



# End-Stage Renal Disease: Arresting the Epidemic

With the number of patients with end-stage renal disease increasing, renal and dialysis programs must begin promoting renal health and disease prevention to encourage early referral for nephrology care.

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**T**he number of patients with end-stage renal disease (ESRD), as defined by those receiving renal replacement therapy (RRT), continues to increase — both nationally and internationally. Renal replacement therapy is either renal transplant or chronic dialysis, peritoneal or hemo. In 1999, there were 23,601 patients receiving RRT with

13,922 on chronic dialysis in Canada.<sup>1</sup> This has increased by almost 100% over the last decade, rising from 413 per million population in 1989 to 774 per million population in 1999. The incidence has increased by 100% over this same time frame from 77 new patients per million in 1989 to 143 per million in 1999. The prevalence of dialysis has increased by 150% from 207 per million in 1989 to 456 per million population in 1999, while transplant has only increased by 50% over this time period.<sup>1</sup> In Manitoba, which has had the highest prevalence of ESRD in Canada over the last decade, each new dialysis patient cost the Manitoba Provincial Dialysis Program between \$25,000 and \$60,000 per annum, depending on the treatment modality and site. This does not include hospitalization costs and physician fees. This problem is not unique to

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Canada. In fact, the prevalence is lower in Canada than in the U.S. The major cause of ESRD worldwide, including Canada, is a complication of Type 2 diabetes mellitus. By 2005, the number of ESRD patients in Canada is projected to be twice what it was in 1996.<sup>2</sup>

Planning the future of nephrology cannot involve simply building dialysis units to accommodate the anticipated growth. Strategies must be developed to prevent the progression of chronic renal disease through various stages to ESRD. As many as 50% of

patients undergoing initial dialysis are dialyzed under urgent circumstances.<sup>3</sup> This not only prevents appropriate preparation for renal replacement therapy, but negates any opportunity to have either prevented progressive renal failure, or, at least, attenuated the rate of decline. All renal or dialysis programs must begin to develop renal health promotion and disease prevention clinics that encourage early referral for nephrology care.

### Summary

## End-Stage Renal Disease: Arresting the Epidemic

**There are four stages of renal disease. They are as follows:**

**Stage A:** The point at which glomerular filtration rate (GFR) or creatinine clearance (CrCl) is normal, but the patient is identified as high risk for renal disease progression. The therapeutic focus is prevention of declining renal function.

**Stage B:** GFR has begun to decline but is still  $> 30$  ml/min/1.73 m<sup>2</sup>. Patients are generally asymptomatic and clinically and serologically normal, except for elevated blood urea and creatinine. Therapy involves strategies to attenuate the rate of decline in GFR.

**Stage C:** GFR  $< 30$ , but  $> 10$  ml/min/1.73 m<sup>2</sup>. Complications of chronic renal failure, such as anemia and renal osteodystrophy become more apparent. The therapeutic focus at this stage is the management of the multisystem complications of chronic renal failure and preparation for renal replacement therapy.

**Stage D:** End-stage Renal Disease (ESRD). Renal replacement therapy should commence and be maintained at this stage. Such therapy ranges from a pre-emptive living-donor transplant (*i.e.*, planned transplant before commencing dialysis) to peritoneal dialysis or hemodialysis.

Table 1

## Stages of Progressive Chronic Renal Disease

Stage		CrCl (ml/min/1.73 m <sup>2</sup> )	Therapeutic focus
A	Chronic renal disease	$> 80$	Specific disease remitting therapy
B	Chronic renal insufficiency	30 to 80	Anti-progression therapy
C	Chronic renal failure	10 to 30	Chronic complications & preparation for RRT
D	End-stage renal disease	$< 10$	RRT (Renal Replacement Therapy)

## Definitions

Under the auspices of its Provincial Dialysis Program, Manitoba is developing a chronic renal disease prevention initiative, called a Renal Health Outreach. One of the problems is the lack of universally accepted terminology to describe the various stages of renal disease preceding ESRD. A recent review cited 23 terms used by nephrologists to describe the various stages of progressive renal disease.<sup>4</sup> While ESRD (the point where renal replacement therapy is required) is the only universally accepted definition used consistently by nephrologists around the world, other terms, such as chronic renal disease, chronic renal failure, chronic renal insufficiency, *etc.* have merely created confusion.

## Defining The Stages of Chronic Renal Disease

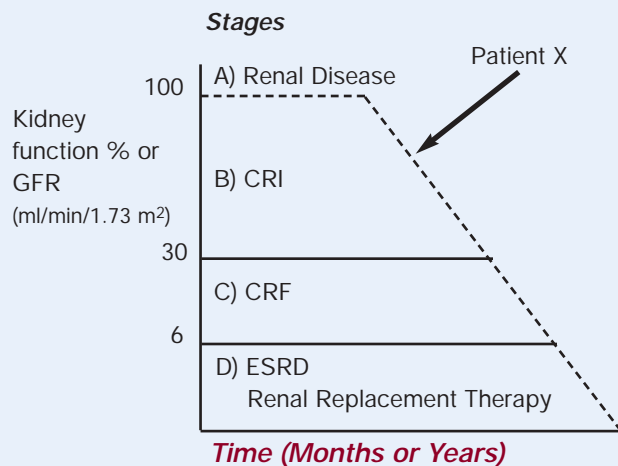
The importance of the identifying and defining stages of renal disease relates to the change in the therapeutic focus at each stage. If we simply ignore specific terms and ascribe “stage A through D” (*i.e.*, the ABC’s of chronic renal disease) and accept a certain amount of overlap between the stages, we can focus on therapeutic goals at each stage. The stages may be defined by the following (Table 1):

- *Stage A:* The point at which glomerular filtration rate (GFR) or creatinine clearance (CrCl) is normal, but the patient is identified as high risk for renal disease progression. The therapeutic focus is prevention of declining renal function. It has been suggested that in order to impact the rate of decline, patients must be identified before their serum creatinine reaches 150  $\mu\text{mol/L}$ .
- *Stage B:* GFR has begun to decline but is  $> 30 \text{ ml/min/1.73 m}^2$ . Patients are generally asymptomatic, clinically and serologically normal, except for elevated blood urea and creatinine. The therapeutic focus at this stage involves strategies to attenuate the rate of decline in GFR (anti-progression therapy).
- *Stage C:*  $\text{GFR} < 30$ , but  $> 10 \text{ ml/min/1.73 m}^2$ . Complications of chronic renal failure, such as anemia and renal osteodystrophy, become more apparent. The therapeutic focus at this stage is the management of the multisystem complications of chronic renal failure and preparation for renal replacement therapy. For most patients, it is too late to attenuate the rate of decline in kidney func-

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Figure 1

### Progression of Chronic Renal Disease in Patient X: The ABC's



ESRD = end-stage renal disease; CRI = chronic renal insufficiency; CRF = chronic renal failure

should commence and be maintained at this stage. Such therapy ranges from a pre-emptive living-donor transplant (*i.e.*, planned transplant before commencing dialysis) to peritoneal dialysis or hemodialysis.

### Specific Stages of Chronic Renal Disease

**Stage A.** This includes chronic renal disease patients, who are at risk of developing progressive renal disease or failure. The principle at this stage is early identification of high-risk patients and the introduction of potential disease-remitting therapies, when appropriate. While the most common scenario is the diabetic patient with albuminuria, there are other diseases

tion.

- **Stage D:** ESRD. Renal replacement therapy

that either predictably progress or are at risk of progression. Some of these are amenable to specific

Table 2

### Disease Remitting Strategies in Stage A (Chronic Renal Disease at Risk for Progression)

Type 1 diabetes mellitus with microalbuminuria	Angiotensin II reduction;* target HgA1 < 7%
Type 2 diabetes mellitus with microalbuminuria	Angiotensin II reduction;* target HgA1 < 7%
IgA nephropathy with proteinuria > 2.0g/day	Fish oils +/- steroids
Membranous GN	Cytotoxic drugs <sup>†</sup>
Focal segmental glomerulosclerosis	Prolonged high-dose steroids <sup>†</sup>
Amyloid	Underlying disease or stem cell transplant (AL)
SLE with class IV lupus nephritis	Steroids/cyclophosphamide
Vasculitis	Steroids/cyclophosphamide
Crescentic GN (RPGN)	Steroids/cyclophosphamide <sup>∞</sup>

\* Ace inhibitor or angiotensin receptor blocker

<sup>†</sup> With high risk prognostic factors such as amount of proteinuria, presence of elevated serum creatinine, histologic features, age

<sup>∞</sup>Plus therapeutic plasma exchange in certain conditions

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disease remitting therapy that, if initiated early, can decrease the likelihood of progression to the next stage and beyond (Table 2).

Patients presenting with hematuria or proteinuria, detected asymptotically on a urinalysis or with symptoms leading to their detection, should be evaluated to determine if they are at risk of progressive renal disease. In patients with hematuria who are over 35 years of age, the absence of a red blood cell cast(s) (which is pathognomonic of a proliferative GN) or glomerular range proteinuria necessitates a search for a urologic malignancy. The absence of a malignancy or another obvious cause for hematuria, such as trauma, stones or cystic disease, defaults the cause to a glomerular disease. The next question becomes the type of glomerular disease and the risk of progression. While the differential diagnosis includes lupus and the various vasculitides, in the absence of extrarenal manifestations and abnormal creatinine clearance, the most common cause in adults is IgA nephropathy. The prognostic marker for progression in IgA nephropathy, as it is for all chronic glomerular nephropathies, is the degree of proteinuria.<sup>5</sup> In patients with this diagnosis, not only should aggressive non-specific anti-glomerular disease progression therapy be used, but specific treatment with fish oils or immunosuppressive therapy should be considered.

In patients presenting primarily with proteinuria without significant hematuria, the differential diagnosis includes minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy in addition to diabetes, paraprotein states and amyloid. All but MCD are at risk of progression. Membranous nephropathy and FSGS have variable prognoses and if identified (which requires a renal biopsy) early (*i.e.*, serum creatinine  $< 200 \mu\text{mol/L}$ ), they may be amenable to specific immunosuppressive therapy.

The most common cause of ESRD is diabetic nephropathy, which may be preventable if high-risk patients are identified at an early stage. All patients with Type 1 or 2 diabetes mellitus, with renal disease ranging from incipient nephropathy with microalbuminuria (24 urinary albumin  $> 30 \text{ mg}$ ) to overt nephropathy with macroalbuminuria (24 urinary albumin  $> 300 \text{ mg}$ ) to nephrotic range proteinuria (24 hour protein  $> 3.5 \text{ g}$ ) to renal failure with a serum creatinine  $\leq 225 \mu\text{mol/L}$  should be treated aggressively with angiotensin II reduction. Treatment should involve using either angiotensin-converting enzyme (ACE) inhibitors,<sup>6</sup> or angiotensin receptor blockers (ARB) to reduce proteinuria.<sup>7-9</sup> Treatment of underlying conditions is equally important (*i.e.*,  $\text{HbA}_{1c} < 7\%$ ) for diabetics.

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Table 3

### Anti-Hypertensive Targets

Disease Type	Proteinuria	Target BP
Diabetes mellitus	< 1.0 g/day	< 125/80 mmHg
Diabetes mellitus	> 1.0 g/day	< 125/75 mmHg
Non-diabetic glomerular disease	> 1.0 g/day	< 125/75 mmHg
Non-glomerular disease	< 1.0 g/day	< 125/85 mmHg

Table 4

### Contraindications to Peritoneal Dialysis

- Non-compliance
- Poor hygiene
- Complex intra-abdominal surgery (with adhesions)
- Abdominal wall hernia
- Diverticular disease
- Body size > 100 kg
- Patient refusal

In patients with non-glomerular disease, which may include polycystic kidney disease or other tubulointerstitial disease, there are no specific disease-remitting therapies other than avoiding potential offending toxins that may be implicated in specific cases (*i.e.*, analgesics in analgesic nephropathy).

**Stage B.** This includes patients with declining renal function to a CrCl > 30 ml/min/1.73 m<sup>2</sup>. In patients with various glomerular diseases, specific disease-remitting therapies may still be indicated. At this stage, however, aggressive non-specific anti-progression therapy is of paramount importance. This includes aggressive blood pressure (BP) con-

trol (Table 3). All patients with proteinuria > 1.0 g/day should have a target BP < 125/75 mmHg.<sup>10,11</sup> This may require the use of three to four antihypertensive drugs. Independent of BP, angiotensin II reduction should be used for all patients with proteinuria. Prognosis for most glomerular diseases correlates with the degree of proteinuria. Angiotensin reduction has been shown to reduce proteinuria, usually by 40%, but may induce a complete remission with large doses. It also has been shown to decrease the rate of progression.<sup>12,13</sup> It has been proven beneficial in both Type 1 and Type 2 diabetic patients with renal disease, ranging from microalbuminuria to nephrotic range proteinuria to serum creatinine values of < 225 µmol/L.<sup>6,8,9</sup> First-line therapy remains ACE inhibitors, but recent evidence supports the use of ARBs in patients with Type 2 diabetes.<sup>7-9</sup>

In non-diabetic glomerular disease, ACE inhibitors have been shown to decrease the rate of progression in patients with protein excretion rates > 2.0 g/day.<sup>13</sup> Aggressive hyperlipidemia management also may decrease the rate of progression.<sup>14</sup> The role for dietary protein modification remains controversial. At this stage, avoiding excessive protein is prudent, but rigorous restriction may have minimal benefit. Any dietary modification must involve a renal dietician to prevent protein malnutrition.<sup>10,15</sup>

**Stage C.** Although there is an overlap as one

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evolves from one stage to another, once the patient's CrCl is  $< 30$  ml/min/1.73 m<sup>2</sup>, there is little hope of attenuating the rate of decline. The therapeutic focus changes to managing chronic renal failure complications, and equally important, preparing for renal replacement therapy. Complications that require particular attention include anemia, renal osteodystrophy and bleeding diatheses if active bleeding is involved. Physicians also should pay attention to nutritional status and cardiovascular risk reduction. At this point, blood pressure reduction and lipid management are more for cardiovascular (CV) reduction than attenuation of renal failure.

As patients' hemoglobin declines, other causes of anemia should be pursued, including blood loss, nutritional deficiencies and hemolysis. If none is found and the patient's iron is replete (as determined by an iron saturation  $> 20$  % and serum ferritin  $> 100$  g/L), erythropoietin should be initiated to achieve a hemoglobin of 110 g/L to 120 g/L. Management of osteodystrophy includes dietary phosphate restriction, calcium supplementation, phosphate binding (with calcium salt or sevelamer) and activated vitamin D to increase calcium gut absorption and/or suppress parathyroid hormone.

A multidisciplinary team should become involved when the patient is approximately one year from requiring renal replacement therapy (based upon the known rate of decline, CrCl  $> 15$  ml/min/1.73 m<sup>2</sup>, or serum creatinine of 400  $\mu$ mol/L).<sup>16</sup> The first question to address is whether the patient would benefit from life-sustaining therapy. While there are contraindications to peritoneal dialysis, the only reason not to provide hemodialysis relates to poor quality of life. This becomes a subjective analysis done in consultation with the patient's family and members of the multidisciplinary team. If suitable for renal replacement therapy, the patient is assessed for transplant candidacy. If so, the health-care team should pursue the option of a living-donor transplant, aiming for a pre-emptive transplant prior to the patient receiving any dialysis therapy. If a potential donor is not identified, the patient should be placed on a cadaveric transplant list and worked-up for peritoneal dialysis. If there are no contraindications, plan to insert a peritoneal catheter two to four weeks before the anticipated initiation of dialysis. If peritoneal dialysis is unsuitable, the patient should be referred to vascular surgery to have of a vascular access created. The preferred access is an autologous arteriovenous (AV) fistula should be placed when the CrCl is 15 ml/min/1.73 m<sup>2</sup> to 20 ml/min/1.73 m<sup>2</sup>.<sup>17</sup> If an AV fistula cannot be created, the second choice is a synthetic graft, which, unlike an autologous AV fistula, can be placed too early. It should be

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placed between three to six weeks before anticipated need. In patients in which neither an AV fistula or graft can be created, a tunnelled internal jugular catheter is inserted when dialysis is initiated.

**Stage D.** Unless a pre-emptive living donor transplant is planned, patients should ideally commence dialysis before becoming symptomatically uremic. While there are no absolute criteria, this is generally when CrCl < 6 ml/min/1.73 m<sup>2</sup> or greater if the patient is already symptomatic or malnourished.

**Timing of referral to nephrology.** Patients are often referred late, with up to 50% of patients requiring urgent dialysis. Late referral to nephrology, previously defined as 30 days within dialysis initiation, has shown an increase in morbidity, hospitalizations and health-care costs.<sup>3,16</sup> It is prudent, however, to refer patients with sufficient time to impact upon their progression of chronic renal disease. If we are to have any impact on decreasing the rate of the ESRD epidemic, this is as early as a serum creatinine of 150 µmol/L. The patient should be referred to a nephrologist, unless the cause of the abnormality is confidently known, reversible diseases have been excluded and disease-remitting and/or anti-progression therapies have been maximized, where appropriate. [CME](#)

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