Clinical Practice Guidelines for supplemental therapies and issues

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4.1 Supplemental Therapies in the Treatment of Anemia
Population: all patients with chronic kidney disease

Clinical Practice Guidelines

4.1.1 Do not use androgens as supplemental therapy for the treatment of anemia (Grade C).

4.1.2 There is insufficient evidence of efficacy and safety to recommend l-carnitine, vitamin C, ultrapure dialysis, pentoxifylline, statins, vitamin B6, or quotidian dialysis as supplemental therapies for the treatment of anemia (Grades C–D).

BACKGROUND

Supplemental therapies are treatment strategies to enhance the responsiveness of erythropoietic-stimulating agents (ESAs) in the management of anemia in chronic kidney disease (CKD) patients, including those who exhibit resistance to ESAs. The desired outcome is an improvement in hemoglobin levels, reduction in ESA dose, or both. Although the outcomes of these studies (hemoglobin level, ESA dose) are arguably the relevant outcomes of interest, as the outcome is not a ‘clinical outcome,’ each of the studies is assigned either a Grade C or D level of evidence.

Androgens

Although androgen therapy was used prior to the availability of ESAs, administration is associated with significant short-term and long-term toxicity (including acne, virilization, hepatic dysfunction, hepatocellular carcinoma, and pain at injection site). In addition, evidence for efficacy of androgens to improve anemia or reduce the requirement for ESAs is lacking¹⁻⁵ (Table 1).

L-Carnitine

Six small randomized control trials (RCTs)⁶⁻¹¹ in hemodialysis patients have been performed, with low overall study quality⁵ (Table 2). Although these RCTs do not indicate compelling evidence of efficacy, a meta-analysis of randomized studies¹² suggested a possible beneficial effect on anemia management with reduction of ESA dose. However, this meta-analysis included only three of the RCTs identified here, and included three additional studies presented in abstract form only. In addition, the conclusions of reduced ESA use were less robust due to detected heterogeneity. High-quality evidence for effectiveness is currently lacking, and as such, l-carnitine administration is not recommended.

Vitamin C

Four small RCTs have evaluated the use of vitamin C in patients with CKD and anemia (Table 3),¹³⁻¹⁶ with no clear evidence of benefit noted. A more recent RCT of 42 patients with epoetin α resistance (epoetin α ≥450 U/kg/week) reported an improvement in anemia in the treatment group compared with the control group over 6 months (93–105 g/l vs 93–96 g/l, respectively; between-group difference 9 g/l at P = 0.0001).¹⁷ A small reduction in epoetin α use in the intervention group was also noted (477–429 vs 474–447 U/kg/week). Concerns regarding the possible side effects of prolonged administration of vitamin C have been raised (pro-oxidant effects, oxalosis), and as yet the safety of vitamin C in CKD patients has not yet been established.

Ultrapure dialysate

Four randomized trials of ultrapure dialysate have been performed (Table 4). Three studies,¹⁸⁻²⁰ enrolling a small number of hemodialysis patients (≤35 total) using high-flux
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study population</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Arm 1</th>
<th>Outcome</th>
<th>Results</th>
<th>Other outcomes</th>
<th>Adverse events</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brockenbrough (2006)4</td>
<td>Hypogonadal males on ESA &gt; 3 months</td>
<td>40</td>
<td>6</td>
<td>100 mg topical 1% testosterone patch Control</td>
<td></td>
<td>ESA dose</td>
<td>204b</td>
<td>Minor, equal in both arms</td>
<td>C</td>
</tr>
<tr>
<td>Sheashaa (2005)3</td>
<td>HD patients on stable ESA dose</td>
<td>32</td>
<td>6</td>
<td>Nandrolone decanoate 50 mg IM 2 times per week Control</td>
<td></td>
<td>Mean Hb at 6 months</td>
<td>10.4b</td>
<td>Transient flu-like symptoms, 4 females withdrew (hirsutism, elevated transaminases and triglycerides)</td>
<td>C</td>
</tr>
<tr>
<td>Gaughan (1997)2</td>
<td>HD patients on ESA</td>
<td>19</td>
<td>6</td>
<td>Nandrolone decanoate 100 mg IM weekly Control</td>
<td></td>
<td>Mean Hct at 6 months</td>
<td>33.2%c</td>
<td>Acne, injection site pain</td>
<td>C</td>
</tr>
<tr>
<td>Berns (1992)1</td>
<td>HD patients on ESA</td>
<td>14</td>
<td>4</td>
<td>Nandrolone decanoate 2 mg/kg IM weekly Control</td>
<td></td>
<td>Mean weekly rise in Hct</td>
<td>0.37% per weekb</td>
<td>Intolerable acne</td>
<td>D</td>
</tr>
</tbody>
</table>

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; IM, intramuscular.

*Owing to the nature of the outcomes considered in the section (ESA dose, Hb), the maximum quality grade is C.

*Between-arm comparison not statistically significant.

*Between-arm comparison statistically significant, P<0.05.
membranes indicated that the dose of ESAs may be reduced by up to 33%. A recent RCT of 78 hemodialysis patients using low-flux membranes did not detect a difference in hemoglobin or ESA dose after 12 months. In addition, the costs and cost-effectiveness of providing ultrapure dialysate are unclear.

## Other supplemental therapies
A recent systematic review noted mixed results regarding the impact of nocturnal hemodialysis on ESA requirements and improvement of anemia. Only one RCT of nocturnal dialysis has been performed, and no difference in ESA requirement or anemia control was noted. Other therapies

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### Table 3 | RCTs of ascorbic acid for the treatment of anemia

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study population</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Outcome</th>
<th>Results</th>
<th>Other outcomes</th>
<th>Qualitya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attallah (2006)17</td>
<td>HD patients with ESA resistance</td>
<td>42</td>
<td>6</td>
<td>IV ascorbic acid 300 mg three times weekly</td>
<td>ESA dose</td>
<td>429b</td>
<td>Hb: 10.5 vs. 9.6; statistically significant difference between arms</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Taji (2004)16</td>
<td>HD patients (ESA and IV Iron treatment as required)</td>
<td>61</td>
<td>6</td>
<td>IV ascorbic acid 100 mg three times weekly</td>
<td>Change in Hct</td>
<td>−0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ESA dose: no difference between arms</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Keven (2003)15</td>
<td>HD patients (ESA and IV iron treatment as required)</td>
<td>60 (crossover)</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>IV ascorbic acid 500 mg three times weekly</td>
<td>ESA dose</td>
<td>7200/6679&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>ESA dose: within-arm reduction in one phase of crossover</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Deira (2003)13</td>
<td>HD patients with iron overload (ferritin &gt;800 ng/ml and TSAT &gt;30%)</td>
<td>20</td>
<td>6</td>
<td>IV ascorbic acid 200 mg three times per week</td>
<td>ESA resistance index</td>
<td>56.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hb: no difference between arms</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Giancaspro (2000)14</td>
<td>HD patients on ESA</td>
<td>27 (crossover)</td>
<td>3</td>
<td>IV ascorbic acid 500 mg three times per week</td>
<td>Hb</td>
<td>10.0/9.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ESA dose held constant for each 3-month period</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; HD, hemodialysis; IV, intravenous; TSAT, transferrin-iron saturation percentage.

<sup>a</sup>Owing to the nature of the outcomes considered in the section (ESA dose, Hb), the maximum quality grade is C.
<sup>b</sup>Between-arm comparison statistically significant, P < 0.05.
<sup>c</sup>Between-arm comparison not statistically significant.
<sup>d</sup>Crossover at 6 months.
<sup>e</sup>Crossover at 3 months.

### Table 4 | RCTs of ultrapure dialysate for the treatment of anemia

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study population</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Outcome</th>
<th>Results</th>
<th>Other outcomes</th>
<th>Qualitya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamas (2006)21</td>
<td>Stable HD patients, low-flux membrane</td>
<td>78</td>
<td>12</td>
<td>Additional ultrafilters to obtain &lt;0.05 EU/ml endotoxin and &lt;0.1 CFU/ml Conventional dialysate</td>
<td>ESA dose (darbopoietin µg/kg/week)</td>
<td>0.48&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hb: no difference between arms</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Hsu (2004)18</td>
<td>Stable HD patients, high-flux membrane</td>
<td>24 (crossover)</td>
<td>6</td>
<td>Ultrapure dialysate by additional polysulfone filter Conventional dialysate</td>
<td>ESA dose (U/months)</td>
<td>12,760/10,440&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>Hct: no difference between arms</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Sitter (2000)20</td>
<td>Male HD patients, high-flux membrane</td>
<td>30</td>
<td>12</td>
<td>On-line produced ultrapure dialysate Commercial dialysate</td>
<td>ESA dose (U/kg/week)</td>
<td>64&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hb: no difference between arms</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Schiffl (1999)19</td>
<td>HD patients, high-flux membrane</td>
<td>24 (crossover)</td>
<td>3</td>
<td>On-line produced ultrapure dialysate using polysulfone filter Commercial dialysate</td>
<td>ESA dose (U/kg/week)</td>
<td>87&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hb: no difference between arms</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

CFU, colony-forming units; ESA, erythropoiesis-stimulating agent; EU, endotoxin units; Hb, hemoglobin; Hct, hematocrit; HD, hemodialysis; IV, intravenous.

<sup>a</sup>Owing to the nature of the outcomes considered in the section (ESA dose, Hb), the maximum quality grade is C.
<sup>b</sup>Between-arm comparison not statistically significant.
<sup>c</sup>Between-arm comparison statistically significant, P < 0.05.
<sup>d</sup>Crossover at 6 months.
<sup>e</sup>Crossover at 3 months.
such as statins, pentoxifylline, and vitamin B6 have been hypothesized to improve anemia in CKD, but high-quality evidence of efficacy is currently lacking. The vast majority of studies to date have been performed in the hemodialysis population. Although these guidelines specifically apply to this population, by extension they are relevant to nondialysis-chronic kidney disease (ND-CKD) and peritoneal dialysis-chronic kidney disease (PD-CKD) patients.

**RESEARCH RECOMMENDATION**

- Determine the effect of supplemental anemia therapies on safety and clinically relevant outcomes using adequately powered RCTs. Emphasis should be placed on studying patients with resistance to erythropoietic substances.

### 4.2 Assessment and Management of ESA Resistance

#### BACKGROUND

A relative resistance to ESAs for the treatment of anemia in patients with CKD is commonly encountered. This may manifest as a failure to reach hemoglobin targets or the requirement for administration of high doses of ESAs to maintain the target hemoglobin.

A validated definition of ESA resistance has not yet been established. Other international organizations have set varying ESA dose thresholds to indicate resistance, such as epoetin ≥ 9000 U/week; ~ 20,000 U/week; and ~ 35,000 U/week. Canadian Nephrology Practice Pattern data indicate that in 24 renal centers across Canada between 1995 and 1998 (n = 8791), 15.7% of HD patients and 5.5% of PD patients received epoetin ≥ 200 U/kg/week. Although any proposed threshold will be to some extent arbitrary, the guideline committee decided that there was value in drawing attention to patients receiving high doses of ESAs, given the association with poor outcomes.

For the purposes of this document, ESA resistance is defined as the prolonged administration of a high dose of erythropoietic substances (threshold ≥ 300 U/kg/week or 20,000 U/week of epoetin or ≥ 150 μg/kg/week or 100 μg/week darbepoetin) to patients with erythropoietin resistance should be done cautiously, given the additional cost, unproven efficacy of dose escalation, and potential adverse effects.

#### RESEARCH RECOMMENDATIONS

- Establish a standardized, validated measure of ESA resistance.
- Evaluate the safety, effectiveness, and cost-effectiveness of escalating ESA dosages in patients with ESA resistance, using adequately powered RCTs.
- Evaluate the impact and safety of ESA dose reductions in patients with ESA resistance.

### 4.3 Administering ESAs in Acute Renal Failure

There are several issues related to anemia, ESA use, acute illness, and acute renal failure (ARF).

#### ESA use in ARF

Despite extensive clinical investigations of the role of ESA in the management of anemia of CKD, there are few data on the efficacy of ESAs during ARF in humans. Initial experimental studies of ESA use in ischemic ARF demonstrated improvement in both hematocrit and mortality; however, no RCTs in humans have addressed this important question. In a recent retrospective study of intensive care patients with ARF requiring dialysis, ESA administration did not improve outcomes in terms of transfusion requirements, renal recovery, or survival. This novel study needs to be interpreted with caution because it used relatively low doses of epoetin (mean dose 112 U/kg/week), did not have preset targets for transfusion, and was underpowered to detect clinically important differences. At present, there is no compelling evidence to support the use of erythropoietin in ARF.
ESA use in anemic critically ill patients without renal failure

Several large studies have shown that ESAs may be useful for treating anemia in critically ill patients. Three randomized, double-blind, placebo-controlled studies demonstrated reduced need for transfusions and increased hemoglobin in the ESA-treated arm. However, the use of erythropoietin in critically ill patients has not been shown to affect important clinical outcomes, in that neither long-term outcomes nor mortality were addressed by these studies. In a cost-effectiveness study, the number needed to treat to avoid any transfusion-related adverse event ranged from 5246 to 81,000, with corresponding costs of $4.7 million to $72 million to avoid one transfusion-related adverse event. Without information about the impact of ESAs on clinical outcomes and safety, and given the high dose (and related cost) of ESAs used for this indication, the use of ESAs in critically ill patients is not recommended.

ESAs as renoprotective agents

A number of experimental studies have demonstrated the tissue-protective effect of ESAs in models of ischemic acute renal injury and failure, with improvement in renal survival and anemia (reviewed in Sharples and Yaqoob). Although these findings are interesting, clinical trials have not been performed, and therefore the potential benefit of this therapy in ARF remains unknown.

RESEARCH RECOMMENDATIONS

- Evaluate the effect of ESA administration on anemia, renal recovery, and mortality in ARF using a valid RCT.
- Evaluate the effect of ESA administration for the prevention of ischemia-induced ARF.

REFERENCES