CARE AND REFERRAL OF ADULT PATIENTS WITH REDUCED KIDNEY FUNCTION

Position Paper from the Canadian Society of Nephrology

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See appendix for complete list of CSN Referral and eGFR Committee members

September 2006

Introduction

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In 2004, the Clinical Practice Guidelines Committee (CPG) for the Canadian Society of Nephrology (CSN) and the CSN Executive Committee recognized the need to publish recommendations for the management of patients in Canada with non-dialysis dependent chronic kidney disease (CKD). The initial step in this process was to address the existing controversies around the classification of CKD and the measurement of kidney function, with special reference to estimating glomerular filtration rate (eGFR). The natural extension to this process was to provide guidance to primary care providers for the referral of patients with CKD to kidney specialists. The final step, recommendations for the medical management of CKD, is currently underway.

The position statements that follow were developed under the supervision and guidance of Dr. Adeera Levin and Dr. David Mendelssohn. These individuals were chosen for their clinical and research expertise in the specific areas addressed within this position paper and their involvement in a prior related document from the CSN (Elevated levels of serum creatinine: recommendations for management and referral. *CMAJ* 161 (4), 1999). The committee for the current position paper was populated by academic and community nephrologists with content expertise, and members from the Kidney Foundation of Canada, the Canadian Society of Clinical Chemists, and the College of Family Physicians of Canada.

An initial meeting of this group was held at the CSN Annual Meeting in Calgary, Alberta (May 2005). Several teleconferences were held over the subsequent 8 months and a preliminary draft of the position paper was distributed for review to all CSN members in April 2006. The document was also presented at the 2006 CSN Annual General Meeting in Quebec City. All comments and concerns were addressed by the committee and a final draft of the position paper was endorsed by the CSN council in September, 2006. Endorsement of the position paper has also been received from the Kidney Foundation of Canada.

Background

In 1999, the Canadian Society of Nephrology (CSN) published "Guidelines for Management and Referral of Patients with Elevated Creatinine" in the Canadian Medical Association Journal[1]. The prime motivation for creating this guideline was the accumulating data describing the negative impact of non-referral and late referral for dialysis, and the consequent need for earlier referral of patients to a nephrologist. At the time of its publication, CSN was the only national or international society to have created this kind of document.

Since then, the nephrology community worldwide has focused its attention on patients with reduced kidney function prior to end stage renal disease (ESRD). The key stimuli to this renewed interest have been:

1) new nomenclature, definitions and a staging system for chronic kidney disease (CKD)[2]

2) calls for the reporting of kidney function as an estimate of glomerular filtration rate (eGFR) using equations and standardized creatinine measurements[2-11]

3) an appreciation that predictive equations of eGFR have been validated primarily in patients referred to nephrologists, with lesser evidence of validity in non-referred populations

4) an increased awareness that patients with reduced kidney function have high rates of cardiovascular disease, and that many patients die before progressing to ESRD[12-17]

5) an increased understanding that not all people with reduced kidney function experience a progressive loss of function, particularly in the absence of proteinuria

6) an appreciation that the elderly population have an increased prevalence of reduced kidney function, as determined by eGFR

7) recent recommendations for investigation of patients with reduced kidney function that no longer require 24 hour urine collection for estimation of creatinine clearance or GFR, or for quantification of urinary protein excretion for most patients[2]

8) the impact that a diagnosis of reduced kidney function (at whatever stage of CKD) might or might not have on a patient's treatment or care plan.

Canada is no longer alone in publishing scholarly articles that champion improved care of patients with CKD and appropriate referral to nephrologists. Indeed, it was the USA based National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2002 initiative that led the way in promoting several new approaches with its staging and classification guidelines[2]. National nephrology societies in Australia[18] and the United Kingdom[19] have done more recent, and detailed work in this area, culminating in an international initiative (with Canadian representation) that has adapted and promoted many of these ideas on a global level (Kidney Disease Improving Global Outcomes, or KDIGO)[20].

As a national subspecialty society, the CSN recognizes the need to establish and communicate clearly articulated standards of practice which are particularly pertinent to Canadians with CKD. The CSN also has a responsibility to disseminate new recommendations to other stakeholder groups within Canada.

CSN Strategy to Address CKD and Referral

In view of the important contributions of other national and international nephrology societies in establishing guidelines on CKD care, the CSN Referral and eGFR Committee has adopted the following strategy to address these issues for its members, Canadian practitioners, patients, and other stakeholders:

a) Creation of this concise document, which sets outs CSN recommendations on various issues related to CKD care and referral of adults, which avoids redundancies with other published materials, and which will be maintained on the CSN website.

b) Development of an education and implementation strategy to disseminate this knowledge to Canadian partner organizations, physicians and to the public, with follow-up on the impact of these implementation efforts. CSN has created a new Implementation of Guidelines Committee whose first task is to disseminate these recommendations.

c) Preparation of a companion document that reviews and recommends clinical practice guidelines for the management of patients with CKD, building on previous work of hypertension and diabetes guidelines. A preliminary short version is available (appended at the end of this document and at the CSN website) as an interim measure. The target date for finalization of this document is May, 2007.

The following recommendations attempt to balance the need for clarity, the current state of uncertainty and the need for a simple message. Educational tools will be developed based on these tenets.

CSN Recommendations and Position Statements

1) CSN recognizes that the recommendations which follow must be accompanied by a significant change in the practice of physicians in order to be fully effective. As such, CSN believes that effective dissemination strategies need to be developed, and that a structured educational program must be implemented to ensure understanding and appropriate application of these recommendations.

2) CSN endorses a case finding approach to testing for CKD, which should be focused on high-risk groups. CSN does not endorse mass population screening for CKD with either serum creatinine based tests or with urine dipstick testing. There is ample evidence to suggest that persons in high risk groups have a high incidence of reduced kidney function and/or proteinuria, and that both are associated with adverse outcomes. These adverse outcomes include death, cardiovascular events, hospitalizations, and less commonly, ESRD. High risk groups include patients with hypertension, diabetes mellitus, heart failure, atherosclerotic coronary, cerebral or peripheral vascular disease, unexplained anemia, family members of patients with ESRD, and first nation's peoples.

3a) CSN endorses the staging and classification system initially proposed by NKF-KDOQI group, and the minor modifications described by the KDIGO group, as a framework for clinical practice, education, and ongoing research.

3b) CSN encourages its members to participate in clinical research studies to advance the understanding of the utility and applicability of different eGFR equations.

4a) CSN endorses routine laboratory reporting of eGFR based on the use of a conventional mathematical formula, provided it is accompanied by a plan for appropriate physician education and for standardization of the serum creatinine assay. The a) the Cockcroft Gault formula (corrected for body surface area (BSA)), or b) the abbreviated MDRD formula, are equally valid tools for quantifying kidney function, and for earlier detection of kidney disease in adult populations. Both formulae have been validated in various populations with moderate to severe impairment of GFR; however, they may be less reliable in patients with near-normal (>60 ml/min/1.73m^2) GFR or in patients with markedly abnormal body composition (eg. extreme obesity, cachexia, paralysis, amputations). Similarly, there remain controversies as to the applicability of these equations to various ethnic groups, the very elderly, and to unreferred populations with modest decreases in kidney function. Nonetheless, the CSN recognizes the need to endorse the use of equations as an alternative to the direct use of serum creatinine concentration, which tends to be ineffective in general practice as an early marker of kidney injury. At the present time, it is recognized that long-term outcome studies of individuals and populations with Stages 1, 2 and early stage 3 CKD are relatively limited and that these equations will likely undergo modification as research progresses.

4b) Standard laboratory practice in some parts of Canada is to calculate and report the 3-factor "modified" MDRD equation based on age, gender and serum creatinine

concentration for patients over 18 years of age. Since the laboratory does not know the race of the patient, multiplication by a correction factor (1.21) for the higher muscle mass attributed to persons of "African descent" should be performed by the physician who receives the laboratory report, if required.

5a) CSN recommends standardization of serum creatinine assays to isotope dilution mass spectrometry (IDMS). This will improve accuracy (trueness) and reproducibility (precision) in the measurement of creatinine across laboratories and geographic locations.

5b) It should be noted that as laboratories update their methods to IDMS traceable assays, serum creatinine concentrations may be slightly decreased by approximately 5 to 10% in many, but not all laboratories depending on their current methodology.

6a) The CSN recognizes that not all laboratories in Canada are able to provide automated eGFR reporting at this time. However, CSN recommends that laboratories institute measures that permit them to report eGFR in the near future. In the meantime, physicians are encouraged to transform serum creatinine concentrations to estimates of kidney function based on conventional equations (e.g. Cockcroft Gault or MDRD) using readily available calculators or tools. These are available on line at the USA National Kidney Foundation website.

6b) It should be noted that the eGFR results reported by some laboratories may not be exactly the same as those calculated individually by physicians using the reported serum creatinine concentration. This may occur when a laboratory participates in a harmonization program that provides and monitors a correction factor for the serum creatinine concentration which is applied only as part of the automated eGFR calculation.

6c) It is not recommended that clinicians rely on serum creatinine concentrations alone when assessing kidney function. If neither eGFR reporting, nor calculators are available to a physician, tables based on serum creatinine and other variables are available to provide approximations of eGFR.

7) The CSN endorses the clinical diagnosis and reporting of calculated eGFR numbers < 60 ml/min/1.73m^2. As values over 60 ml/min /1.73m^2 may be misleading, CSN recommends categorical reporting such as "eGFR > 60 ml/min /1.73m^2". It is important to note that patients with stable measurements of eGFR > 60 but <120 do not have kidney disease <u>unless</u> there is also significant proteinuria or a urinary anatomical abnormality. Such patients do not require investigation, treatment or referral to a nephrologist.

8) CSN endorses the position that 24 hour urine collections (either to assess creatinine clearance or protein excretion rate) are <u>not</u> <u>routinely</u> required. A calculated eGFR is preferred, except in the situation of a markedly abnormal body composition (eg. extreme obesity, cachexia, paralysis, amputation). Albumin or protein excretion should be quantified and followed serially with either a urine albumin to creatinine ratio (ACR) or a urine protein to creatinine ratio (PCR).

9) CSN recommends that most patients with non-progressive CKD can be managed by non-nephrologists, without referral. The recognition that many patients with an eGFR between 30 and 60 ml/min/1.73m^2 do not have a high risk of progressive kidney disease is important. As such, for patients with a new finding of an eGFR between 30-60 ml/min1.73m^2, CSN recommends that clinicians determine the stability of the patient's eGFR (repeat test within 2-4 weeks, and then in 3-6 months) and the extent of comorbidity, and then determine the need for referral (see below). Note that CSN will soon provide a detailed management guide for CKD to be applied by non-nephrologists. In the interim, a short tool is available appended to the end of this document and on the CSN website.

10) CSN recommends that patients with CKD (as defined by an eGFR < 60 ml/min/1.73m^2 for > 3 months), or those in high risk groups with persistent urine sediment abnormalities require serial evaluations at a frequency depending on their level of kidney function.

11) CSN endorses co-management of patients referred to a nephrologist with their primary care physicians and other health care providers, and strategies to enable a shared care model. Nephrologists should participate in educational activities that improve the knowledge, skills and confidence of other physicians who routinely care for patients with CKD.

12) The CSN recommends that decisions about investigation, treatment or referral should not be made based on a single isolated test of kidney function. It is recognized that a number of patients may have transient reductions in eGFR due to intercurrent illness, medications or other conditions. In a primary care setting, many patients will show improvement or normalization of kidney function upon repeat testing. The diagnosis of CKD is based on serial measurements of kidney function as it is not possible to diagnose CKD on the basis of a single serum creatinine concentration transformed using equations. Thus, serial testing of kidney function should be performed within 1-3 months of identification (eg. at 2 to 4 weeks, and then again at 3 to 6 months). At this time, there are no data on which to base recommendations about frequency of testing for those with eGFR just below values of 60 ml/min/1.73m^2, but at least two consecutive measurements corroborating the stability of a value would be reasonable (individual circumstances may vary).

13) CSN endorses aggressive management of patients with both progressive and non-progressive CKD. The tasks involved are a) searching for reversible disease, b) implementing measures to slow progression of CKD, c) active management of CV risk factors and of the co-morbid conditions that coexist with CKD, and d) if required, preparation for renal replacement therapy. The CSN will develop and disseminate recommendations for the management of CKD and CVD based on best current evidence, to help non-nephrologists achieve this recommendation. The central premise of these pending recommendations is that the cornerstones of management of CKD include: blood pressure management, interruption of the renin angiotensin system, glucose control, treatment of CVD risk factors, and smoking cessation. There are many existing guidelines that address most of these cardio-renal protective issues in patients with diabetes mellitus, hypertension, and cardiovascular disease.

14) Referral to a nephrologist is recommended in the following situations:

a. acute renal failure

b. eGFR < 30 ml/min/1.73m^2

c. progressive loss of kidney function

d. persistent proteinuria on dipstick, or quantified protein to creatinine ratio (PCR) >100 mg/mmol or urine albumin to creatinine ratio (ACR) of >60mg/mmol. Persistent is defined as present on 2 out of 3 urine samples; this indicates proteinuria of significant degree requiring investigation. (Note: a PCR of 100 mg/mmol corresponds to an approximate 24 hour protein excretion rate of 900-1000 mg)

e. if the practitioner is unable to achieve treatment targets for blood pressure, is unable to maintain the use of ACEi/ ARB or other renal protective or cardiovascular protective strategies, or feels otherwise sufficiently unprepared to manage the CKD patient, the CSN would recommend referral to a nephrologist or internist. Again, this would be dependent on local resources and disease severity, and will not apply to all locations.

References

1) Mendelssohn DC, Barrett BJ, Brownscombe LM et al: Elevated levels of serum creatinine: recommendations for management and referral. CMAJ 161:413-417, 1999.

2) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39:S1-266, 2002.

3) Hostetter T, Gladstone EH, Sica DA: National Kidney Disease Education Program in 2004: a program in evolution. J Clin Hypertens (Greenwich) 6:299-302, 2004.

4) Hostetter TH: Chronic kidney disease predicts cardiovascular disease. N Engl J Med 351:1344-1346, 2004.

5) Levey AS, Beto JA, Coronado BE et al: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 32:853-906, 1998.

6) Parker TF, III, Blantz R, Hostetter T et al: The chronic kidney disease initiative. J Am Soc Nephrol 15:708-716, 2004.

7) Schoolwerth AC, Engelgau MM, Hostetter TH: A public health action plan is needed for chronic kidney disease. Adv Chronic Kidney Dis 12:418-423, 2005.

8) Stevens LA, Levey AS: Clinical implications of estimating equations for glomerular filtration rate. Ann Intern Med 141:959-961, 2004.

9) Stevens LA, Levey AS: Measurement of kidney function. Med Clin North Am 89:457-473, 2005.

10) Stevens LA, Coresh J, Greene T et al: Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med 354:2473-2483, 2006.

11) British Columbia Provincial Renal Agency. Identification, Evaluation and Management of Patients with Chronic Kidney Disease, 2006.

12) Collins AJ, Li S, Gilbertson DT et al: Chronic kidney disease and cardiovascular disease in the Medicare population. Kidney Int SupplS24-S31, 2003.

13) Foley RN, Murray AM, Li S et al: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol 16:489-495, 2005.

14) Go AS, Chertow GM, Fan D et al: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296-1305, 2004.

15) Keith DS, Nichols GA, Gullion CM et al: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164:659-663, 2004.

16) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43:S1-290, 2004.

17) K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 45:S1-153, 2005.

18) CARI (Caring for Australian's with Renal Impairment) Guidelines, 2006.

19) Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral of Adults, 2005.

20) Levey AS, Eckardt KU, Tsukamoto Y et al: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 67:2089-2100, 2005.

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Appendix 2: Websites of Interest

1) The Canadian Society of Nephrology

http://www.csnscn.ca

2) The National Kidney Foundation

http://www.kidney.org/

3) Caring For Australians with Renal Impairment

http://www.cari.org.au/index.php

4) The UK Renal Association

http://www.renal.org/

5) Kidney Disease Improving Global Outcomes

http://www.kdigo.org/

6) The Kidney Foundation of Canada

http://www.kidney.ca/

7) The Canadian Diabetes Association

http://www.diabetes.ca/

8) The Canadian Hypertension Society/ Canadian Hypertension Education Program

http://www.hypertension.ca/

Appendix 3: Quick Tips on Referral and Management of Chronic Kidney Disease

Most patients with non-progressive CKD can be managed without referral to a nephrologist. The goals of therapy are listed below:

1) **Consider reversible factors**, such as medications, intercurrent illness, volume depletion, or obstruction. An abdominal ultrasound may be indicated when eGFR <60 ml/min/1.73m^2.

2) **Minimize further kidney injury** by avoiding, if possible, nephrotoxins such as NSAID's, aminoglycoside antibiotics, IV contrast, etc (if eGFR < 60 ml/min/1.73m^2).

3) **Remember to adjust dosages of renally excreted medications.**

4) **Implement measures to slow the rate of progression of CKD:**
   a. Target BP is < 130/80 mmHg. Most patients will need 3 or more medications. Diuretics and salt restriction are very useful, and if needed, consider furosemide BID dosing when eGFR < 30 ml/min/1.73m^2
   b. Target urine protein/creatinine ratio (mg/mmol) is < 60 (< ~ 500 mg/day) or target urine albumin/creatinine ratio (mg/mmol) is < 40. ACEI and/or ARB are first line therapies in patients with albuminuria or proteinuria.
   c. Control blood sugar in diabetes, target HbA1C < 7%.

5) **Implement measures to modify CV risk factors (NB: CV risk >> ESRD risk).**
   Follow the Canadian Hypertension Education Program, the Canadian Diabetes Association, and the Canadian Cardiovascular Society guidelines as per groups at highest risk for CV disease.

6) **Referral to a nephrologist is recommended for**:
   a. acute kidney failure
   b. eGFR < 30 ml/min/1.73m^2. (CKD stage 4 and 5)
   c. progressive decline of eGFR
   d. urine protein/creatinine ratio (PCR) > 100 mg/mmol (~900 mg/24 hours) or urine albumin to creatinine ratio (ACR) > 60 mg/mmol (~500 mg/24 hr)
   e. inability to achieve treatment targets

NOTE: detailed CSN CKD management guidelines are under development, these quick tips should be considered as an interim approach.