

# Elevated levels of serum creatinine: recommendations for management and referral

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## Abstract

**Background:** The potential benefits of earlier referral to a nephrologist of patients with elevated levels of serum creatinine include identifying and treating reversible causes of renal failure, slowing the rate of decline associated with progressive renal insufficiency, managing the coexisting conditions associated with chronic renal failure and facilitating efficient entry into dialysis programs for all patients who might benefit.

**Methods:** A subcommittee of the Canadian Society of Nephrology, which included representatives from family practice and internal medicine, conducted a MEDLINE search for the period 1966 to 1998 using the key words referral and consultation, dialysis, hemodialysis, peritoneal dialysis, renal replacement therapy and kidney diseases. Where published evidence was lacking, conclusions were reached by consensus.

**Guidelines:** Earlier referral to nephrologists of patients with elevated creatinine levels is expected to lead to better health care outcomes and lower costs for both the patients and the health care system. All patients with newly discovered renal insufficiency (as evidenced by serum creatinine elevated to a level above the upper limit of the normal range of that laboratory, adjusted for age and height in children) must undergo investigations to determine the potential reversibility of disease, to evaluate the prognosis and to optimize planning of care. All patients with an established, progressive increase in serum creatinine level should be followed with a nephrologist. Adequate preparation for dialysis or transplantation (or both) requires at least 12 months of relatively frequent contact with a renal care team. Nephrologists should provide consultation in a timely manner for any patient with an elevated serum creatinine level. In addition, they should provide advice about what aspects of the condition require particularly urgent or emergency assessment.

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The virtual epidemic in Canada of end-stage renal disease (ESRD), which is increasing in prevalence by approximately 10% annually,<sup>1,2</sup> has made it difficult for Canadian provincial governments to provide adequate resources to meet growing needs for treatment.<sup>3-5</sup> The Canadian Society of Nephrology recently endorsed a policy document entitled *Principles of End Stage Renal Disease Care*,<sup>6</sup> a document that raised concern about inappropriate rationing of ESRD therapy in Canada. Its authors argued for facilitation of early referral to dialysis centres, as well as pre-dialysis education and efficient entry into ESRD treatment programs for those who choose to undergo dialysis or kidney transplantation. A similar philosophy is increasingly being adopted in other jurisdictions. For example, the US National Institutes of

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## Education

## Éducation

The authors constituted the Referral Guideline Subcommittee of the Canadian Society of Nephrology's Professional and Public Policy Committee. Dr. Mendelssohn (chair) is with the Canadian Society of Nephrology — Ontario and St. Michael's Hospital, University of Toronto, Toronto, Ont.; Dr. Barrett is with the Canadian Society of Nephrology — Newfoundland and the General Hospital, Memorial University of Newfoundland, St. John's, Nfld.; Dr. Brownscombe is with the London Health Sciences Centre, University of Western Ontario, London, Ont.; Dr. Ethier is with the Canadian Society of Nephrology — Quebec and the Hotel-Dieu Hospital, Montreal, Que.; Dr. Greenberg is a family physician with The Medicine Group, Toronto, Ont.; Dr. Kanani is with the College of Family Physicians of Canada, Toronto, Ont.; Dr. Levin is with the Canadian Society of Nephrology — British Columbia and St. Paul's Hospital, University of British Columbia, Vancouver, BC; and Dr. Toffelmire is with the Canadian Society of Nephrology — Ontario and Kingston General Hospital, Queen's University, Kingston, Ont.

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Health consensus conference on morbidity and mortality associated with dialysis<sup>7</sup> stated that an important goal of appropriate care is early referral to a multidisciplinary renal team. In this way, interventions may be initiated that will allow for the timely, elective creation of access for dialysis (such as an arteriovenous fistula or graft or insertion of a catheter for peritoneal dialysis), to prevent the need for urgent commencement of dialysis and the associated prolonged stay in hospital. Because all of this pre-dialysis care can be accomplished on an outpatient or day-surgery basis, the savings to the health care system may be substantial.

The potential benefits of early referral to a nephrologist include identifying and treating reversible causes of renal failure, slowing the rate of decline associated with progressive renal insufficiency and managing the multiple coexisting conditions associated with chronic renal failure. In addition, with their knowledge of the expanded acceptance criteria for modern renal replacement therapy and an understanding of the tasks and time required to prepare a patient for ESRD therapy, nephrologists are uniquely placed to facilitate efficient entry into dialysis programs of all patients who might benefit.

## Methods

A referral subcommittee, including a general internist and 2 family physicians, of the Canadian Society of Nephrology's Professional and Public Policy Committee was created in 1996. A MEDLINE search was performed for the period 1966 to 1998 with the key words referral and consultation, dialysis, hemodialysis, peritoneal dialysis, renal replacement therapy and kidney diseases. The search identified 112 articles. English-language articles and those judged to be related to referral criteria were chosen for further scrutiny. Additional relevant articles were identified from the reference lists of the identified articles or were suggested by the subcommittee members.

There is no framework for grading evidence related to referral. Most of the evidence was found in retrospective case-control studies of lower quality than would be ideal. Where good evidence was lacking, issues were resolved by consensus.

## Guidelines

### Earlier referral

Earlier referral to nephrologists of patients with elevated serum creatinine levels is expected to lead to better health care outcomes and lower costs for both the patient and the health care system.

There is evidence that late referral is a problem in Canada. For example, family physicians in Ontario were asked about their referral practices for patients with various levels of serum creatinine.<sup>8</sup> Most (84.3%) of the physicians indicated that they would not refer patients with creatinine levels of 120 to 150  $\mu\text{mol/L}$  (which represents a loss of filtration function of more than 50%). A smaller but still substantial proportion (27.8%) indicated that they would not refer patients with creatinine levels between 151 and 300  $\mu\text{mol/L}$ . Only for creatinine levels above 301  $\mu\text{mol/L}$  did almost all of the physicians

indicate that they would make a referral. These findings suggest that many patients with potentially serious yet possibly reversible renal disease are not referred until substantial irreversible scarring has occurred. The problem of late referral has also been documented in England,<sup>9-11</sup> Scotland,<sup>12</sup> France,<sup>13</sup> the United States,<sup>14</sup> and Brazil.<sup>15</sup>

Several reports have documented the health effects of late referral,<sup>9-14,16</sup> and this topic has been the subject of 3 recent reviews.<sup>9,17,18</sup> In addition, several retrospective analyses have compared earlier with later referral. Patients referred shortly before dialysis was needed had higher rates of major complications,<sup>11</sup> longer and more frequent stays in hospital,<sup>11,13,14</sup> worse values for homeostatic indicators at the start of dialysis,<sup>13</sup> suboptimal vascular access<sup>13</sup> and worse survival than patients referred early.<sup>10,11,14</sup> The only prospective study to date, from a Brazilian setting, also showed worse survival in patients referred less than 1 month before initiation of dialysis than in those referred earlier.<sup>15</sup>

Three prospective studies have examined multidisciplinary, intensive interventions applied to patients who were referred early. These studies have demonstrated better vocational outcomes,<sup>19</sup> delays in the onset of ESRD,<sup>20</sup> better values for homeostatic indicators, less use of temporary devices for vascular access and lower consumption of hospital resources<sup>21</sup> in these patients.

Non-referral for dialysis is also a problem in Canada.<sup>8</sup> The reported incidence of ESRD in Canada (which counts only patients treated with renal replacement therapy, not those who presumably die of untreated renal failure) is less than half that reported for the United States (104.1 per million in 1996<sup>1</sup> and 262 per million in 1995<sup>22</sup> respectively). Some of this difference may be related to non-referral of patients who might benefit from treatment.

The survey of Ontario family physicians and community internists<sup>8</sup> showed that some patients with ESRD were not referred to a nephrologist and that non-referral was influenced by age and coexisting disease. For example, an otherwise healthy 85-year-old person with renal failure would have been referred for dialysis by only 65.9% of the physicians surveyed. Even more disturbing was the finding that an 85-year-old person with diabetes would have been referred by only 44.1% of the respondents. Finally, most of the physicians (62.4%) thought that dialysis was being rationed in Ontario at the time of the survey (1994; there was no rationing at that time), and even more (90.5%) predicted that rationing would occur in the future. Therefore, at least part of the reason for the difference in reported incidence of ESRD between Canada and the United States is non-referral of Canadian patients who could benefit from dialysis.

Non-referral for dialysis has also been reported in England,<sup>23</sup> Scotland<sup>12</sup> and Brazil.<sup>12,23,24</sup> Age and comorbidity are associated with both late referral<sup>12</sup> and non-referral.<sup>8,23,24</sup>

In summary, it appears that earlier referral has the potential to lead to an improvement in coexisting diseases that begin in the pre-dialysis stage (e.g., left ventricular hypertrophy and renal osteodystrophy), a delay in the onset of



ESRD, better patient survival, less use of temporary devices for vascular access, greater use of native arteriovenous fistulae (rather than synthetic grafts), an optimized biochemical, physical and psychological state on initiation of dialysis, better vocational outcomes and reduced health care costs.

### Investigation of renal insufficiency

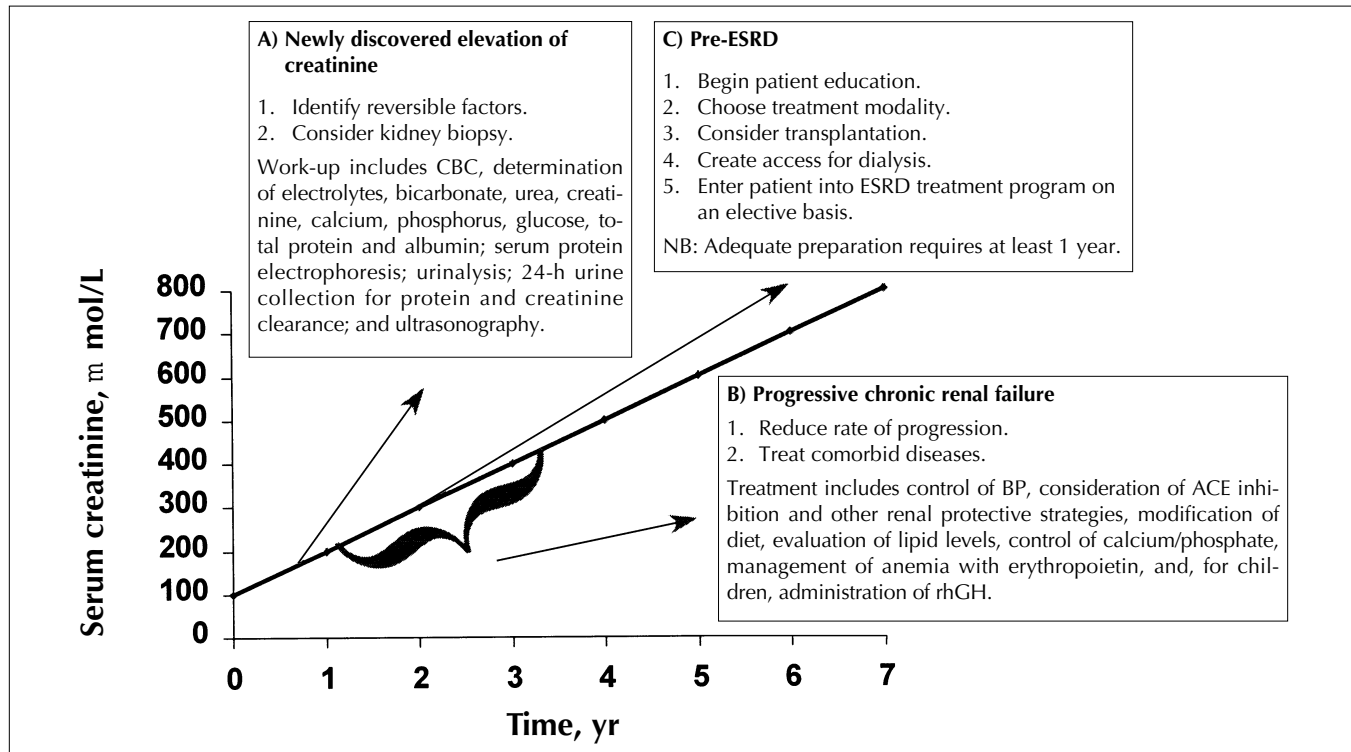
All patients with newly discovered renal insufficiency (as evidenced by serum creatinine elevated to a level above the upper limit of the normal range in that laboratory, adjusted for age and height in children), must undergo investigations to determine the potential reversibility of disease, to evaluate the prognosis and to optimize planning of care.

Most patients with even mildly elevated serum creatinine levels have lost about 50% of their renal filtration function and already have mild to moderate renal insufficiency. These patients must usually undergo a variety of investigations (Fig. 1, scenario A) to determine if reversible factors can be identified. For example, obstruction of the urinary tract is easy to diagnose with ultrasonography and is often amenable to urological intervention. In addition, many inflammatory renal diseases can be treated with immunotherapy if diagnosed before irreversible scarring occurs. A kidney biopsy is often required to establish the diagnosis and to guide therapeutic decisions.

Many kidney diseases progress inexorably toward ESRD, through immune-mediated injury or through many non-immune-mediated pathways that ultimately lead to chronic fibrosis. Accurate and timely diagnosis and treatment can favourably alter the natural history of many of these diseases.

Elevated levels of serum creatinine are often identified during investigation of other disorders in adult patients with hypertension, atherosclerotic disease, diabetes mellitus or unexplained anemia, in adults with known renal insufficiency, in adults with abnormal findings on urinalysis, and in infants and children who fail to thrive, feed poorly, or have recurrent vomiting, polyuria or episodes of dehydration. The upper limits of normal for serum creatinine are considerably lower in infants and children than in adults. The normal range of serum creatinine for children less than 5 years of age is 26 to 45  $\mu\text{mol/L}$ , and this normal range gradually increases from age 5 to adulthood.

Elevation of serum creatinine is not a normal feature of ageing, nor is advanced age a contraindication to referral. Patients with rapidly increasing serum creatinine (e.g., a 20% increase over a matter of days, weeks or months) must undergo investigations (usually including kidney biopsy) on an urgent basis and should be referred promptly to a nephrologist. For this reason, for any newly discovered increase in serum creatinine, the test must be repeated to determine if the creatinine level is stable or rising. If it is rising, the



**Fig. 1: Approaches to diagnosis and treatment of patients with elevated levels of serum creatinine, at 3 stages of disease: newly discovered elevation of creatinine level (A), progressive chronic renal failure (B) and just before end-stage renal disease (C). The creatinine values and time course are hypothetical and are intended for illustrative purposes only. The thresholds for referral are lower for children than for adults. CBC = complete blood count, BP = blood pressure, ACE = angiotensin-converting enzyme, rhGH = recombinant human growth hormone, ESRD = end-stage renal disease.**



nephrologist should be alerted to the fact that the referral is urgent (not elective) and should agree to see the patient soon. One possible exception to these guidelines is that patients with known stable, mild renal insufficiency, documented by serial determination of creatinine level over a period of a few years (especially if dipstick testing shows no hematuria or proteinuria), may be followed carefully, with particular attention to serial monitoring of blood pressure, protein excretion rate and kidney function, without referral to a nephrologist.

All children with elevated levels of serum creatinine should be assessed by a pediatric nephrologist because of special problems related to growth, nutrition, and bone and metabolic disorders seen in children with even mild renal insufficiency. Concurrent care by the primary care physician and pediatric nephrologist can then be arranged.

### **Follow-up by the nephrologist**

All patients with an established, progressive increase in serum creatinine level should be followed with a nephrologist.

In chronic renal insufficiency, management of the concomitant pathophysiological processes that can occur requires attention to many details (Fig. 1, scenario B). Even if specific therapy for the renal disease is not available, there are many nonspecific therapies that may slow the rate of progression to ESRD or affect the natural history of the various conditions associated with progressive kidney disease, such as left ventricular hypertrophy, accelerated atherosclerosis, malnutrition, renal osteodystrophy and, in children, growth retardation. Therapeutic possibilities include control of blood pressure, consideration of angiotensin-converting enzyme inhibition and other renal protective strategies, modification of diet, evaluation of lipid levels, control of calcium phosphate, management of anemia with erythropoietin and, for children, administration of recombinant human growth hormone. A recent review provides more information about these therapies.<sup>25</sup>

A recent British study showed that management of diabetic patients before referral to a nephrologist was not ideal, given that such patients were not likely to be receiving angiotensin-converting enzyme inhibitor therapy,<sup>26</sup> a strategy of proven benefit in diabetic kidney disease.<sup>27</sup> Ifudu and colleagues<sup>28</sup> showed, in a prospectively evaluated inner-city cohort, that care prior to ESRD provided by a nephrologist was superior to both care provided by a non-nephrologist physician and no medical care at all. Optimal health outcomes are more likely if a nephrologist is involved in caring for these patients from the time creatinine elevation is discovered.

### **Preparation for dialysis and transplantation**

Adequate preparation for dialysis or transplantation (or both) requires at least 12 months of relatively frequent contact with a renal care team.

Any patient who is being followed concurrently by a nephrologist and the primary care physician, as outlined above, will be automatically offered the option of undergoing dialysis; if this type of therapy is desired, the patient will be prepared for dialysis as a matter of course. However, patients with known chronic, progressive renal insufficiency who are not being followed by a nephrologist and patients with newly diagnosed moderate or severe renal failure must be referred promptly. At best, a full year of relatively frequent visits are necessary to provide adequate education about dialysis, to help the patient choose the most suitable ESRD treatment modality, to plan elective creation of the dialysis access and to facilitate efficient entry into the dialysis program for those who choose this life-sustaining therapy (Fig. 1, scenario C). For some patients, kidney donation from a living relative or nonrelated person can be considered; if carefully planned, this procedure may preempt the need for dialysis. Peer counselling of potential new patients by those already receiving treatment for ESRD can be helpful in many cases. To accomplish these goals, referral should occur, at the latest, when the serum creatinine level is 300  $\mu\text{mol/L}$  or higher or when creatinine clearance is less than 30 mL/min (0.5 mL/s), whichever situation is worse, and sooner if the creatinine level is increasing rapidly.

For children, referral should occur at much lower creatinine levels. A serum creatinine level of 150  $\mu\text{mol/L}$  in a 6- to 10-year-old child often reflects a glomerular filtration rate as low as 30 mL  $\cdot$  min<sup>-1</sup>  $\cdot$  1.73 m<sup>-2</sup>. For younger children, a level of 100  $\mu\text{mol/L}$  may signify loss of at least 70% of filtration function. Growth failure has been documented in children with glomerular filtration rates below 70 mL  $\cdot$  min<sup>-1</sup>  $\cdot$  1.73 m<sup>-2</sup>. This situation can be improved in certain renal disorders by sodium chloride supplementation, correction of acidosis, nutritional supplements and treatment with recombinant human growth hormone.

It is important for primary care physicians to understand the acceptance criteria for modern dialysis so that they can refer patients appropriately. Most elderly patients undergoing dialysis perceive their quality of life to be good, and their life expectancy is often reasonable.<sup>29-33</sup> There are no longer any technical reasons why a competent, informed patient who might benefit from dialysis should not be referred for this treatment. Certainly an experienced multidisciplinary pre-dialysis team, including physicians, nurses and social workers, can most accurately portray the prognosis and expectations for quality of life, so that truly informed decisions can be made.

No Canadian provincial ministry of health has ever called for rationing of ESRD therapy. Ontario, Quebec and British Columbia have publicly affirmed the importance of access to ESRD therapy.<sup>4,34,35</sup> Notwithstanding these claims, availability of dialysis in Canada has not always kept up with demonstrated need,<sup>3</sup> a situation that has created difficulties in fulfilling the standard of accessibility. However, perceived resource constraints must not be used by physicians to justify refusal to refer suitable candidates for dialysis.



## Timely consultation

Nephrologists should provide consultation in a timely manner for any patient with an elevated serum creatinine level. In addition, they should provide advice about what aspects of the condition require particularly urgent or emergency assessment.

There are 332 practising nephrologists in Canada, providing 201 full-time equivalents of clinical service.<sup>36</sup> A large portion of their collective time involves caring for dialysis and transplant patients. Most of these specialists practise in cities. For these reasons, elective appointments may be scheduled several months from the time of the initial request.

This delay in scheduling an elective appointment for a patient with elevated creatinine level may create problems for the referring physician. First, the delay may unintentionally (and incorrectly) signal that the problem is not serious. Second, without specific instructions, the referring physician may not appreciate the definite indications that would warrant a request for urgent or emergency consultation. For example, urgent consultation is needed if the creatinine level is rising or if a creatinine level above 300  $\mu\text{mol/L}$  has been newly discovered. Emergency consultation might be warranted if, in addition to these criteria, the patient has systemic symptoms or severe homeostatic derangements such as overload of extracellular fluid volume, acidosis or hyperkalemia.

If an appointment cannot be given promptly, the nephrologist should communicate with the referring physician, setting out clearly the indicators that might create cause for alarm and dictate the need for an early assessment.

Application of these guidelines in rural settings may be a challenge. It is recommended that rural physicians establish a link with a nephrologist, who might perform a preliminary chart review to determine if or when a patient with elevated creatinine level should travel for a formal consultation and to give interim advice. However, it must be stressed that many rural patients can be treated by satellite- or home-based hemodialysis or by home-based peritoneal dialysis. Indeed, it may be possible for the nephrologist to work with the rural patient and the primary care physician to prepare the patient for dialysis while minimizing travel and disruption to the patient's lifestyle. Distance from a nephrologist or dialysis centre is not a sufficient reason for non-referral.

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