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Introduction to the Canadian Society of Nephrology Clinical Practice Guidelines for the management of anemia associated with chronic kidney disease

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In 1999, the Canadian Society of Nephrology (CSN) published clinical practice guidelines (CPG) for the treatment of patients with chronic kidney disease (CKD),[1,2] which included CPGs for the management of anemia coexistent with chronic renal failure. In 2003, responding to new evidence and emerging controversies, the CSN Executive Committee recognized the need to update these guidelines and establish new guidelines in areas of perceived clinical need. It was decided that guidelines for the management of hemodialysis, peritoneal dialysis, and non-dialysis CKD patients, as well as anemia management for all patients with CKD, would be developed or revised in a staggered manner over 3–5 years. The overriding objective was to establish national guidelines to improve the quality of health care delivered to patients with CKD in Canada.

Since the release of the original CSN anemia guidelines in 1999, several potentially practice-altering clinical trials have been published, with the most pertinent recent literature focusing on appropriate hemoglobin targets.[3–5] The aim of these revised CSN anemia guidelines is to define optimal management of anemia in CKD patients, where potential adverse effects are balanced against potential improvements in quality of life and avoidance of transfusion.

The guidelines that follow are intended to reflect the available evidence, as well as the human and financial resources in Canada at the time of this publication. Although the majority of proven therapies are currently funded in Canada, there are many therapies for which evidence of effectiveness on clinical outcomes is limited, or for which the only evidence is measured by non-clinical endpoints. These therapies are either not funded at all or funded only for select groups of patients. Health care professionals are often uncomfortable taking resource constraints and medication costs into account when making therapeutic decisions. However, in health care systems with constrained budgets, directing excessive resources toward expensive, marginally effective therapies limits the resources available to be used for other, effective therapies. As physicians are often in a good position to compare the benefits and risks of specific therapies, they should take an active role in deciding which therapies should be made available, by reimbursement, to Canadian patients. Thus, resource implications have been considered for each guideline presented in this document, though only after a thorough consideration of the safety and effectiveness of the therapy or test in question.

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[8]Dr Bruce F. Culleton was the Chair of the CSN Guidelines while these guidelines were being developed and was based at the University of Calgary.

METHODS AND PROCESS FOR GUIDELINE DEVELOPMENT

Although content expertise was a prerequisite, geographic factors were also considered when choosing the CSN Anemia Work Group members. In addition to content expertise, it was necessary that the Work Group Chair have no personal financial or research relationships with the companies manufacturing products for the treatment of anemia. The Anemia Work Group was asked to utilize the extensive content and methodological review of the relevant literature obtained by the prior CSN guidelines committee[1] and the recent relevant publication from the Kidney Disease Outcomes Quality Initiative (KDOQI) Work Group.[6] This literature was supplemented by using the work group members' content expertise to identify new evidence as well as an English-language-focused literature search in nephrology and general medical journals. The Work Group assumed that new evidence of sufficient magnitude to warrant the revision of existing national guidelines would be discovered by using these two

Table 1 | Conflict of interest statements for CSN anemia guideline members for last 3 years

CSN member	Type of potential conflict of interest	Role	Time period	Sponsor[a]	Total value
Barrett	Consultant	Consultant	2006–2007	Bracco Diagnostics Inc.	$25,000
Barrett	Unrestricted research grant–investigator initiated	Co-PI	2004–2007	Amgen Canada	$750,000
Barrett	Unrestricted research grant–investigator initiated	Co-PI	2004–2007	Ortho Biotech	$750,000
Culleton[b]	Unrestricted research grant – investigator initiated	Co-Investigator (Alberta kidney disease network)	2004–2007	Amgen	$480,000
Culleton[b]	Consultant	Consultant	2004–2007	Amgen	$25,000
Foley	Consultant	Consultant	2005–2007	Affymax	$2000
Foley	Consultant and speaker	Consultant and speaker	2005–2007	Amgen	$21,500
Foley	Consultant and speaker	Consultant and speaker	2005–2007	Janssen-Ortho-Johnson and Johnson	$16,500
Foley	Consultant	Consultant	2005–2007	Luitpold	$5000
Foley	Consultant	Consultant	2005–2007	KDOQI	$3000
Foley	Consultant	Consultant	2005–2007	Veteran's Administration Financial Services	$2000
Foley	Consultant	Consultant	2005–2007	Genzyme	$3000
Foley	Speaker	Speaker	2005–2007	United Healthcare Services	$750
Foley	Speaker	Speaker	2005–2007	Los Angeles Biomedical Research	$1750
Foley	Speaker	Speaker	2005–2007	Winthrop University Hospital	$1000
Foley	Consultant	Consultant	2005–2007	Abbott	$3000
Klarenbach	Unrestricted research grant–investigator initiated	Co-investigator (Alberta kidney disease network)	2004–2008	Amgen	$480,000
Madore	Unrestricted research grant–investigator initiated	PI	2002–2006	Gambro	$45,000
Madore	Unrestricted research grant–investigator initiated	PI	2005–2006	Sigma-Tau Pharmaceuticals	$65,000
Madore	Funding for an industry clinical trial	Co-investigator	2003–2004	Ortho Biotech	$30,000
Madore	Funding for an industry clinical trial	Co-investigator	2006–2007	Luitpold Pharmaceuticals, Inc.	$20,000
Manns	Unrestricted research grant–investigator initiated	Co-investigator (Alberta kidney disease network)	2004–2008	Amgen	$480,000
Moist	Unrestricted research grant–investigator initiated	PI	Sept 2006–Dec 2006	Ortho Biotech Products, L.P.	$10,000
Moist	Unrestricted research grant–investigator initiated	Co-investigator	Sept 2006–2008	Ortho Biotech	$20,000
Moist	Unrestricted research grant–investigator initiated	Co-investigator	2004–2008	Roche	$30,000
Moist	Unrestricted research grant–investigator initiated	PI	2005	Ortho Biotech	$10,000
Moist	Research grant	Site investigator (DOPPS study)	2002–2008	Amgen	$5000/year
Moist	Unrestricted research grant–investigator initiated	Principal investigator		Amgen	$2000
Moist	National Education Forum	Attendee	2005–2007 once yearly	Amgen	Flight and hotel accommodation
Tonelli	Unrestricted research grant–investigator initiated	Co-investigator (Alberta kidney disease network)	2004–2008	Amgen	$480,000
White	Provincial advisory board	Member	Fall 2006–2007	Amgen	Honoraria donated to Fellow Education Fund ($750)

PI, principal investigator.
[a]List restricted to companies that make products for anemia management or dialysis companies.
[b]After the CSN anemia guidelines were completed, Dr Culleton became an employee of Baxter Healthcare. Baxter Healthcare provided no funding for the guidelines, and provided no input into the drafting or final version of the guidelines.

methods. Although this approach might be criticized for lack of methodological rigor, such an approach is pragmatic and has been utilized and advocated by others.[7,8]

The CSN anemia guidelines that follow are intended to rely on evidence and avoid opinion-based statements, where possible. Other similar work groups have made a distinction between clinical practice guidelines and clinical practice recommendations, with guidelines being provided when the work group thought that the evidence was sufficiently strong to make definitive statements about the appropriateness of

clinical practice.[6] Alternatively, clinical practice recommendations were provided for statements based upon a lesser grade of evidence. The main reason for making this distinction was to highlight the areas where adherence to a guideline would be particularly likely to improve outcomes. Although this is a reasonable goal, it is unclear whether it was achieved, and distinguishing between guidelines and recommendations is very subjective.

Given the potentially arbitrary nature of the distinction between guidelines and recommendations, and to be consistent with previous CSN guidelines, we present only clinical practice guidelines. In all cases, guidelines are made only if the Work Group is confident that adherence would do more good than harm. The evidence in support of each guideline is graded using the scheme developed by the Canadian Hypertension Education Program[9] and used by the CSN Guidelines Committee in the past.[10]

Where studies yield conflicting findings, or where lack of good-quality evidence makes it difficult to create clinical practice guidelines, we provide an overview of existing evidence, which we hope will guide management by practitioners. In these situations, specific research recommendations are also made.

The following anemia guidelines are organized into four sections: the first focuses on the evaluation of anemia in patients with CKD; the second deals with the assessment and management of iron deficiency in CKD patients; the third discusses the administration and monitoring of erythropoietin-stimulating agents (ESAs) and the appropriate target hemoglobin; finally, the final section discusses the safety and effectiveness of supplemental therapies for anemia, and the assessment and management of patients with erythropoietin resistance.

The document focuses on the management of anemia in hemodialysis (HD-CKD) and peritoneal dialysis (PD-CKD) patients and non-dialysis patients with CKD stages 3–5 (ND-CKD). It does not discuss the management of anemia in children with CKD, nor in patients with functioning renal allografts. Where guidelines differ by CKD patient type, or are applicable to only one patient subgroup (for example, only those patients on hemodialysis), the relevant patient population is clearly stated.

The creation of these guidelines was facilitated by a face-to-face meeting at the 2006 CSN annual meeting in Quebec City, and by teleconferences as needed. The entire Work Group reviewed and modified the first draft of this document. The document was then distributed to all members of the CSN and relevant stakeholders, including the Kidney Foundation of Canada and provincial ministries of health, and was subsequently presented to the CSN membership at the CSN Annual meeting in May 2007. Comments from this external review were considered in detail, and responses to these comments can be viewed on the CSN website (www.csnscn.ca). The final revised draft of the anemia guidelines was completed in July 2007.

SPONSORSHIP

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