Comparison of Evidence Review Process for Five Primary Global Anaemia Guidelines

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The Guidelines

Australia: CARI 2005
Canada: CSN 1999
Europe: EBPG 2004
U.K. (Adopted) NICE 2006
USA KDOQI 2006/7
WHO: Improving the Use of Research Evidence in Guideline Development (17 articles)

2 Priority setting
3 Group composition
4 Managing conflicts of interest
5 Group processes
6 Determining which outcomes are important
7 Deciding what evidence to include
8 Synthesis and presentation of evidence
9 Grading evidence and recommendations
Priority Setting

CARI – Australia & New Zealand Society of Nephrology and Kidney Health (research, patient and carer help, communities awareness)

CSN – Canadian Society of Nephrology, Committee for Clinical Practice Guidelines. Teleconferences – anaemia – controversy regarding target haemoglobin

EBPG – Update because of changes in field

NICE – National Institute for Clinical Excellence (NICE)
  - Renal Association / Registry
  - National Service Framework
  - Variation in practice, improve standard of care, and commissioning of cost effective treatment

K/DOQI – Update previous guidelines
Group Composition

**CARI** – Nephrologists, patient representatives

**CSN** – Nephrologists, patient representatives (approved by Kidney Foundation of Canada) and at least one representative from another profession, eg nurse

**EBPG** – Nephrologists from 9 European countries

**NICE** – 23 members. Chair – respiratory physician, GP, haematologist, anaemia nurses, paediatrician, pharmacist, patient & carer representatives, 4 nephrologists, diabetologist, geriatrician, Public Health consultant, Health economists, HSR, project managers, information scientists

**K/DOQI** – 18 members. Nephrologists, pharmacist, paediatrician, dietitian (USA, Canada, Mexico). Liaison members – Italy, UK. 

Also ERT – Tufts NEMC - 7 members
Managing Conflict of Interest

CARI

- Level 1 precludes participation, eg paid consultancy by company
- Level 2 participation allowed but conflict of interest will be identified, eg paid work (speakers fees / advisors fees) for a company active in area under consideration

K/DOQI

- All conflicts of interest cited in biography of work group members
Group Processes

CARI

• Initial Guideline group teleconference
  - decide sub topics within broad area
  - decide who will write each subtopic
• Critical appraisal workshop – 1 day
• 3 Face-to-Face meetings
  (Domestic Terminal 3 Sydney Airport!)
  ⇒ Peer review
12 months
**CSN** — 12 months. 2nd draft at 9/12 to all CSN members, nurses, SW, dieticians

**EBPG** — Reviewed on line by EDTA/ERA members

**NICE** — 12 months, monthly meetings,

? Not out for review.

**K/DOQI update 07** — Series of conference calls, one face-to-face meeting, then out for public review
Developing Search Questions & Outcomes

CARI – PICOM - populations, interventions, comparison group, outcomes of interest

CSN - no specific mention

EBPG - outcomes pre-specified

NICE - questions published, outcomes sometimes in question

K/DOQI - PICOD – (D study design)
Deciding what evidence to use

CARI - Systematic reviews
RCTs
Cohort & case control studies
Searched Cochrane – Register of RCTS & Central Database
Embase, Medline

CSN - all relevant publications post DOQI

EBPG - Medline, Embase
NICE - Study type filters for each question started in advance, eg Sys Reviews & RCTS, Medline, Embase, Cochrane, Cinahl, Psych info

K/DOQI - From previous EBPG & DOQI/KDOQI Medline update
Synthesis & Grading of Evidence

Research Officer - performs searches
Abstracts of articles → guidelines writers
Full text copies of chosen articles
Data abstraction by guideline writers

Tables - produced by Research Officer
Characteristics of included studies
Quality of RCTs
Results of dichotomous outcomes
Results of continuous outcomes
For each clinically important outcome group members review aggregate of studies, formulate a grade for evidence
- study quality
- consistency & directness of evidence

THEN

Review evidence across all important outcomes and assess net medical benefit and grade overall quality of evidence
Levels of Evidence

Level 1: Evidence obtained from a systematic review of all relevant RCTs

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from comparative studies (cohort studies, case control studies, pseudo-RCTs etc)

Level IV: Evidence obtained from case series (either post-test or pre-test/post-test)
Guidelines for evidence levels I and II
Suggestions for clinical care for evidence levels III and IV
Levels of Evidence for Rating Studies of Treatment, Prevention & Quality Assurance

I  A randomized, controlled trial (RCT) that demonstrates a statistically significant difference in at least one important outcome (e.g., survival or major illness) or if the difference is not statistically significant, an RCT of adequate sample size to exclude a 25% difference in relative risk with 80% power, given the observed results.

II An RCT that does not meet the level I criteria

III A nonrandomized trial with contemporaneous controls selected by some systematic method (i.e., not selected by perceived suitability for one of the treatment options for individual patients) OR Subgroup analysis of a randomized trial

IV A before-after study of case series (of at least 10 patients) with historical controls or controls drawn from other studies

V Case series (at least 10 patients) without controls

VI Case report (fewer than 10 patients)
• Made Guideline statement with level of evidence (or opinion) at the end
Synthesis & Grading of Evidence

- Search coordinator performs searches and decides which full articles to obtain.
- Articles to research team
- Data abstraction by research team on study quality, interventions and outcomes for each publication (randomly selected articles reviewed by second researcher)
• Data abstraction forms reviewed by Working Group members
• RCTs and systematic reviews used where available
• If not - best available evidence or expert opinion
Levels of Evidence

A. Evidence from at least one good, randomised, or quasi randomised controlled trial or meta-analysis, or a Cochrane review.

B. Evidence from several uncontrolled non-randomised open studies

C. Case studies or expert opinions

Made Guideline statement with level of evidence (or opinion) at the end
Synthesis & Grading of Evidence

• Information Scientist developed strategy
• Health Services Research Fellow
  - reviewed abstracts
  - decided which full articles to retrieve
  - critically appraised the full papers
  - extracted data
• Guideline Development Group reviewed evidence and formulated recommendations
### Table 2.2 Grading the evidence statements and recommendations

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Classification of recommendations</th>
</tr>
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<tbody>
<tr>
<td><strong>1++</strong></td>
<td>High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.</td>
</tr>
<tr>
<td><strong>1+</strong></td>
<td>Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.</td>
</tr>
<tr>
<td><strong>1−</strong></td>
<td>MA, SR of RCTs, or RCTs with a high risk of bias.</td>
</tr>
<tr>
<td><strong>2++</strong></td>
<td>High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.</td>
</tr>
<tr>
<td><strong>2+</strong></td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.</td>
</tr>
<tr>
<td><strong>2−</strong></td>
<td>Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Non-analytic studies (for example case reports, case series).</td>
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<tr>
<td><strong>4</strong></td>
<td>Expert opinion, formal consensus.</td>
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</tbody>
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#### Levels of evidence:
- **A**: Level 1++ and directly applicable to the target population
- **B**: Level 2++, directly applicable to the target population and demonstrating overall consistency of results
- **C**: Level 2+, directly applicable to the target population and demonstrating overall consistency of results
- **D**: Level 3 or 4

#### Classification of recommendations:
- Not used as a basis for making a recommendation.
Synthesis & Grading of Evidence

- Evidence Review Team (expertise in nephrology and evidence based guidelines) performed the literature searches
- Retrieved articles screened by ERT, potentially relevant studies to Work Group members for re-screening and data extraction
• ERT made evidence tables from data extraction forms - summarised individual studies
• From that made summary tables with grades for study quality (A,B,C) for each study
• Quality of evidence for a particular outcome categorised (high, moderately high, low, very low)
Overall quality of evidence for all outcomes determined (high, moderately high, low, very low)

Guideline recommendation graded (strong or moderately strong) based on quality of the overall evidence

Additional considerations implicitly considered - feasibility, availability of service, regional and population differences

If evidence weak could elect to give opinion based clinical practice recommendation
GUIDELINES

The recommended haemoglobin concentration for patients with proven or likely significant cardiovascular disease should not exceed 120g/L (Evidence level 1)

Suggestions for clinical care
(suggestions are based on Level III and IV evidence)

- The recommended minimum Hb concentration in chronic dialysis patients is 110g/L
- An Hb concentration between 120 and 140g/L has a beneficial effect in patients without proven or likely significant cardiovascular disease.
“The target haemoglobin during erythropoietin therapy is 110 to 120 g/L for both adult males and females (opinion)”
Recommendation

In general patients with chronic kidney disease should maintain a target haemoglobin concentration of > 11 g/dl regardless of age, gender or ethnicity (Evidence level B)
Recommendation

In people with anaemia of CKD treatment should maintain stable haemoglobin levels between 10.5 and 12.5 g/dl, adjusting treatment typically when Hb rises above 12 or falls below 11 g/dl (C)
Recommendation

In the opinion of the Work Group in dialysis and non-dialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11 to 12 g/dl (clinical practice recommendation).

In dialysis and non-dialysis patients with CKD receiving ESA therapy the Hb target should not be greater than 13 g/dl (clinical practice guideline - moderately strong evidence).
Priority Setting:
Subcommittee of Joint Committee of Australian & New Zealand Society of Nephrology, and Kidney Health Australia

Group composition:
Conveners: chosen by CARI Steering Committee, approved by Subcommittee
Members: register interest and chosen by Conveners based on area of expertise and availability
Managing conflict of interest

Level I Conflict - Precludes participation eg paid employment including paid consultancy for Pharmaceutical company active in clinical area

Level II Conflict - Participation allowed, but identified, eg paid work (speakers /advisors fees) for Pharmaceutical company active in clinical area
Level I evidence (Systematic Review)

“The systematic review (Strippoli et al 2003) includes 16 randomised controlled trials and evaluated the effect of low versus high Hb targets on mortality, serious cardiovascular events, access thrombosis, renal function, seizures, hypertension and quality of life (see Table 1).”

“The authors conclude that the benefits associated with higher Hb targets (reduced seizures) are outweighed by the risks (increased risk of hypertension and increased mortality) in patients with cardiovascular impairment. Haemoglobin targets >133g/L at best implied no reduction in deaths and at worst, implied an increase in the number of deaths.”
- Data extraction
  - study setting
  - demographics
  - eligibility criteria
  - causes of kidney disease
  - numbers of subjects
  - study design
  - study funding source
  - dialysis characteristics
  - co-morbid conditions
  - risk factors/interventions
  - descriptions of outcomes
  - statistical methods
  - study quality
  - study applicability
“The target haemoglobin during erythropoietin therapy is 110 to 120 g/L for both adult males and females (opinion)”

Discussion
The optimal physiologic haemoglobin in the ESRD population has not been established. However, in patients with a haemoglobin <100 g/L there is clear evidence of deterioration in left ventricular hypertrophy, cerebral function, and quality of life (11,12) (evidence level IV).
“using erythropoietin and intravenous iron to achieve a haemoglobin of 130 to 150 may be associated with increased mortality in patients with clinically evident congestive heart failure or ischemic heart disease(13) (evidence level II).

Therefore, patients’ haemoglobin should usually not plateau below 100 g/L or above 130 g/L. Accounting for fluctuations in the haemoglobin resulting from both laboratory and physiologic factors, if 115 g/L is used as a target haemoglobin, 96% of patients will have their haemoglobin maintained between 110 and 120 g/L”
“Hence, in patients with chronic kidney disease and cardiovascular impairment, the preferred Hb target should be <120g/L. Data relating to other populations (pre-dialysis patients with chronic renal insufficiency and patients without cardiovascular impairment) are unclear and need further investigation.”