KDIGO Controversies Conference
New Data & Developments since publication of latest guidelines:
Iron Supplementation

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Acknowledgement

• Dr Anatole Besarab, Henry Ford Hospital, Detroit kindly shared several slides discussed in this presentation.
Presentation Objectives

• Review new developments in iron supplementation since last guidelines
  – Development of new iron formulations
  – Diagnostic tests for iron deficiency
  – Risks of IV iron
  – Benefits of IV iron, independent of anemia correction
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• Review new developments in iron supplementation since last guidelines
  – Development of new iron formulations
  – Diagnostic tests for iron deficiency
  – Risks of IV iron
  – Benefits of IV iron, independent of anemia correction
# Existing IV Iron Preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Warnings</th>
<th>Total Dose Infusion</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric gluconate (Ferrlecit)</td>
<td>HD pts receiving ESA</td>
<td>General</td>
<td>No</td>
<td>$$$</td>
</tr>
<tr>
<td>Iron sucrose (Venofer)</td>
<td>HD, PD, CKD pts</td>
<td>General</td>
<td>No</td>
<td>$$$</td>
</tr>
<tr>
<td>LMW iron dextran (INFeD)</td>
<td>Iron-deficiency anemia</td>
<td>Black box</td>
<td>Yes</td>
<td>$$</td>
</tr>
<tr>
<td>HMW iron dextran (DexFerrum)</td>
<td>Iron-deficiency anemia</td>
<td>Black box</td>
<td>Yes</td>
<td>$</td>
</tr>
</tbody>
</table>
Investigational Iron Preparations: Ferumoxytol

• Characteristics
  – Semi-synthetic polysaccharide-coated iron oxide
  – Average particle size: 30 nm
  – Molecular weight: 750,000 daltons
  – Minimal analytically free iron (<.1%)
Investigational Iron Preparations: Ferumoxytol

<table>
<thead>
<tr>
<th></th>
<th>1 mg Fe/kg (n=8)</th>
<th>2 mg Fe/kg (n=8)</th>
<th>4 mg Fe/kg (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life, h*</td>
<td>9.3 ± 1.1</td>
<td>10.2 ± 1.5</td>
<td>14.7 ± 2.2</td>
</tr>
<tr>
<td>( C_{\text{max}} ), ( \mu g \text{ Fe/mL} )*</td>
<td>26.3 ± 7.0</td>
<td>62.0 ± 11.6</td>
<td>130 ± 32.5</td>
</tr>
<tr>
<td>AUC, ( \mu g \text{ Fe•h/mL} )*</td>
<td>396 ± 122</td>
<td>997 ± 320</td>
<td>2912 ± 683</td>
</tr>
<tr>
<td>( V_d ), mL/kg</td>
<td>36.3 ± 10.0</td>
<td>31.1 ± 7.4</td>
<td>30.4 ± 7.3</td>
</tr>
<tr>
<td>CL, mL/hr•kg*</td>
<td>2.82 ± 1.21</td>
<td>2.17 ± .63</td>
<td>1.44 ± .33</td>
</tr>
</tbody>
</table>

- Significant increases in TSAT, serum iron, and serum ferritin with rapid IV injection at rate of 60 mg iron/min
- Drug well tolerated

*\( P<0.01 \), one-way analysis of variance.
Investigational Iron Preparations: Ferumoxytol

PK Results of Open-Label, Ascending-Dose Study of 20 HD Patients

<table>
<thead>
<tr>
<th>Half-life</th>
<th>Dose-dependent and similar to that in healthy patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>Dose-dependent</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td></td>
</tr>
</tbody>
</table>

- Patients received single bolus dose of 125 mg or 250 mg shortly after the start of dialysis
- Increases were observed in serum iron, TSAT, serum ferritin, and reticulocyte count at 48 hours posttreatment
- Ferumoxytol was not removed with HD

Ferumoxytol in non-HD patients

- Phase 2, open-label trial
- 21 PD or CKD patients; 13 on ESA, 8 no ESA
- ESA dose could be changed
- Randomized to:
  - 4 doses of 225 mg in 2 weeks
  - 2 doses of 510 mg in 1-2 weeks
- Rapid push 30 mg iron/sec
- Seven possibly related AEs in 5 patients
  - Constipation, chills, tingling, GI viral syndrome, delayed pruritic erythematous rash, pain at injection site

Time Course of Hgb Response

**Investigational Iron Preparations: Ferumoxytol**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Week</th>
<th>4 Weeks</th>
<th>6 Weeks</th>
<th>8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin, ng/mL</td>
<td>232 ± 216*</td>
<td>711 ± 430*</td>
<td>748 ± 495*</td>
<td>584 ± 310*</td>
<td>548 ± 291*</td>
</tr>
<tr>
<td>TSAT, %</td>
<td>21 ± 10</td>
<td>37 ± 22.1</td>
<td>27 ± 11.3</td>
<td>31 ± 9.6</td>
<td>27 ± 8.7</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>10.4 ± 1.3</td>
<td>10.4 ± 1.1</td>
<td>11.3 ± 1.2</td>
<td>11.4 ± 1.2</td>
<td>11.3 ± 1.2</td>
</tr>
</tbody>
</table>

*P<0.05 compared to baseline.
Investigational Iron Preparations: Ferumoxytol

Results of 4th and Final Phase 3 Study: Open-Label, Multicenter, Randomized Trial in HD-CKD

<table>
<thead>
<tr>
<th></th>
<th>Ferumoxytol Doses in 1 Week</th>
<th>200 mg Oral Iron Daily for 3 Weeks</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Hb from baseline to day 35, g/dL</td>
<td>1.02 ± 1.13</td>
<td>.46 ± 1.06</td>
<td>0.0002</td>
</tr>
<tr>
<td>Patients with ≥1.0 g/dL increase in Hb from baseline to day 35, %</td>
<td>49.1</td>
<td>25</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean increase in serum ferritin from baseline at day 21, ng/mL</td>
<td>356.7 ± 247.1</td>
<td>-37.6 ± 107.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- 230 HD-CKD patients receiving stable ESA doses randomized 1:1 to ferumoxytol or oral iron
- Significantly greater mean increase in Hb compared with oral iron (primary end point)
- No anaphylactoid events

Investigational Iron Preparations: Ferumoxytol

- Clinical program
  - 4th and final phase 3 study has been completed
  - NDA planned for 4th quarter of 2007

Investigational Iron Preparations: Ferumoxytol

• Potential advantages
  – Rapid bolus possible
  – Larger doses possible
  – Fewer injections to restore iron stores
  – Test dose?
  – Black box?
Investigational Iron Preparations: VIT-45

• Characteristics

  – Ferric carboxymaltose injection (American Regent Laboratories, Inc)

  – In development worldwide for variety of anemia-related indications, including CKD, whether HD or not
Investigational Iron Therapies: VIT-45

- Clinical program
  - NDA submitted 2007, currently under review
  - Market launch expected 2008 or 2009
  - 2 phase 3 trials under way (vs oral iron in predialysis CKD and long-term safety study in same population)
Investigational Iron Preparations: VIT-45

- Potential advantages
  - Can be administered in single and repeated high doses within short time period (in clinical trials, dosing of 200- to 1000-mg IV push over 15 minutes)
  - Not removed by high-flux or high-efficiency dialysis membranes in clinically significant amounts over 4-hour dialysis session\(^1\)

## Other New Agents

<table>
<thead>
<tr>
<th>Product</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric pyrophosphate</td>
<td>• Dialysate concentrate product containing ferric pyrophosphate (FePPi), water-soluble form of iron, for anemia in HD patients</td>
</tr>
<tr>
<td>Rockwell Medical Technologies, Inc</td>
<td>• In phase 2 clinical development</td>
</tr>
<tr>
<td></td>
<td>• Company believes administration method may be safer and more effective in maintaining iron balance and reduce administration costs</td>
</tr>
<tr>
<td>Iron oligosaccharide</td>
<td>• IV iron oligosaccharide (FeOS)</td>
</tr>
<tr>
<td>Abbott Laboratories, Inc (US) and Pharmacosmos A/S (Denmark)</td>
<td>• Currently in clinical trials with Pharmacosmos</td>
</tr>
<tr>
<td></td>
<td>• Potentially lower incidence of hypotensive events at higher doses</td>
</tr>
</tbody>
</table>
Data after K/DOQI...

Is IV iron really needed in non-dialysis CKD?
In a study of oral iron vs iron gluconate in patients not treated with ESA (N=75), the change from baseline in Hb between the oral and IV iron groups was similar.

However, intravenous iron was more effective than oral iron in another report of predialysis patients. In this study, ESA were allowed.

In 126 peritoneal dialysis patients, IV iron sucrose (as an adjunct to ESA) increased Hb effectively.

- Oral iron was not tested in this study.

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**DRIVE and DRIVE-II Studies:**

*(HD Patients With High Ferritin/Low TSAT)*

**Control (No Iron)**

- Drive Study (6 weeks)
  - ESA dose held constant
  - Randomization and 25% increase in baseline ESA dose

**IV Iron 1 g Ferric Gluconate**

- Drive Study (6 weeks)
  - ESA dose held constant
- Drive-II Study (6-Week Follow-Up)
  - ESA and IV iron doses per investigator discretion

**Week 0 Screening/ Baseline**

- Local lab Hb, TSAT, ferritin collected

**Week 1**

- Week 1
- Week 2
- Week 3
- Week 4
- Week 5
- Week 6

**Week 7**

- Week 7
- Week 8
- Week 9
- Week 10
- Week 11
- Week 12

**L=complete laboratory panel; H=Hb and reticulocyte hemoglobin (CHr) testing; X=125 mg ferric gluconate**

**ESA=erythropoietin-stimulating agent; IV=intravenous; Hb=hemoglobin; TSAT=transferrin saturation**

IV Iron Increases Hb Response and Percentage of Patients Responding to an ESA Increase

Hb at Baseline and 6 weeks

- **Baseline**
  - Control (n=65): 10.2 g/dL
  - IV Ferric Gluconate (n=64): 10.4 g/dL

- **Week 6**
  - Control (n=65): 11.3 g/dL
  - IV Ferric Gluconate (n=64): 11.9 g/dL

*P* < 0.028

**Percentage of Patients Achieving ≥2 g/dL Increase in Hb at 6 Weeks**

- Control: 29.2%
- IV Ferric Gluconate: 46.9%

*P* = 0.041

**Rate of Responders (%)**

- Control: 29.2%
- IV Ferric Gluconate: 46.9%

*IV*=intravenous; *Hb*=hemoglobin; *ESA*=erythropoietin-stimulating agent

ESA Use Decreased Significantly Following Administration of IV Iron

- ESA dose was significantly lower at 12 weeks in the IV iron group vs the control group ($P=0.017$)
- Control group: ESA doses remained significantly elevated ($P=0.0004$)
- IV Iron group: ESA doses returned to baseline level ($P=0.6039$)

**ESA Use Decreased Significantly Following Administration of IV Iron**

**Graph: ESA Dose (U/week)**

- **ESA changes per investigator discretion**
- Protocol-Mandated 25% Increase
- **ESA Dose Difference ~10,000 U/wk**

**Legend:**
- IV Iron
- Control

**Notes:**
- ESA = erythropoietin-stimulating agent
- IV = intravenous

After week 6, patients returned to routine anemia management. Epoetin dose was adjusted per usual dialysis unit practice.

Hb=hemoglobin; IV=intravenous; ESA=erythropoietin-stimulating agent

DRIVE Study Conclusions

- In anemic dialysis patients with high ferritin and TSAT ≤25%, IV iron and an increase in ESA dose
  - Greater Hgb response & in observational follow up to
  - Lowered ESA requirements

TSAT=transferrin saturation; IV=intravenous; ESA=erythropoietin-stimulating agent; Hb=hemoglobin

Presentation Objectives

- Review new developments in iron supplementation since last guidelines
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Intravenous iron causes oxidative stress in hemodialysis patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim PS 1999</td>
<td>50</td>
<td>Interventional, observational</td>
<td>IV infusion of 100 mg ferric saccharate</td>
<td>Patients with serum ferritin &gt;601 ng/mL had greater increase in plasma lipid peroxides and greatest fall in superoxide dismutase with exposure to IV iron.</td>
</tr>
<tr>
<td>Roob JM 2000</td>
<td>22</td>
<td>Cross-over randomized trial</td>
<td>All received 100 mg IV iron sucrose either with or without 1000 IU of Vitamin E.</td>
<td>Lipid peroxidation was seen with IV iron. Vit E reduced but did not abolish the generation of oxidative stress.</td>
</tr>
<tr>
<td>Salahudeen AK 2001</td>
<td>22</td>
<td>Interventional, observational</td>
<td>Infusion of 700 mg IV iron dextran on a non-dialysis day</td>
<td>Free F2-isoprostanes did not increase but esterified F2-isoprostanes were increased.</td>
</tr>
<tr>
<td>Drueke, T 2002</td>
<td>60</td>
<td>Cross sectional study</td>
<td>None</td>
<td>Iron therapy was associated with advance oxidation protein products, and carotid intima-media thickness</td>
</tr>
<tr>
<td>Anraku, M 2004</td>
<td>22</td>
<td>Randomized controlled trial, parallel group</td>
<td>IV saccharated ferric oxide 40 mg every dialysis for 4 weeks.</td>
<td>Increased plasma protein carbonyl content by oxidation of albumin with IV iron.</td>
</tr>
</tbody>
</table>
Intravenous iron causes renal injury in CKD patients

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Trial Design</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal R 2004</td>
<td>20</td>
<td>RCT, parallel group</td>
<td>RCT, infusion of 100 mg iron sucrose on two occasions one week apart with or without n-acetyl cysteine.</td>
<td>Increase in malondialdehyde within 15-30 minutes and proteinuria with IV iron sucrose. Iron infusion led to increase in monocyte chemoattractant protein-1 accumulation and oxidation of urinary albumin.</td>
</tr>
<tr>
<td>Leehey, DJ 2005</td>
<td>8</td>
<td>Four-way, cross-over RCT</td>
<td>IV iron infusion either 125 mg or 250 mg of ferric gluconate with or without n-acetyl cysteine every week.</td>
<td>Ferric gluconate caused oxidative stress but no renal injury.</td>
</tr>
<tr>
<td>Agarwal R 2007</td>
<td>12</td>
<td>Cross-over RCT</td>
<td>IV iron sucrose 100 mg or same dose of IV ferric gluconate administered 1 week apart in random order</td>
<td>IV iron sucrose caused greater proteinuria and albuminuria compared to ferric gluconate. Enzymuria occurred with either drug in similar amount.</td>
</tr>
</tbody>
</table>
Controversies...

- Long term significance
  - Accelerated renal injury?
  - Accelerated cardiovascular disease?
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• Review new developments in iron supplementation since last guidelines
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Hemoglobin Independent Benefits of Iron

• Iron deficiency impairs
  – Physical Performance
  – Thermoregulation
  – Cognition
  – Immune function

• Iron deficiency also is associated with
  – Restless legs syndrome (RLS)
  – Reduced Aluminum absorption (animal data)

QOL Change From Baseline to Day 43 or Early Termination

Mean Change From Baseline

-6 -4 -2 0 2 4 6 8

IV Iron Oral Iron

Effects of kidney disease
Symptoms/problems of kidney disease
Burden of kidney disease
SF-12 mental health composite
SF-12 physical health composite

### Hemoglobin Independent Benefits of Iron in non-dialysis CKD

<table>
<thead>
<tr>
<th>Subscale</th>
<th>IV iron n=36</th>
<th>Within gp change</th>
<th>PO iron n=39</th>
<th>Within gp change</th>
<th>P value: IV vs PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Composite</td>
<td>35.9</td>
<td>4.8</td>
<td>36.4</td>
<td>0.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Mental Composite</td>
<td>49.8</td>
<td>3.3</td>
<td>49.8</td>
<td>-0.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Kidney Dis Burden</td>
<td>72.7</td>
<td>6.4</td>
<td>71.5</td>
<td>-3.6</td>
<td>0.056</td>
</tr>
<tr>
<td>Symptoms/Problem List</td>
<td>78.1</td>
<td>3.0</td>
<td>75.6</td>
<td>-2.7</td>
<td>0.025</td>
</tr>
<tr>
<td>Effects of Kidney Disease</td>
<td>86.2</td>
<td>2.7</td>
<td>80.5</td>
<td>-2.3</td>
<td>0.048</td>
</tr>
</tbody>
</table>