use of ESAs. In the case series reported during the 1980s and 1990s, the seizures were often associated with hypertension, and were more commonly reported within 90 days of starting ESA, a time when hemoglobin was rising and higher doses of ESA were being employed. The rate of seizures associated with ESA use in current practice is not clear, but must be low given the absence of concern during recent clinical trials".</p>