Comparison of Evidence Review Process for Five Primary Global Anaemia Guidelines

Professor Alison MacLeod
University of Aberdeen
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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 RCTS, Medline, Cochrane, Cinahl, Psych info Sys Reviews & Embase,

K/DOQI - From previous EBPG & DOQI/KDOQI Medline update

CARI

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

CARI

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

CARI

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)

CARI

- Guidelines for evidence levels I and II
- Suggestions for clinical care for evidence levels III and IV

CSN

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 (eg 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 trail with contemporaneous controls selected by some systematic method (ie not selected by perceived suitability for one of the treatment options for individual patients) OR Subgroup analysis of a randomized trail
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)

CSN

- 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)

EBPG

- Data abstraction forms reviewed by Working Group members
- RCTs and systematic reviews used where available
- If not – best available evidence or expert opinion

EBPG

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

NICE

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

NICE

Table 2.2 Grading the evidence statements and recommendations[2]

Levels of evidence		Classification of recommendations	
Level	Type of evidence	Class	Evidence
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* Level 1+ and directly applicable to the target population AND consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1–	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation.	
2++	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.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results. *or* Extrapolated evidence from 1++ or 1+.
2+	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.		
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or*

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

K/DOQI

- 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)

K/DOQI

- 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

CARI

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.

CSN

"The target haemoglobin during erythropoietin therapy is 110 to 120 g/L for both adult males and females (opinion)"

EBPG

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)

NICE

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)

K/DOQI

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)

CARI

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

CARI

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."

K/DOQI

- 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

CSN

"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).

CSN

“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”

CARI

"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."