Nephrol Dial Transplant (1999) 14 [Suppl 6]: 16–23

Nephrology
Dialysis
Transplantation

The pattern of referral of patients with end-stage renal disease to the nephrologist—a European survey

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Abstract Much attention has been paid recently to an early or 'healthy' start of chronic dialysis in patients suffering from end-stage renal disease (ESRD). It is hoped that earlier initiation of dialysis will reduce the increased morbidity and mortality that is observed during the early months in patients who are referred too late to the nephrological unit. This report deals with a survey of the referral pattern of patients with ESRD in 14 European centres. Late referral was defined as those patients presenting to the renal unit within 1 month before chronic dialysis was needed. Between 1993 and 1995, 2236 ESRD patients started dialysis in these 14 centres. A total of 583 patients, representing 26%, were late referrals as defined above. A high variability between the individual centres, even within the same country, was observed. More detailed surveys in both Flemish and European centres revealed that late referrals more frequently started on haemodialysis, had significantly greater co-morbidity and mortality in the first year of dialysis and were transplanted less frequently. It can also be deduced from these results that late referral has important economic consequences, leading to increased costs because of longer initial hospitalization times, the lack of choice for the cheaper form of peritoneal dialysis the lower transplantation rates in the late referrals.

Introduction

According to Nissenson *et al.* [1], five non-medical factors have an impact on the dialysis modality selection in a given country: financial and reimbursement policies, educational deficits in patients, doctor and physician bias, resource availability, social mores and cultural habits. Educational deficits in both patients and doctors were the second most important factors. The poor education of patients and doctors in terms of available dialysis options impact importantly on modality selection [1].

Education of end-stage renal disease (ESRD) patients on these dialysis options should start as early as possible and is, to a certain extent, dependent on the patient referral pattern of the chronic renal failure (CRF) patient by the primary care physician or non-nephrological specialist to the renal dialysis unit.

Figure 1 depicts the hypothetical flow of ESRD patients in need of dialysis as they may present to a renal unit. (i) In the majority of these patients, the progression towards ESRD is slow, and the end-point, i.e. the moment of need of dialysis, is more or less predictable. Some of these patients will be followed by a renal unit and will be taken into a patient education programme. Some of the patients, unknown to the unit, will be referred late, and will often arrive in an emergency and cannot, therefore, be offered the options of the different dialysis techniques. (ii) Some of the patients are presenting as an 'acute on chronic renal failure patient', i.e. the renal function in a patient who is either known or not known to be suffering from CRF suddenly and acutely deteriorates due to a number of supplementary ischaemic or toxic aggressions. These aggressive factors are either not recognized or cannot be corrected, and the patient develops ESRD much more rapidly than could have been predicted.

This group also includes those patients with true acute renal failure (ARF) who do not recover their renal function and remain on dialysis after the acute episode is over. This group is usually not more than 3–4% of all ARF patients, although this type of patient may become more frequent as more and more elderly patients survive admissions to an ICU but do not always recover from their ARF. By definition, these 'acute' patients will be late referrals and will not have been informed accurately of the different dialysis modalities.

According to studies in Sweden [2] and a recent hypothesis using the Danish National Registry Report on Dialysis and Transplantation 1995 [3,4], ~70% of ESRD patients who have the opportunity to receive adequate education on treatment options select peritoneal dialysis (PD). In contrast, if, because of late referral, no education on the different dialysis modalities is possible, the patient is almost always started on haemodialysis (HD) in an emergency. The patient often remains on this form of therapy, because later no option for change in modality is provided.

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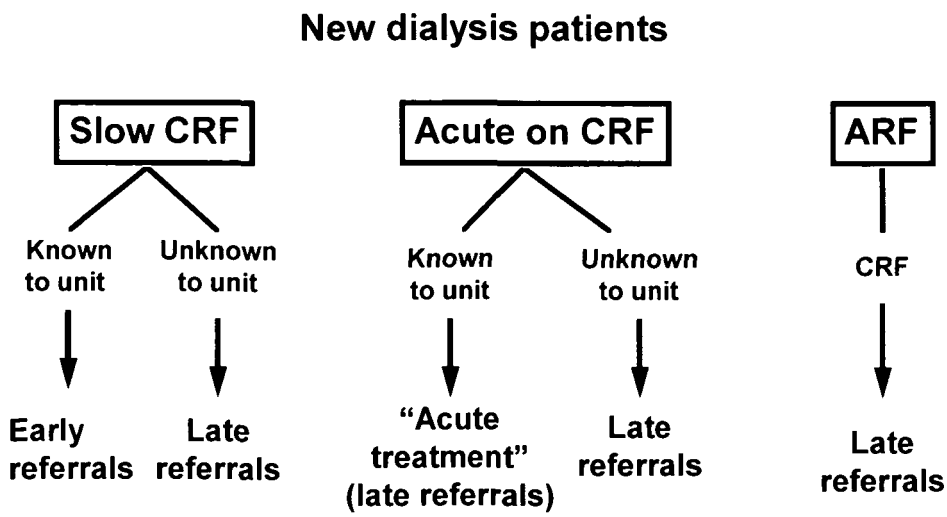

Fig. 1. Flow of ESRD patients and pattern of referral to the renal unit.

Late referral occurs in ~20–50% of ESRD patients [5–8] and, according to an earlier US study [6] and more recent French [7] and Swiss studies [9], an improvement in this referral pattern with time is not observed. The percentage of late referrals remained constant over the years 1983–1988 in the University of Missouri [6] and during the years 1990–1995 at the Necker Hospital in Paris [8]. In a follow-up survey at the University of Missouri [10], an absence of firm guidelines for referral and lack of good communication between primary care providers and nephrologists were recognized as emergent needs

Not only does late referral affect the lack of choice between dialysis modalities but, according to several studies, it also determines to a certain extent the outcome of these patients. Because of the greater morbidity, the initial duration of hospitalization is longer, with important consequences for the cost of therapy. Both earlier [11] and more recent reports [8,12–15] suggest that late referral to a nephrologist might contribute to early deaths on renal replacement therapy (RRT).

In a recent analysis of the impact on patient mortality in late *vs* early referral in São Paulo, the 6-month patient survival was 87% in the early referral and 69% in the late referral group. Despite the fact that in the late referral group the hazard ratio of mortality was 2.77 times that of the early referrals, in a multivariate analysis the time of referral was no longer associated with an increased mortality risk [13]. This early mortality, which was 12% in a large US renal unit, was associated with co-existing diseases and hypoalbuminaemia, but also with presentation with advanced renal failure [14].

Preliminary European survey

Because relatively few data are available on the actual flow of pre-dialysis patients and the referral pattern in most of the countries in Europe, we organized a postal survey of 14 European dialysis centres to gather information on the number of new ESRD patients admitted for dialysis in 1993–1995, the referral pattern of the patients and the selection of the mode of dialysis. Parts of this study have been published [16].

The following renal divisions or units have collaborated in this survey: the Academic Medical Center (Amsterdam), the Rudolf Virchow University Hospital (Berlin), the University Civil Hospital (Brescia), the St Jan Hospital (Bruges), the Brugmann Hospital (Brussels), the University Hospital (Caen), the Civil Hospital (Colmar), the Leicester General Hospital (Leicester), the University Hospital La Paz (Madrid), the Manchester Royal Infirmary (Manchester), the AHEPA Aristotelian University Hospital (Thessaloniki), the St. Bortolo Hospital (Vicenza), the University Hospital (Vienna) and the University Hospital (Gent). These 14 centres were selected because of their long-standing interest and knowledge of the issues involved in ESRD modality selection. Furthermore, the nephrologists responsible in these centres are also known to have no bias towards either PD or HD.

The definitions used in the survey were simple and straightforward. (i) *Early referral* was defined as an ESRD patient known in the renal unit for at least 1 month and to whom the different modes of dialysis could be explained sufficiently. (ii) *Late referral* was defined as a patient who was admitted for dialysis in an emergency and who therefore was not offered sufficient information. In both categories, the number of patients, the dialysis modality and the eventual change of modality after the initial hospitalization period were noted. In the late referral group, one or two HD sessions were sometimes performed in an emergency via a central venous catheter (e.g. over a weekend), followed by a start of PD within 2–3 days of admission. These patients were considered as treated initially by PD.

Table 1 summarizes the number of patients, some of the demographic characteristics, the number of diabetic patients and the distribution of both early and late referrals in these 14 centres. A total of 2236 ESRD patients were taken into dialysis between 1993 and 1995. The mean age was 57.3 years and the male to female ratio was 1.5/1. The percentage of diabetics was 17%. Overall, 1653 early and 583 late referrals, as defined above, were reported. This represents an overall figure of 26% late referrals.

A rather high variability between the individual centres was noted, the late referral patients ranging from as many as 51% in Brussels (Hopital Brugmann) to as few as 14% in Leicester and Berlin. Striking differences in referral patterns between centres in the same country were noted, such as between Leicester and Manchester in the UK and between Vicenza and Brescia in Italy.

Figures 2 and 3 show the distribution of the two dialysis modalities (HD and PD) in the early referral (Figure 2) and late referral (Figure 3) patients. Assuming that these patients have been offered some education about dialysis modalities, again a strikingly high variability in the applied dialysis strategies between centres, even in the same country, is observed. The admittance of these patients to a PD programme varies from as many as 94% in Manchester to as few as 15% in Bruges. Part of this variability can certainly be explained by local circumstances such as a lack of sufficient HD posts in Manchester, for example.

It is remarkable to note the difference in policies in the two French centres: 73% of early referral patients are taken on PD in Colmar and only 29% in Caen.

The interpretation of the results for the late referrals is more problematic since some unexpected data were obtained. Although in the majority of the centres, HD was applied in a greater percentage of these patients, in some centres, such as Thessaloniki, Colmar, Manchester and Gent, patients may be treated at onset in an emergency with 1–3 HD sessions and afterwards be transferred to PD. At least in our unit, if a rapid evaluation of the medical, social and psychological situation in such a patient leads to the conclusion by both the medical and nursing staff and the family that chronic HD is not suitable, such a late referral patient will receive a PD catheter and be started with an in-hospital CAPD programme. Such a decision can be taken within a few days after admission. We considered such late referral patients as initially started on PD.

Changes of modality after the initial start of therapy

After the start of HD in the early referrals, no major changes in treatment modality occurred except for 43 of the Leicester early referral patients who initially had been taken on HD and later changed to PD.

In the late referral group, almost no change of dialysis modality occurred after the start of the dialysis treatment.

Recent European and Flemish survey

The present survey evaluates the impact of late referral of ESRD patients on the choice of dialysis modality, and on the morbidity and mortality of these patients. In view of the large economical impact of ESRD treatment, these aspects of late referral were also evaluated. Duration of initial hospitalization was used as a parameter since hospitalization costs account for >40% of the ESRD treatment budget [17,18]. Since, by definition, a timely start of dialysis is impossible in late referred patients, the consequences of late referral for the concept of an 'early' or 'healthy' start were evaluated.

A retrospective analysis was performed by means of a questionnaire sent to 18 nephrology units in seven European countries. Patients who started RRT between January 1, 1996 and December 31, 1997 were included in this study. Eight nephrological units that are part of a quality surveillance group in Flanders, comprising 331 patients, completed an extended ques-

Table 1. Absolute number of ESRD patients admitted between 1993 and 1995

	Total	Mean age	M/F	Non-diabetic	Diabetic	Early referrals	Late referrals
Gent	122	58.2	64/58	97	25	91	31
Manchester	238	–	142/96	205	33	148	90
Amsterdam	94	57.1	55/39	80	14	75	19
Colmar	129	58.9	79/50	103	26	86	43
Leicester	457	56.7	294/163	371	86	392	65
Berlin	119	–	69/50	91	28	102	17
Madrid	160	–	77/83	128	32	136	24
Thessaloniki	93	60.26	57/36	67	26	58	35
Caen	111	59.4	72/39	97	14	85	26
Brugge	93	57.87	53/40	69	24	75	18
Brescia	153	61	98/55	123	30	137	16
Brussels	98	55.33	65/33	82	16	48	50
Vicenza	113	55.17	75/38	89	24	76	37
Vienna	256	55	144/142	–	–	144	112
Total	2236	57.72	1344/892	1602	378	1653	583

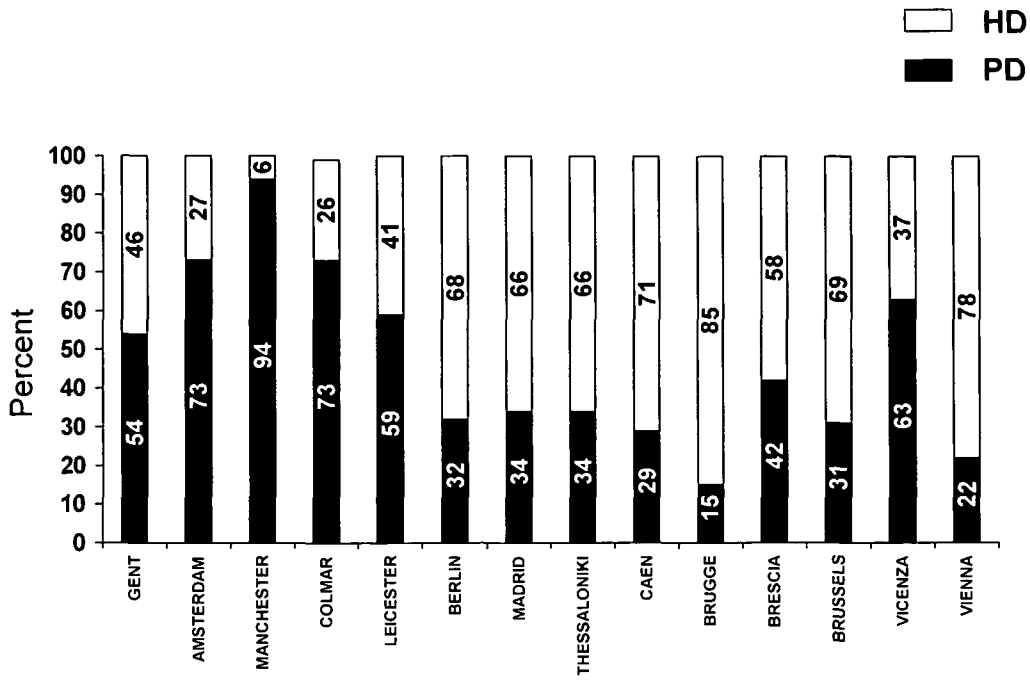

Fig. 2. Distribution of the dialysis modalities in the early referral patients.

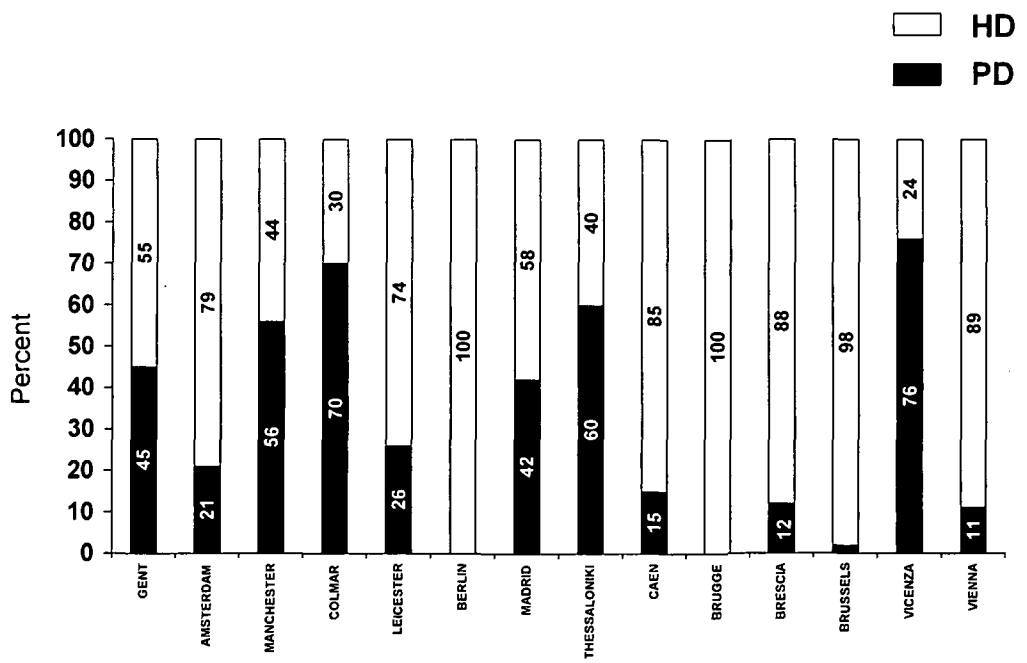

Fig. 3. Distribution of the dialysis modalities in the late referral patients.

tionnaire, while 10 other European centres, comprising 450 patients, completed a limited version of the questionnaire. All the participating centres provide both HD and PD.

The variables and the results of the limited and extended questionnaires are given in Tables 2 and 3, respectively. In the extended questionnaire, the specialty of the referring physician (general internal medicine, general practitioner, endocrinologist, cardiologist, urologist, etc.) and the status of the patient 1 year after the start of RRT (death, transplanted, still on dialysis or recovery of renal function) were registered.

As shown in Table 2, of a total of 781 patients, 65% were early and 35% were late referrals. There was a slight predominance of males (57% *vs* 43%). About one in three patients in the total group was started on

Table 2. Results of the European survey

	Total group ($n=781$)	Late referral ($n=271$)	Early referral ($n=510$)	P-value
M/F	57%/43%	57%/43%	57%/43%	0.97
PD/HD	33%/67%	23%/77%	49%/51%	<0.001
Creatinine first (ml/min)	21.7±22.3	6.9±8.8	28.1±23.4	<0.001
Residual creatinine (ml/min)	7.4±4.2	7.1±4.6	7.6±3.9	0.18
Hospitalization at start of RRT (days)	19.3±19.8	27.8±23.7	15.1±16.0	<0.001
Age (years)	61.1±15.7	62.1±16.3	60.5±15.5	0.2
No. of antihypertensive drugs	1.5±1.0	1.4±1.1	1.5±1.0	0.4
Diastolic RR (mmHg)	83.3±16.1	85.2±19.5	82.4±14.4	0.13
Pulmonary oedema (Y/N)	21%/79%	31%/69%	17%/83%	0.003
Uraemic symptoms (Y/N)	71%/29%	83%/17%	66%/34%	0.001

Table 3. Results of the extended survey in Flemish renal units

	Total group $n=331$	Late referral	Early referral	P-value
Diabetes mellitus	32.1%	30.1%	26.5%	0.5
Haematocrit at start of RRT (%)	29.7±5.9	29.5±6.0	30.1%±5.6%	0.4
Intact parathyroid hormone level at start of RRT (pg/ml)	285.1±311.5	314.7±397.5	270.1±3.9	0.4
Bicarbonate levels at start of RRT (mEq/l)	19.9±4.2	19.5±4.7	20.2±3.9	0.2
Serum albumin (g/dl)	3.8±0.6	3.4±0.4	3.8±0.6	0.1
Status of the patients 1 year after start of RRT				
Death		26.7	16.4	0.07
Transplanted		4.7	17.5	0.02
Still on dialysis		67.2	65.2	0.5
Recovery of renal function		1.4	0.9	0.4

PD. Late referral patients started relatively more frequently on HD than early referral patients (77% *vs* 51%, $P<0.001$).

The creatinine clearance at first visit to the renal unit was greater in the early compared with the late referred patients (28.1±23.4 *vs* 6.9±8.8 ml/min, $P<0.001$); in contrast, the creatinine clearance at the start of RRT was not different (7.6±3.9 *vs* 7.1±4.6 ml/min, $P=0.18$) between both groups. The number of hospitalization days at the start of RRT was significantly less in the early compared with the late referral patients (15.1±16.0 *vs* 27.8±23.7 days, $P<0.001$). There were no differences in age (60.5±15.5 *vs* 62.1±16.3 years, $P=0.20$), diastolic blood pressure (82.4±14.4 *vs* 85.2±19.5 mmHg, $P=0.13$) or number of antihypertensive drugs (1.5±1.0 *vs* 1.4±1.1, $P=0.4$) between early and late referral patients. There were more patients without any antihypertensive medication in the late referral group (28.6% *vs* 15.5%, $P=0.004$); diastolic blood pressure in the patients not taking antihypertensive drugs was higher in the late referral patients (83.5±15.8 *vs* 74.4±15.0 mmHg, $P=0.03$), whereas in those patients with antihypertensive medication, no difference (86.8±13.9 *vs* 84.1±13.9 mmHg, $P=0.6$) was found (Figure 2). The prevalence of both uraemic symptoms (82.8% *vs* 17.2%) and pulmonary oedema (31.2% *vs* 17.2%, $P=0.003$) at the start of RRT was higher in the late referral patients.

The results for the variables of the extended Flemish survey are shown in Table 3. The biochemical parameters in both patient groups, including haematocrit, serum parathyroid hormone, serum bicarbonate and serum albumin at the start of dialysis were not different.

At the start of RRT, the residual creatinine clearance was between 10 and 15 ml/min in only 18% of the patients, between 5 and 10 ml/min in 54% of the patients and <5 ml/min in 34% of the patients. These percentages were comparable in early and late referral patients.

One year after the start of RRT, the number of deaths was more (26.7% *vs* 16.4%, $P=0.07$) and the number of transplanted patients less (4.7% *vs* 17.5%, $P=0.02$) in the late referrals.

The specialty of the physician referring the patient to the nephrologist is shown in Figure 4. The majority of patients are referred by a general practitioner, but the percentage of late referrals in this specialty is lower than for the other specialties. The absolute number of patients coming from general internists, endocrinolog-

ists, cardiologists and urologists is less, but the fraction of late referrals is higher in these specialties than for general practitioners.

Access for the first HD was an arteriovenous fistula in only 7 and 51% of late and early referral patients, respectively.

The creatinine clearance at the start of RRT was significantly greater (9.5 ± 3.6 *vs* 7.0 ± 3.5 ml/min, $P = 0.001$) in the patients who survived compared with those who died during the first year of RRT.

Discussion of the survey results

Although the optimal moment of initiation of RRT is still debated, there is evidence that a 'too late' start has detrimental and partly irreversible consequences for the outcome of the patient [19–22]. It is conceivable that, besides the attention given to a number of secondary medical complications during the pre-ESRD phase, such as anaemia [23,24], left ventricular hypertrophy [25], hyperparathyroidism [26] and malnutrition [27], non-medical factors such as education and information given to pre-ESRD patients also may exert a positive impact on their prognosis [1,2].

Between 25 and 30% of ESRD patients are referred to the nephrologist <1 month before the start of dialysis. The explanation for the late referral of CRF patients to a nephrologist is not clear. One of the explanations may be the insidious evolution of CRF in the majority of the patients. In some patients, the renal insufficiency only becomes obvious by the appearance of frank uraemic symptoms, leading to consultation with a physician. This type of late referral can only be avoided by regular screening of renal function in otherwise asymptomatic patients, which is economically unrealistic. Other patients may have been known to a non-nephrologist but are referred to the nephrologist too late, for a variety of reasons. It may be that the referring physician was not aware of the severity of the disease or of the importance of adequate pre-ESRD care. It has also been suggested that the medical plethora in some of the European countries might play an important role in the problem of late referral [28].

It is also possible that some late referral patients are in fact hidden non-referrals. Khan *et al.* [29] in the UK and Mendelssohn *et al.* [30] in Canada found that a substantial number of ESRD patients were not referred, the number increasing with age and co-morbid conditions. This suggests that many physicians probably decide for themselves whether RRT should or should not be applied in a patient with certain co-morbid conditions, without asking for the prior advice of a nephrologist [6,31].

Also, a recent study from Italy [32] found that the trend for late referral was greater in elderly patients; this makes it difficult to foresee the possible expansion of the dialytic pool in elderly patients. Some of these seriously ill or old patients may still appear in a dialysis unit, where RRT is started in an attempt to improve the general condition of the patient. In some of these patients, RRT is indeed futile, explaining the relatively large number of deaths due to withdrawal of dialysis in this category, as shown by Innes *et al.* [12].

For other patients however, a timely start of RRT could have prevented the further deterioration of their general condition. Correct education of the whole medical community on the actual status and outcome of RRT could prevent these misconceptions. It is remarkable that the problem of late referral was already mentioned several years ago, without any apparent change in referral policy [7,12,20,33–35].

In another group of patients, ESRD is the consequence of a sudden and unexpected deterioration of a pre-existing mild or moderate renal insufficiency. This deterioration frequently is due to iatrogenic diagnostic or therapeutic procedures. That this may be an important cause for late referral is suggested by our observation that the greatest percentage of late referral patients come from general internists and cardiologists (Figure 4). Screening of renal function in patients at risk, and consulting a nephrologist before certain high risk investigations are planned or medications are started can have great preventive value. In this context, the nephrologist should develop guidelines on prevention of deterioration of renal function in high risk patients.

Finally, some patients suffering from severe ARF do not recover and remain dialysis dependent. This type of patient has been excluded from this analysis because their prognosis is generally poor due to the severe underlying pathology.

The proportion of patients opting for PD is greater in the early referrals. It is clear from Table 2 that the reasons for starting RRT are different in early and late referral patients, the latter often arriving in an emergency situation. In such cases, an urgent HD session results in a prompt correction of the clinical status of the patient. Moreover, motivating a patient to start with PD needs time and persuasive power from the dialysis team, and confidence and comprehension from the patient, which are often lacking in the late referral patient. The impact of intensive education and information on modality choice has been demonstrated by Ahlmen *et al.* [2] and Slingeneyer *et al.* [36].

In agreement with the results of many other studies [12,29,36], late referral in our survey also had a clearly negative impact on the morbidity and mortality of ESRD patients, as demonstrated by a longer duration of hospitalization at the start of RRT, a lower number of succesfully transplanted patients and a higher mortality during the first year of treatment.

Although there was apparently no difference in diastolic blood pressure or number of antihypertensive drugs taken between early and late referrals in this study, the incidence of untreated hypertension was much higher in the late referrals. In the group taking antihypertensive drugs, however, diastolic blood pressure was not different between early and late referrals.

Late referral also has important economical consequences. First, there is the prolonged need for hospitalization at the start of RRT, which substantially

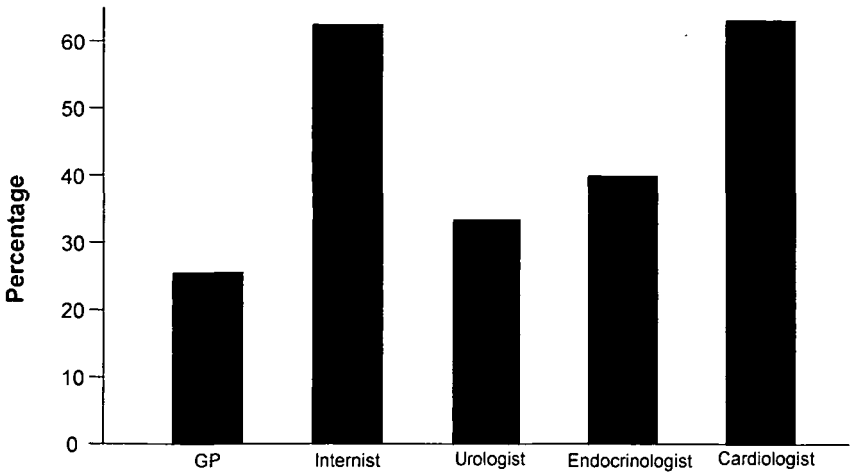

Fig. 4. Specialty of the referring physicians of the late referral patients in Flanders as a percentage of the absolute number of patients referred in that category.

increases the costs of ESRD treatment [6,17,18]. Second, there is the lower take on rate for transplantation, and the preferential choice for HD, both also resulting in the increased costs of an ESRD programme. Levin *et al.* [37] performed a limited economical analysis to assess the cost–benefit of a pre-ESRD treatment education programme. Even with inclusion of all the costs of the teaching programme, there was still a major economic benefit in favour of the programme. Other studies have demonstrated that in well-prepared ESRD patients, the rate of employment is higher [38].

There was no difference in creatinine clearance at the start of RRT between early and late referral patients. It is remarkable to note that there were no differences in serum creatinine or residual renal creatinine clearances, either mean or median values, at the initiation of dialysis between the different patient groups. Similar results have been found by Halabi *et al.* in Lausanne, Switzerland [9]. In contrast, a study in Valenciennes showed that serum creatinine was higher (10.34 *vs* 8.21 mg/dl) and creatinine clearance calculated with the Cockroft and Gault formula was lower (7.08 *vs* 9.03 ml/min) in late referrals compared with early referred patients [39]. Jungers *et al.* [8] also found a slightly lower calculated creatinine clearance in patients with delayed referral.

The mean creatinine clearance at the start of RRT was 7.4 ± 4.1 ml/min in our study, which is far below the value of 10–15 ml/min recommended by the 'healthy start' DOQI guidelines [40]. Although Slingeneyer *et al.* [36] found a higher creatinine clearance at the start of dialysis in the early referrals, in this study only 1.7 and 4.6% of late and early referrals, respectively, were started at a creatinine clearance > 12 ml/min. At first glance, the referral pattern seems thus not to have many effects on the 'healthy start' concept. However, this is partly due to the low number of the early referral patients who started according to the DOQI guidelines. The 'healthy start' concept and the DOQI guidelines were only formulated at the end of this study period. It is thus conceivable that their acceptance and application by nephrologists will only become widespread after some time. Furthermore, it appeared that in some of the centres participating in this survey, budget restrictions made an early start impossible, even in early referred and well-prepared patients. The finding that creatinine clearance at the start of RRT was lower in the patients who died compared with those who survived during the first year of RRT is in favour of the concept of an early start. Urea kinetic modelling has been used recently to predict the optimum timing of commencement of dialysis [22], and the Kt/V urea at the start of dialysis was inversely correlated with the hospital admission rate and with the number of in-patient days during the first 6 months after the start of dialysis.

These findings thus suggest that patients may well benefit from earlier commencement of dialysis, perhaps at a time when their Kt/V urea has declined to the point at which CAPD would be considered inadequate.

The first important comment that can be made is that the degree of renal dysfunction, whether it is judged by serum creatinine or creatinine clearance, or for that matter by residual Kt/V urea, is not the direct cause for initiation of dialysis in almost one-third of ESRD patients. In late referral patients, urgent dialysis is performed mostly for serious overfilling sometimes at residual creatinine clearances well above 15 ml/min. It appears, however, that, probably due to the induced ultrafiltration, the residual renal function rapidly declines to very low levels, necessitating the continuation of dialysis.

Secondly, substantial efforts in continuing education on the management and referral policy for pre-terminal renal failure patients should be focused in the future, not only on general practitioners, but also on other specialists of internal medicine, notably general internists and cardiologists.

The question can be raised of whether these efforts should not take priority over those for an earlier start of dialysis, otherwise at least one-third of patients will

continue to be admitted in an emergency situation. It is this latter category of patients that to a large extent determines the early outcome in dialysis, which will probably be less affected by initiating dialysis earlier in those patients who are already under adequate nephrological care.

In conclusion, this report demonstrates that still today, one in three ESRD patients is a late referral patient. This late referral has consequences for the choice of dialysis modality, for the general outcome of the patient and for the cost of ESRD treatment. The establishment and widespread dissemination of adequate and clear guidelines for general practitioners and non-nephrological specialists on when and how to refer patients to a nephrologist, information about the importance of close nephrological follow-up and development of educational programmes for chronic renal failure patients are urgently needed.

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