Coordination of Future Anemia Guidelines—What Can be Done?

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Australia 2005	≤12g/dl for patients with proven or likely CV disease ≥11g/dl recommended minimum Hb between 12-14g/dl has beneficial effect when no CV disease
CSN-Canada 1999	11-12 g/dl
EBPG-Europe 2004	>11 g/dl
KDOQI-US 2006	11 to 12 g/dl; avoid target > 13 g/dl
UK-Guidelines 2002	>10 g/dl

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Editorial Comments

Latest US KDOQI Anaemia Guidelines update—what are the implications for Europe?

Iain C. Macdougall[1], Kai-Uwe Eckardt[2] and Francesco Locatelli[3]

Guidelines Need to Consider Variable Clinical Practices and Outcomes

- Patient demographic differences
  - Disease prevalence, obesity prevalence, etc
  - Patient education, socioeconomic status, etc
- Limitations in access to CKD health care, dialysis, transplantation
- Distribution of patients among in-center HD-home HD-PD
- Geographic variability in timing of pre-dialysis ESA treatment, dialysis initiation, HD access

Guidelines Need to Consider Variable Clinical Practices and Outcomes

- Product labeling
  - Customs, legality, reimbursement with off-label use
- Product marketing
- Financial circumstances:
  - Governmental regulations and financial controls
  - Private insurance policies
  - Patient financial constraints; out-of-pocket expense
- Dialysis facility ownership and management influences

Guidelines Need to Consider Variable Clinical Practices and Outcomes

- Local “custom”: same physiology—different practices
- Patient expectations
- Medical malpractice environment
- Care driven by QI initiatives
  - Irrational decisions about care may result
  - Focus on the number rather than the patient and circumstances
- “One-size fits all” anemia management practices

The Science: What Role for KDIGO?

- Objective, unbiased, on-going assessment and interpretation of research
  - How can, and should, industry support of a study be taken into consideration when strength of evidence and quality of study is determined?
    - Bias in design

- Emphasize differences in patient-oriented RCT and other prospective studies vs. observational studies
  - Scientific merit
  - Outcome differences

The Science: What Role for KDIGO?

- Surrogate vs. critical outcomes
  - Is Hgb level itself an “outcome”?
  - Quality of life
  - LVH
  - Morbidity (which)
  - Mortality
- Other considerations:
  - CKD by stage
  - Comorbidity
  - Ethnicity
  - Nationality
- Data-driven risk-benefit assessment

The Science: What Role for KDIGO?

- What, if any, data should be applied from one study population to another?
  - Non-CKD to CKD
  - CKD to ESRD
  - ESRD to CKD
- How should ESA responsiveness or hyporesposiveness be defined?
- Explore complex relationships between ESA dose—iron—targeted Hgb—achieved Hgb—Outcomes
- Consideration of new agents for anemia treatment in a "real-time" fashion
  - Science-based rather than marketing-based guidance as products are released

The Science: What Role for KDIGO?

- Assessment of CPG's as potential clinical performance measures
  - Build-in caveats when appropriate
- Sensitivity analysis
  - Would different grading methodology produce same result?
  - What is the consistency among graders?
- Should costs affect CPG process?

Science vs. Guidelines: What Role for KDIGO?

- Approach 1: Let the data speak for themselves
  - Analysis of data only; No guidelines

- Approach 2: KDOQI-type document
  - Analysis of data and only Strong Guidelines based on High quality, Least bias studies
    - 2A: Strong Guidelines based on High quality, Least bias studies with Weak Guideline Recommendations
    - 2B: Strong Guidelines based on High quality, Least bias studies with Weak Guideline Recommendations and Consensus Statements

Science vs. Guidelines: What Role for KDIGO?

- Approach 3: Two separate documents
  - One with analysis of data without guidelines
  - One with only Strong Guidelines based on High quality, Least bias studies
    - 3A: Strong Guidelines based on High quality, Least bias studies with Weak Guideline Recommendations
    - 3B: Strong Guidelines based on High quality, Least bias studies with Weak Guideline Recommendations and Consensus Statements

Appendix Table 2. **Quality Rating System for Randomized, Controlled Trials***

Criteria List for Assessment of Methodologic Quality†	Operationalization of Criteria	Score
A. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. An example of adequate methods is a computer-generated random-number table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.	Yes/No/Don't Know
B. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Don't Know
C. Were the groups similar at baseline regarding the most important prognostic factors? *"Yes," if similar:* *Age and sex* *Description of type of pain* *Intensity, duration, or severity of pain*	To receive a "yes," groups have to be similar at baseline regarding demographic factors, duration or severity of symptoms, percentage of patients with neurologic symptoms, and value of main outcome measure(s).	Yes/No/Don't Know
D. Was the patient blinded to the intervention?	The reviewer determines whether enough information about the blinding is given in order to score a "yes."	Yes/No/Don't Know
E. Was the care provider blinded to the intervention?	Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding).	Yes/No/Don't Know
F. Was the outcome assessor blinded to the intervention?		Yes/No/Don't Know
G. Were co-interventions avoided or similar?	Co-interventions should be avoided in the trial design or similar between the index and control groups.	Yes/No/Don't Know
H. Was adherence acceptable in all groups?	The reviewer determines whether adherence to the interventions is acceptable, based on the reported intensity, duration, number, and frequency of sessions for both the index intervention and control intervention(s).	Yes/No/Don't Know
I. Was the dropout rate described and acceptable? *≤15% dropout rate is acceptable.*	The number of participants who are included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and dropouts does not exceed 15% and does not lead to substantial bias, a "yes" is scored.	Yes/No/Don't Know
J. Was the timing of the outcome assessment in all groups similar?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/Don't Know
K. Did the analysis include an intention-to-treat analysis? *"Yes," if <5% of randomly assigned patients were excluded.*	All randomly assigned patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of nonadherence and co-interventions.	Yes/No/Don't Know

* This list includes only the 11 internal validity criteria that refer to characteristics of the study that might be related to selection bias (criteria A and B), performance bias (criteria D, E, G, and H), attrition bias (criteria I and K), and detection bias (criteria F and J). The internal validity criteria should be used to define methodological quality in the meta-analysis.
† Adapted from methods developed by the Cochrane Back Review Group (26).

Chou, R. et. al. Ann Intern Med 2007;147:505-514

Appendix Table 4. Recommendations and Summary Ratings*

Grade	Recommendation
A	The panel strongly recommends that clinicians consider offering the intervention to eligible patients. *The panel found good evidence that the intervention improves health outcomes and concludes that benefits substantially outweigh harms.*
B	The panel recommends that clinicians consider offering the intervention to eligible patients. *The panel found at least fair evidence that the intervention improves health outcomes and concludes that benefits moderately outweigh harms, or that benefits are small but there are no significant harms, costs, or burdens associated with the intervention.*
C	The panel makes no recommendation for or against the intervention. *The panel found at least fair evidence that the intervention can improve health outcomes, but concludes that benefits only slightly outweigh harms, or the balance of benefits and harms is too close to justify a general recommendation.*
D	The panel recommends against offering the intervention. *The panel found at least fair evidence that the intervention is ineffective or that harms outweigh benefits.*
I	The panel found insufficient evidence to recommend for or against the intervention. *Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* Adapted from methods developed by the U.S. Preventive Services Task Force (19).

Chou, R. et. al. Ann Intern Med 2007;147:478-491

Appendix Table 6. **Level of Evidence and Summary Grades for Noninvasive Interventions in Patients with Chronic or Subacute Low Back Pain***

Intervention	Level of Evidence	Net Benefit	Grade
Acetaminophen	Good	Moderate	B
Acupuncture	Fair (some inconsistency vs. sham acupuncture)	Moderate	B
Psychological therapy (cognitive-behavioral therapy or progressive relaxation)	Good for cognitive-behavioral, fair for progressive relaxation	Moderate (cognitive-behavioral) to substantial (progressive relaxation)	B
Exercise therapy	Good	Moderate	B
Interdisciplinary rehabilitation	Good	Moderate	B
Nonsteroidal anti-inflammatory drugs	Good	Moderate	B
Spinal manipulation	Good	Moderate	B
Opioids and tramadol	Fair (primarily indirect evidence from trials of patients with other pain conditions)	Moderate	B
Brief individualized educational interventions	Fair	Moderate	B
Benzodiazepines	Fair	Moderate	B
Massage	Fair	Moderate	B
Yoga	Fair (for Viniyoga) to poor (for Hatha yoga)	Moderate (Viniyoga), unable to estimate (Hatha yoga)	B (Viniyoga)
Tricyclic antidepressants	Good	Small to moderate	B/C
Antiepileptic drugs	Fair (for gabapentin) to poor (for topiramate)	Small (gabapentin in patients with radiculopathy), unable to estimate (topiramate)	C (gabapentin), I (topiramate)
Back schools	Fair (some inconsistency)	Small	C
Firm mattresses	Fair	No benefit or harm	D
Traction	Fair	No benefit (continuous or intermittent traction), small to moderate (autotraction for sciatica)	D (continuous or intermittent traction), C (autotraction for sciatica)
Aspirin	Poor	Unable to estimate	I
Biofeedback†	Poor	Unable to estimate	I
Interferential therapy	Poor	Unable to estimate	I
Low-level laser	Poor	Unable to estimate	I
Lumbar supports	Poor	Unable to estimate	I
Shortwave diathermy	Poor	Unable to estimate	I
Skeletal muscle relaxants	Poor	Unable to estimate	I
Transcutaneous electrical nerve stimulation	Poor	Unable to estimate	I
Ultrasonography	Poor	Unable to estimate	I

* See **Appendix Tables 1, 2,** and 3 for explanation of grades. Low back pain is considered subacute at 1–3 months' duration and chronic at >3 months' duration.
† The use of auditory or visual signals reflecting muscle tension or activity to learn how to inhibit or reduce the muscle activity.

Chou, R. et. al. Ann Intern Med 2007;147:478-491

Recommendations

- "Globalize the evidence"
  - Objective, critical assessment of existing evidence by international collaboration
  - Needs to be buy-in by various national professional organizations and societies
- Prospective determination of type of studies, strength of evidence, outcomes reported that invoke need to update
- Keep what we know separate from what we think we know
  - Consistent, simple, transparent system for grading quality of the evidence
- Keep what we know separate from is recommended
  - Don't strongly recommend beyond what strong high quality data supports
  - Governmental and agency policy should not influence guidelines and clinical practice recommendations—but should be anticipated and addressed

Recommendations

- No industry influence on evidence review or guideline development
  - Funding from professional societies
- Manage potential conflicts of interest among guideline group members
  - Limit industry support to research activities only?
  - No advisory board roles?
  - No marketing-related consulting?
  - No “unrestricted educational grants”?
  - Disclose funding to ERT-type groups?
- More emphasis on individual doctor-patient decision making
  - “Guidelines are for the population…the doctor is for the patient”
  - Less “one size fits all” anemia management
- “Localize the implementation”
  - Translation
  - Action plans to implement into CKD and ESRD practice

Thank You.