Continued late referral of patients with chronic kidney disease
Causes, consequences, and approaches to improvement

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Received July 6, 2005  
Accepted October 14, 2005

To cite the present paper, use exclusively the following reference:  
Free full text in english on www.masson.fr/revues/pm

Summary

Objectives > Efforts in recent years have aimed at increasing physicians’ awareness of the frequent and harmful consequences of late referral to nephrologists of patients with chronic kidney disease (CKD), shown in repeated concordant studies. We sought to determine whether these efforts have led to improved predialysis care of these patients.

Methods > This study included all 1391 consecutive patients who began maintenance dialysis at Necker Hospital between January 1989 and December 2000. We examined baseline data and outcomes and determined for four three-year periods the percentage of patients who received early specialized care (at least 6 months before onset of dialysis).

Results > Late referral (< 6 months before dialysis) did not change significantly over the four periods, remaining around 30%, even during the most recent period (1998-2000). Clinical condition and laboratory indicators of patients referred early but not those referred late improved in the latest period, compared with the initial period (1989-1991). Overall, prevalence of major cardiovascular events (myocardial or cerebral infarction, peripheral arteriopathy, or heart failure) was more than twice as high in patients who received nephrologic care for less than 6 months and nearly twice as high even in those followed 6-35 months than in patients followed for at least 36 months before beginning dialysis. Subsequent mortality after maintenance dialysis was also significantly higher in patients with late referral than in those follo-
The increasing incidence and very high cost of dialysis as renal replacement treatment for end-stage renal disease (ESRD) are causes for concern. A coordinated treatment strategy with well-established rules can slow the progression of chronic kidney disease (CKD), delay the date by which renal replacement treatment must begin (kidney protection) and prevent or at least limit the cardiovascular (CV) damage associated with uremia (cardioprotection) [1,2]. This treatment cannot, however, be truly effective unless it is implemented early enough, before loss of renal function and CV damage have become irreversible.

Although numerous publications stress the unfavorable consequences of late institution of this treatment, delay in referral of CKD patients to specialists remains frequent, even in European countries where all patients have access to the health care system [3].

Conclusion > Late referral of CKD patients for specialist care remains frequent, around 30%, although it is most often unjustified. Late referral deprives the patient of early implementation of a reno- and cardioprotective therapeutic strategy that reduces cardiovascular comorbidity and mortality. Better coordinated cooperation between family doctors and nephrologists, through the implementation of regional health care networks, now appears as the most effective way to improve the care of CKD patients.

What is already known

• Many patients with CKD are not referred to nephrologists until shortly before ESRD.
• This late referral prevents treatment aimed at slowing kidney disease and maintaining CV health from beginning early enough to be useful.
• It necessitates starting dialysis on an emergency basis, without adequate preparation, and increases short-term mortality.

What this article adds

• Despite efforts to raise awareness about this problem, 30% of patients are still referred late for specialized nephrologic care.
• The CV comorbidity of patients seen late is twice as high as that of patients seen for at least 3 years before beginning dialysis, and their long-term mortality is also twice as high.
• The creation of regional health networks should improve management of kidney disease by inciting closer cooperation between general practitioners and nephrologists.

We sought to determine whether management of CKD has improved in recent years, compared with preceding periods [4,5] and, if not, the causes of late referral, its immediate and long-term consequences, and the best approaches to changing it.

Methods

This study concerned all 1391 adult patients (aged ≥ 15 years) with CKD (869 men, 522 women) living in Île-de-France (the Paris metropolitan region) who started dialysis as renal replacement treatment at Necker Hospital between 1 January 1989 and 31 December 2000. Demographic characteristics as well as clinical data and laboratory indicators at the time dialysis treatment began were recorded for all patients. The time elapsed between the first consultation or hospitalization in our department and the first dialysis was determined for each patient. Late nephrologist referral (LNR) was defined as a delay < 6 months and early referral (ENR) as a delay ≥ 6 months. In all cases of referral to nephrologists, general practitioners and the nephrology team at Necker simultaneously and jointly followed the patient. We determined the outcome for each patient through annual surveys conducted of all dialysis units in Île-de-France through 30 June 2004. Results were expressed as means ± 1 standard deviation. Comparisons between groups used Student’s t test, analysis of variance (ANOVA), the χ² test and Pearson’s test. The influence of the timing of referral on CV comorbidity before dialysis was assessed by logistic regression. Risk factors for mortality during dialysis were analyzed with a Cox model. We used NCSS software (Kaysville, UT, US) for the statistical analysis.

Results

Changes in timing of specialist referral

Overall, of 1391 patients, 971 (69.8%) were referred at least 6 months (6 to 35 months in 345 cases and ≥ 36 months in 626) before dialysis, and 420 others (30.2%) less than 6 months, 315 of them < 1 month before. Table 1 summarizes the changes in referral during the four three-year periods covered the study (1989-1991, 1992-1994, 1995-1997, and 1998-2000). Late referral did not change significantly over the four periods, remaining...
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around 30%, even during the most recent periods. The mean age of patients beginning dialysis rose continuously between period 1 (1989-1991) and period 4 (1998-2000), but there was no significant difference in age according to timing of referral during any period.

Factors associated with late referral

Of the 420 patients in the LNR group, 77 (18.3%) had acute or rapidly progressive kidney disease, with a sudden onset (most often associated with myeloma or a systemic disease), while another 40 remained practically asymptomatic until they reached ESRD. Of the other 303 patients in this group, 151 (36%) had consulted in a specialist department earlier but had stopped either through carelessness (121 cases), or reluctance to accept the dialysis treatment proposed (30 cases): the other 152 (36.2%) had never been referred to a nephrologist. Accordingly, this late referral may have been avoidable in 72% of cases. It was observed more frequently for men than women, and the M/F ratio was higher in the late than in the early referral group (2.26 versus 1.65, p < 0.01). The proportion of patients with low socioeconomic and educational status (notably, immigrant workers) was significantly higher in the LNR group (31.2% versus 10.5%, p < 0.001) and their mean age was significantly lower (50.5 ± 17.2 versus 56.3 ± 17.1 years, p < 0.001). Patients with hereditary renal diseases (such as polycystic kidney or Alport syndrome) and symptomatic interstitial or glomerular nephropathy were referred early more often (75-90% of cases) than patients with hypertension-related nephrosclerosis (65%) or diabetic nephropathy (60%). In particular, nearly half the patients with type II diabetes were referred less than 6 months before ESRD.

Clinical and physical consequences

Comparison of the principal laboratory indicators and blood pressure between period 1 and period 4 shows a significant improvement in the condition of patients in the ENR group, while the condition of patients in the LNR group remained poor (table II). In particular, anemia and hypertension improved markedly in the ENR group, because of increased use of recombinant erythropoietin (EPO) and angiotensin-converting enzyme inhibitors; these indicators did not change significantly among the patients in the LNR group.

Table III summarizes the clinical characteristics of the two groups at the beginning of dialysis. The proportion of patients with ominous clinical symptoms (most often pulmonary edema or severe hypertension) was much higher in the LNR group than in the ENR group (65% versus 13%, p < 0.0001). Among the former, hemodialysis had to begin on an emergency basis (within

### Table I

| Changes over time in referral of patients with chronic kidney disease* |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Late (< 6 months) | Number (%) | 83 (26.2) | 112 (30.9) | 104 (29.1) | 121 (34.3) |
| Age (years) | 50.3 ± 15.7 | 55.9 ± 17.7 | 56.0 ± 17.9 | 54.7 ± 18.1 |
| Early (≥ 6 months) | Number (%) | 234 (73.8) | 251 (69.1) | 254 (70.9) | 232 (65.7) |
| Age (years) | 50.9 ± 16.9 | 55.3 ± 17.3 | 55.6 ± 17.2 | 59.0 ± 17.2** |

* from 1989 through 2000, at Necker Hospital.
** global χ²: p < 0.001

### Table II

| Changes over time in laboratory indicators and blood pressure between the 1989-1991 period and 1998-2000 period according to timing of referral: early (ENR) or late (LNR) |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Creatinine levels (µmol/L) | 708 ± 132 | 540 ± 124 | 920 ± 318 | 822 ± 292 |
| aCcr (mL/min/1.73 m²) | 7.1 ± 1.5 | 8.9 ± 1.1** | 5.8 ± 1.6 | 7.3 ± 4.2 |
| Hb (g/dL) | 8.8 ± 1.4 | 10.3 ± 1.2** | 7.6 ± 1.4 | 8.9 ± 1.7 |
| EPO treatment (%) | 11 | 53 | 3 | 17 |
| Low serum albumin (g/L) | 38.2 ± 0.4 | 38.5 ± 0.5 | 35.1 ± 0.4 | 33.0 ± 0.6 |
| SBP (mmHg) | 147 ± 15 | 143 ± 17 | 173 ± 19 | 169 ± 28 |
| DBP (mmHg) | 84 ± 8 | 77 ± 8* | 99 ± 12 | 93 ± 16 |
| Treatment by ACE inhibitors/ARB (%) | 21 | 64 | 4 | 12 |

1998-2000 period versus 1989-1991: *p < 0.01, **p < 0.001.
aCcr: creatinine clearance estimated from creatinine levels according to Cockcroft-Gault’s formula.

### Table III

| Patients’ clinical characteristics and treatment modalities according to whether referral to nephrologist was early (ENR) or late (LNR) |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| LNR (n = 420) | ESR (n = 971) | p |
| Age (years) | 56.9 ± 17.1 | 56.7 ± 17.1 | NS |
| Major clinical symptoms (%) | 65 | 13 | < 0.0001 |
| Central catheter | 76 | 57 | < 0.0001 |
| Duration of hospitalization (days) | 33 ± 18 | 6 ± 9 | < 0.0001 |
| In-center dialysis (%) | 73.9 | 63.1 | < 0.001 |
| Out-center dialysis (%) | 26.1 | 36.9 | < 0.001 |
| Transplantation (%) | 15 | 37 | < 0.001 |
48 hours of admission for 58%), with a temporary central catheter, in the absence of a functional arteriovenous fistula. Among patients referred for specialist treatment at least 6 months earlier, only 56 patients (5.7%) started dialysis on an emergency basis because of sudden aggravation of their CKD, most often occasioned by a cardiac complication. Duration of hospitalization was considerably longer for LNR than ENR patients. The proportion of patients directed to dialysis outside hemodialysis centers (by hemodialysis at home, self-care units, or peritoneal dialysis) was significantly higher in the ENR group, as was the proportion that ultimately received kidney transplantation.

**Cardiovascular comorbidity and long-term survival**

*Table IV* reports the prevalence of CV comorbidity at the beginning of dialysis as well as mortality rate at 3 months, 1 year and 5 years of dialysis as a function of the timing of specialist referral. The proportion of patients with at least one CV event (CVE+) was significantly higher among patients referred less than 6 months or between 6 and 36 months, than among those referred ≥36 months before starting dialysis.

The mortality rate, both in the short (3 and 12 months) and long (5 years) term, was significantly better among patients referred ≥36 months than among those referred later, including among those referred from 6-35 before starting dialysis. The excess mortality among patients referred less than 6 months before dialysis was especially marked in the short term (3 months and 1 year).

Logistic regression analysis showed that the risk of preexisting CV damage when starting dialysis was nearly twice as high in the LNR group than in the ENR group (odds ratio (OR) 1.83 [95% CI: 1.31-2.56]; p < 0.0001). The prevalence of CV damage in patients followed for at least 36 months before beginning dialysis was slightly less than half that in the reference group of late referrals (OR 0.48 [95% CI: 0.37-0.67]; p < 0.0001), and it was nearly half that of those followed 6-35 months (OR 0.97 [95% CI 0.67-1.38]; p = 0.87).

Multivariate analysis of the Cox proportional hazards model identified 5 independent and significant factors predictive of mortality after starting dialysis (*table V*): age, CV damage, comorbidity cancer, diabetes, and timing of referral. Late specialist referral was associated with an increased risk of 54%.

In a second model assessing the influence of timing from referral to dialysis (referral ≥36 months as the reference group), referral 6-35 months before dialysis was associated with a 27% increase in risk of death, and referral < 6 months before dialysis with an 85% increase. Overall, age-adjusted mortality of patients with diabetes was double that of patients without diabetes (OR 2.04 [95% CI: 1.65-2.53]; p < 0.0001). Nonetheless mortality among those referred at least 36 months before dialysis was almost half that of those referred < 6 months before dialysis (OR 0.97 [95% CI: 0.84-1.14]; p = 0.34). Low socioeconomic status was associated with a mortality risk 28% higher than the reference group in the univariate analysis, but its effect was no longer significant after adjustment for age and referral time in the multivariate model.

**Discussion**

Two principal conclusions emerge from this study. The first is disappointing: despite all the efforts of communication, the proportion of patients referred late to specialist treatment although CKD was already diagnosed has not decreased at all in recent years and remains around 25%. The second is encouraging: the condition of patients referred early for specialist care improved significantly over time. This observation makes it all the more regrettable that patients referred late could not benefit from the recent progress in treatment.

The problem of the persistence of late referral for CKD appears universal, as shown by studies from the United States [6-9], Australia [10], Europe [11-13], and other regions in France [14, 15]. Despite the different definitions of late referral used in these studies (ranging from 1 to 6 months), it is clear that 30-50% of

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**Table IV**

Cardiovascular (CV) comorbidity and short- and long-term survival as a function of the timing of referral before dialysis

<table>
<thead>
<tr>
<th>CV comorbidity (%)</th>
<th>&lt; 6 months (n = 420)</th>
<th>6-35 months (n = 345)</th>
<th>≥36 months (n = 626)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>47.5</td>
<td>42.2</td>
<td>21.4</td>
</tr>
</tbody>
</table>

*Table V*

Independent risk factors for mortality during dialysis identified by analysis with a Cox model

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (by 1 year)</td>
<td>1.04</td>
<td>1.03-1.05</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>History of CV complications</td>
<td>2.04</td>
<td>1.63-2.54</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.31</td>
<td>1.79-2.98</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.56</td>
<td>1.24-1.96</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Late referral (reference)</td>
<td>1.54</td>
<td>1.26-1.85</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Referral ≥36 months</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referral 6-35 months</td>
<td>1.49</td>
<td>1.17-1.89</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Referral &lt; 6 months</td>
<td>1.27</td>
<td>1.01-1.61</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Referral adjusted for age + comorbidity</td>
<td>1.85</td>
<td>1.49-2.29</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

patients are referred to specialists at a stage too late to enable the implementation of an effective strategy to prevent CV and kidney damage. Our study used a cut-off point of 6 months before the beginning of dialysis, as have most recent studies. The unfavorable consequences of late referral are many [4, 16-18]: more precarious clinical condition and more severely abnormal laboratory markers at the beginning of renal replacement treatment; lack of a functional vascular approach and need for a central catheter [4,5,16,19,20]; considerably longer hospitalization [4,5]; smaller proportion of patients treated by modalities other than in-center hemodialysis; higher short-term mortality [7-9,15]; lower proportion of patients receiving kidney transplantation [10]; higher long-term mortality [6-9,11,15,21,22].

Our study confirmed these disadvantages of late referral and showed 2 especially harmful consequences: first, age-adjusted CV comorbidity was twice as high at onset of ESRF; second, long-term mortality was also twice as high. Knowing that CV comorbidity at the beginning of dialysis affects survival of patients on dialysis [23], we can fairly assume that early specialist care can, by optimizing control of the risk factors for accelerated atheroma deposits and left ventricular hypertension [24], help to reduce CV comorbidity and improve survival. The finding that only referral that was sufficiently early, that is, at least 3 years before ESRD, was associated with a significant reduction in CV comorbidity and long-term mortality on dialysis is consistent with this hypothesis. Given the evidence of the harmful consequences of late referral of CKD patients, it is astonishing to find so many patients still referred so late to nephrologists. Difficulty in access to care cannot serve as an explanation in France, unlike other countries where numerous patients lack medical coverage [6,16]. Beyond the inevitable cases (those revealed by acute renal failure, and nephropathies that develop asymptotically), which account for only 5% of the cases encountered here, delay in specialist care appears to be related most often to insufficient information about the positive effects of early treatment protecting the kidney and CV system. It is significant that, in this regard, patients with low economic and/or educational level constitute the group of patients most often referred late; this suggests the need to work especially hard at improving management for disadvantaged or underprivileged populations.

This treatment is complex and should best be directed by a nephrologist, working in collaboration with the general practitioner to define the optimal nutritional and drug treatment for each patient, adjust it according to CKD development, and provide psychological and medical preparation for dialysis at the right time [25]. Patients with progressive CKD account for only a very small fraction of the population, so that general practitioners have few occasions to acquire experience in the diagnosis and treatment of this disease [3,25].

Better structuring of the cooperation between general practitioners and nephrologists appears to be the most effective means of improving management of kidney disease. In this regard, the creation of specific healthcare networks appears to be the most appropriate response to this problem. Now governed by article 84 of Law 2002-303 dated 4 March 2002, healthcare networks have as their objective the promotion of healthcare access and the coordination, continuity and interdisciplinary management of healthcare management, especially for some specific populations, diseases or health activities. This definition applies especially well to CKD management. Nearly 10 networks already exist in France and several others are under construction. Patient groups and continuing medical education providers also aid their extension, supported by public authorities. Accelerating creation of these networks to cover the entire country is desirable, because they constitute the most “user-friendly” association between patients, general practitioners, clinical pathologists, and nephrologists.

Conflicts of interest: none

References


