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In-Depth Clinical Review

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Late referral of patients with end-stage renal disease: an in-depth review and suggestions for further actions

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Abstract

Late referral of patients with chronic kidney disease (CKD) is a known problem and a major challenge for practising nephrologists since decades. In this review we report about the reasons for late referral, its epidemiology and socioeconomic impact and the medical particularities of late referred patients. We furthermore highlight on the efforts which have been undertaken so far to avoid late referral and should be undertaken in future to face the ever growing numbers of chronic kidney disease patients.

Keyword: end-stage renal disease

Introduction

Chronic kidney disease (CKD) is gradually emerging as an important health care problem all over the world. The noted increase in its prevalence is partly due to a real increase in incidence, a better detection of CKD and a better survival of patients with renal insufficiency due to secondary causes (age, diabetes, cardiovascular disease) [1]. As early as 1984, Ratcliffe *et al*. [2] demonstrated that late referral (LR) of patients with progressive end-stage renal disease (ESRD) was a major reason for higher morbidity, mortality, cost and lower quality of life. Ever since, numerous studies have been carried out on this issue [3–5], confirming the same detrimental consequences related to LR. It is speculated that improving referral pattern will result in better outcomes of renal replacement therapy (RRT), but studies to validate whether such projects are feasible and cost-effective on a larger scale are still scant.

This paper aims to provide an in-depth review on our current understanding of the prevalence, causes, consequences and solutions for the problem of LR of ESRD patients.

An accurate definition of 'Late Referral'

There is no universally accepted definition of 'LR' of patients with CKD [6–8]. Nearly all authors have used the time of follow-up by a nephrologist before initiation of renal replacement as a measure to define LR. This criterion starts from the premise that it is the preparation for RRT, in particular the creation of a dialysis access, which is of importance to explain the higher morbidity in LR patients.

Depending on the study, different numbers of months prior to the initiation of dialysis (1, 3, 6 months or even 12 months) have been used to define LR of patients with CKD (see Table 1). Apart of the term 'LR', some authors even define a subgroup of 'ultra-late referred patients' in whom dialysis is initiated within 1 month after referral [9]. A period of 3–4 months before initiation of dialysis is most widely accepted to discriminate between early and LR; however, this definition is arbitrary and the evidence to support it is lacking. As maturation of a native AV fistula takes time, a period of 4 months, based on this consideration, seems plausible. In the same line of reasoning, some authors, e.g. the DOPPS registry [10], use the presence of functioning permanent vascular access at the start of RRT as the criterion for defining 'early referral'.

Definitions based on time-to-start of dialysis or the presence of functioning permanent access ignore, however, the large group of patients with impaired renal function, in whom the intervention of a nephrologist can be of use to slow down progression and treat secondary complications. Therefore, a 'narrow definition' based on time-to-start of dialysis might seriously underestimate the impact of LR, as it is well established that the majority of CKD stage 3 patients will die because of cardiovascular diseases even before they will reach ESRD [11]. As a consequence of LR, many of CKD stage 3 patients are deprived of the available prophylactic strategies to slow down the progression of renal disease and the linked cardiac comorbidity. It would thus be more appropriate to define 'LR' as patients not referred according to the existing guidelines, such as those of the Royal College of General Practitioners in the UK, or of the 'The National Kidney Foundation—Kidney Disease Outcomes Quality Initiatives guidelines' [12]. Apparently, knowledge about these criteria is not widespread amongst or implemented by medical practitioners. Agarwal *et al*. [13] demonstrated that internal medicine residents have

Table 1. Studies analysing referral for dialysis

Reference	Time period	Number	Definition of LR	% of LR patients	Mortality	PD//HD	Hospitalization	Special remarks
Cass [32] 2002, AUS/NZ	1 April 1995–31 December 1998	4234	3 months before RRT	26%	Hazard ratio 1.19/95% CI	NA	NA	Excluded unavoidable LR 3.5%; % of transplanted patients
Schwenger [26] 2006, Austria/Germany	1 January 1998–31 December 2001	280	17 weeks before RRT	39.6%	LR 34.2% versus ER 5.5% within 1 year	PD: 18.2% Austria, 10.2% Germany	LR 16 days (4–104), ER 11 days (4–32)	Two-centre study
Roderick [15] 2002, UK	1 June 1996–31 May 1997	361	4 months prior to RRT	35%	Death within 6 months	NA	10 days	Differentiation unavoidable/avoidable
			1 month prior to RRT	23%	16%		18 days	
					32%			
Winkelmayer [50] 2001, USA	January 1991–June 1996	3014	3 months prior to RRT	35%	NA	78% HD, 22% PD	NA	Determinants given for initial modality choice and switch
Nakamura [69] 2007, Japan	1983–2003	366	6 months prior to RRT	47%	Death within 1 year after start of RRT	NA	NA	Single centre
Wauters [70] 2004, France	November 1999–March 2001	279	6 months prior to RRT: ER	71.6%	NA	ER 13.5%, LR 13.9%	NA	Region wide, multi-centre study
			6–1 months: intermediate reference	15.1%				
			Less than 1 month: LR	13.3%				
Sesso [71] 1996, Brazil	October 1992–March 1995	184	1 month prior to RRT	57%	Survival rate: LR 69%, ER 87%; hazard ratio 2.77	LR 2.8%. ER 5.1%;	NA	
						iPD LR 23.6%, ER 32.1%		
Górriz [72] 2002, Spain	1996–97	362	6 months prior to RRT	37.3%	6-month survival rate: LR 10.2%, ER 3.2%; 3 years mortality: LR 36.9%, ER 24.9%	ER/planned 18.3% PD, uPL LR: 5.1%	ER 4.0 days (± 6.2 days), LR 17.7 (±14.6 days)	Multi-centre study, planned and unplanned referrals
Metcalfe [73] 2000, Scotland	October 1997–September 1998	533	Planned and unplanned referral	24.6% unplanned referral	Hazard ratio: unplanned 3.6 (1.4–9.3)	23% of 90 days survivors started on PD	Planned 3 days (0–94 days), unplanned 9 days (0–124 days)	Planned/unplanned, no recovery from ARF
Roubicek [43] 2000, France	January 1989–December 1996	270	4 months prior to RRT	31%	Not significant	NA	NA	

Schmidt [74] 1998, USA	January 1990–April 1997	238	1 month prior to RRT	35%				
Ifudu [75] 1999	1990–94	220	No nephrological care	57%				
Sesso [40] 1996, Brazil	October 1992–March 1995	184	1 month prior to RRT	57%	Survival rate: LR 69%, ER 87%; hazard ratio 2.77	LR 2.8%. ER 5.1%; iPD LR 23.6%, ER 32.1%	NA	
Korevaar [76] 2001, The Netherlands	January 1997–May 1999	253	1 month prior to RRT	37%	Hazard ratio 1.66			
Astor [65] 2001, USA	October 1995–June 1996	356	1 month prior to RRT	25%				
Lameire [77] 1997, Europe	January 1993–December 1995		1 month prior to RRT	35%				
Van Biesen [78] 1998, Europe	January 1996–December 1997		1 month prior to RRT	29%	Deaths in the LRs 26.7 versus 16.4%	23% LR on PD, ER 49% on PD	Late versus early referrals (15.1 ± 16.0 versus 27.8 ± 23.7 days)	
Khan [79] 1994, UK		304	Referred and non-referral to specialist		2-year survival rate: 58.7% referred, 25% non-referred patients			
Navaneethan [80] 2007, USA	March 2003–March 2005	204	GFR <15 ml/min: LR (CKD V), CKD I- IV: ER	22%	1-year survival rate: LR 18%, ER 9%	NA	NA	
Obialo [9], 2005, USA	1999–2002	460	3 months prior to RRT: LR, under 1 month: ultra LR	46% ultralate referred, 37% LR	Mortality 40% ULR versus 15% ER and 26% LR	NA	NA	Socioeconomic implications
Steel [81] 2002, USA	1996–2000	494	Referral 3 months prior to RRT					Sociodemographic factors for LR
Abderrahim [82] 2001, Tunesia	1990–96	299	NA	29–36%	NA	NA	NA	Subgroup analysis: diabetes leading to ESRD
Bhan [83] 2007, Canada	1 year	93	3 months prior to RRT	48%	NA	NA	NA	Analysis on vascular access
Curtis [84,85] 2005, Canada/Italy	1997–1998/1999–30 June 2002	288	3 months prior to RRT	NA	Standard nephrology clinic versus multi-disciplinary clinic attendance (hazards ratio 2.17)	ER patients 40% PD, 60% HD	NA	Includes only ER patients, analysis of multi-disciplinary clinic care

Table 1. *Continued.*

Reference	Time period	Number	Definition of LR	% of LR patients	Mortality	PD//HD	Hospitalization	Special remarks
Frimat [86] 2004, France	1997–99	508 // 148 patients with diabetes type II	3 months prior to RRT	27%		75% HD, 25% PD	NA	Subgroup analysis: type II diabetes leading to ESRD
Kazmi WH [85] 2004, USA	1996–97	2195	4 months prior to RRT	33%	Hazard ratio 1.44 from LR death within 1 year	53% ER 40% LR	NA	WAVE II study
Lorenzo [87] 2004, USA	1998–2003	538	3 months prior to RRT: planned presentation	281 planned patients (52%), 257 unplanned patients (48%)	Unplanned presentation hazard ratio (HR), 1.73	NA	All-cause hospitalization (incidence rate ratio, 1.56; 95% CI, 1.36 to 1.79; $P < 0.001$)	Differentiation planned/ unplanned
Riegel [88] 2005, Germany	July 2002–March 2003	551	CKD IV: ER	58% referred late: CKD V	NA	NA	11.4 days ER, 17.4 days LR	
Ellis [89] 1998, UK	1996–97	198	3 months prior to RRT	32% LR	12-month survival 60.5% versus 72.5%	NA	25 days LR versus 9.7 days ER	
Avorn [36] 2002, USA	1991–96	3014	3 months prior to RRT	34.5%	37% increase in risk of death in the first year of dialysis	NA	NA	
Castellano [90] 2006, Spain	2003–04	117	Planned and unplanned	44% unplanned, 56% planned	6-month mortality 4.6% versus 11.5%	NA	23.6 days unplanned, 3 days	
Gallego [91] 2003, Spain	1994–98	139	6 months prior to RRT	23%	Mean survival time: 73.6 ± 4.3 months (ER) and 73.0 ± 6 months (LR)	NA	NA	
GIMEP [92] 2002, Italy	1998–99	1137	2 months prior to RRT	45%	NA	44% ER, 9.1% LR	NA	Multi-centre study
Gøransson [93] 2001, Norway	1984–98	242	3 months prior to RRT	27%	NA	NA	31 days LR, 7 days ER	
Lhotta [94] 2003, Austria	January 1999–October 2000	75	GFR dependent: referral when GFR <20 ml: LR	56%	2-year follow-up: 45% deaths LR, 24% ER	NA	NA	
Lin [95] 2003, Taiwan	February 1988–June 2001	115	6 months prior to RRT	53%	5-year follow-up: ER: 72.4%; LR: 35.2%	NA	NA	Subgroup analysis of type II diabetes
Pena [96] 2006, Spain	January 1990 to December 2001	178	4 months prior to RRT	22%		NA	NA	

widely differing perceptions of indications for nephrology referral. A few residents chose nephrology referral for proteinuria (45%), uncontrolled hypertension (64%) or hyperkaelaemia (26%). Twenty-eight percent of the residents considered consulting a nephrologist for anaemia of CKD, whereas 45% would do so for bone and mineral disorders. Most of the residents would only involve a nephrologist when estimated glomerular filtration rate (eGFR) was <30 ml/min/1.73 m^2 or for a rapid decline in GFR (79%). Whereas most residents would refer a patient for dialysis initiation at an eGFR between 15 and 30 ml/min/1.73 m^2 (59%), 18% would only do so when eGFR was <5 ml/min/1.73 m^2.

Nevertheless, the use of a broader definition is essential, as this will create more opportunities for intervention and prevention of ESRD. In view of the expected patient numbers, this will change our approach to these patients from an individual patient–nephrologist relationship, to a more structured approach using 'CKD clinics', where the workload is distributed amongst a multi-disciplinary team, using predefined programmes and nurse specialists [14].

Reasons for LR

Lameire *et al*. [8] identified some potential reasons for LR: non-awareness of a renal disease until the patient develops uraemic symptoms and the lack of or inadequate routine screening of patients at high risk of developing a renal insufficiency (such as hypertension or diabetes).

Roderick *et al*. [15,16] point out that we should discriminate two major groups of LRs: those in whom LR was avoidable and those where it was not. 'Avoidable' LR occurs in patients with a slow and constant progression of their underlying kidney disease, among whom the start of RRT could have been easily anticipated. There is some indication that for this latter patient group, there is a small decrease in the prevalence of LR, as a consequence of the augmented awareness for ESRD [17]. The routine measurement of proteinuria has already proven to be of benefit especially in this group of patients, but its use is not yet generally implemented. Another potential pitfall in the screening of patients for kidney disease is the limitation of the commonly used screening marker creatinine [18]. The attentiveness towards a declining, or even already alarmingly decreased, renal capacity can be improved by introducing the estimated 'Modification of diet in Renal Disease' (MDRD) formula-based glomerular filtration rate (eGFR) into the laboratory reports as a standard parameter instead of simple creatinine values [17]. In an Australian study, this method leads to an improvement of the referral patterns [19]. There is, however, substantial concern that the implementation of automatic eGFR reporting by labs would result in a 'tsunami' of (mostly elderly and frail) patients, and this as a consequence of the inaccuracies of the estimation formulae and the physiological decline of kidney function with age [20–22]. It is argued that many of these patients do not have real kidney disease, but rather 'renal impairment', and that nephrology referral is, therefore, pointless. Although this reasoning is in itself correct, it should not be forgotten that especially in this frail population with multiple comorbidities, avoidance of acute-on-chronic deterioration of kidney function by inappropriate investigations (e.g. radio-contrast) or medication (e.g. non-steroidal agents) is of utmost importance. In consideration of the growing number of patients developing chronic kidney disease, this constant percentage of patients at high risk of acute-on-chronic renal failure implies an immense impact on the socioeconomic situation in the coming years. Strategies to educate general physicians and to define and implement accurate criteria, based upon proper and reliable screening tools, for nephrology referral should be developed.

Some patients, however, suffer from a rapid deterioration of their initially mildly abnormal kidney function, either because of an acute intercurrent illness, e.g. rapidly progressive glomerulonephritis, or because of a sudden deterioration of their underlying CKD (acute-on-chronic renal failure), e.g. a contrast-induced nephropathy (CIN) in a patient with risk factors for CIN such as diabetes or hypovolaemia.

For the patients with an acute illness, LR is by definition unavoidable. For the second group, the implementation of the 'broad' definition of LR and a multi-disciplinary approach could potentially lead to avoidance of a substantial number of these cases. In a European survey [23], only a limited number of patients had a follow-up between 1 and 3 months before the start of dialysis, resulting in a 'hyperacute' referral of most of the patients. This would necessitate nephrology units to establish large 'information campaigns' for general practitioners and specialists such as cardiologists, diabetologists, vascular surgeons, etc. to screen for earlier stages of CKD.

There is evidence that LR is negatively influenced by socioeconomic factors, ethnicity [24,25], age and presence of comorbidities [7]. It can be speculated that in older, frailer patients, referral is delayed as general practitioners misinterpret the possibilities and merits of eventual interventions, such as dialysis. This can result in non-referral [14,26,27] or hyperacute referral [28,29]. However, it has been clearly demonstrated that even in e.g. the elderly, LR results in worse outcome [26]. The LR of these 'borderline' patients also raises ethical questions: as the specialist does not know the patient, advanced care planning cannot be established, and most specialists will give the patient the benefit of the doubt and start RRT [30]. Again, as most of the comorbidities, such as diabetes and cardiovascular disease, can be a cause of or be linked to renal impairment, it should be recommended that general physicians are educated properly about the interactions of these comorbidities, and about the outcome of different treatment options, not only in terms of survival but also in terms of quality of life. Whereby the existence of communication channels between general practitioners and specialists seem to improve early referral.

Prevalence of LR

Although the detrimental effect of LR has been highlighted for many years [29,31,32], the prevalence of late referred patients among the patients in whom dialysis is initiated can be regarded as constantly fluctuating around 30% (see

Table 1). In addition, even very recent studies report that LR and non-elective start of dialysis remain a frequent finding [7,33]. The phenomenon appears to exist throughout all industrialized as well as developing countries [29,33] and alike in adults, the elderly and paediatric patients [26,34].

In a French study [35], 23% of the patients were referred less than 1 month before the start of dialysis and 8% were referred only 1–4 months before dialysis. In the United States, Avorn *et al*. [36] and Stack *et al*. [37] report similar numbers of late referred patients (34% of 2398 and 33% of 2264 investigated patients). In a UK [15] and a German [26] investigation, 37% and 40–60% of patients were referred shorter than 4 and 2 months before the start of dialysis, respectively. Studies from developing countries [38] report even higher numbers of late referred patients, although the reasons for this differ from those of industrialized countries, as economic factors and lack of medical infrastructure, might here be the driving forces.

Differences in outcome between late and early referred patients

The late referred patient is often in a challenging clinical condition, often with pulmonary congestion or hyperkaelaemia, necessitating immediate RRT.

But it is not only the hyperacute situation that is causing an increased mortality in this group of patients: the late referred patient presents with already chronic and numerous clinical, haematological, hormonal and metabolic abnormalities, such as anaemia, malnutrition, hyperparathyroidism, hyperphosphataemia, hypocalcaemia, hypertension and congestive heart failure, all of which have been linked to poor dialysis outcomes [39]. Furthermore, late referred patients are described less ACE inhibitors, ARBs and vitamin D analogues, although their beneficial effects are well proven. Sesso *et al*. [40] found a higher number of malnutrition, infective episodes, pulmonary oedema and severe hypertension in late referred patients. Jungers *et al*. [41] observed that in late referred patients the mean systolic and diastolic blood pressures were higher than those in controls, and fluid overload with pulmonary oedema was more often present; also plasma concentrations of phosphate were higher, while plasma levels of bicarbonate, haemoglobin, serum albumin and calcium were lower. Each of these parameters is potentially modifiable and begins its detrimental effect already during the pre-ESRD period [39]. It seems rational that attention to these abnormalities before dialysis initiation has a positive impact on long-term patient outcomes.

Van Biesen *et al*. [23] reported that during the first year after the start of renal replacement, mortality was nearly twice as high in the late versus early referred patients (28.9% versus 8.5%, $P < 0.05$). Lin *et al*. [42] found that early referral was a positive and independent predictor of clinical outcome determining long-term prognosis in ESRD as well in HD as in PD, a finding corroborated by Cass *et al*. [32] who found that even after 5 years, mortality was higher in the late referred group.

Roubicek *et al*. [43] did not find a greater risk of death 1 year after initiation of dialysis in late referred patients, after correction for the presence of the greater initial comorbidity in the late referred patients. However, as already stated before, it is disputable whether correcting for differences in comorbidity at start between early and late referred patients is justified, as LR can be the underlying cause of the higher comorbidity.

These data suggest that there is a more fundamental difference than just the timing of referral or even their difference in comorbidity at start between 'early' and 'late' referred patients. It might be that late referred patients have a different attitude towards their health, e.g. with regard to compliance. It is remarkable, that in late referred patients on PD the outcome deficit in comparison to early referred patients disappears after 1 year of RRT, whereas in late referred patients on HD the weaker outcome remains. It is conceivable that in the PD patients, there is far more attention to education and patient empowerment even in late referred patients. In the same study, mortality was substantially lower in those patients who choose their treatment modality themselves, as compared to patients where the modality was selected by the nephrologist.

All these findings emphasize that 'LR' is more than patients being seen by a nephrologist or not: it is a multidisciplinary strategy focusing on patient empowerment and education [44–47]. All these arguments plead to implement the broad rather than the narrow definition of LR and also indicate that nephrological centres should install multi-disciplinary teams to manage these patients.

LR: modality choice, transplantation and vascular access planning

Modality selection is influenced by the timing of referral: those patients who are referred to nephrology teams early in the course of their disease are more likely to choose PD rather than HD [8,39,48]. The lack of time before initiation of dialysis results in an information gap in the late referred patient; thus, one finds significantly lower numbers of PD patients amongst late referrals, even after clinical stabilization. This fact directly influences the quality of life of the patients and the cost-effectiveness of the treatment.

As a cause of their clinical condition, LR patients are often condemned to rapid access for initializing dialysis [36,49,50]. Because of the short interval between first contact with a specialist and the initiation of dialysis, an arteriovenous (AV) fistula as permanent vascular access can often not be created in due time [51]. Catheters, either tunnelled or not, are associated with a significantly higher rate of complications and mortality [52]. At least part of the higher mortality in late referred patients is potentially attributable to the use of inferior access strategies [10]. It is important to mention that even after 6 months, the majority of patients started on a tunnelled catheter were still depending on this device as vascular access. It is ill defined whether this is due to refusal of the patient (again pointing to a difference in disease-coping capability and strategies between late and early referred patients) or due to the medical impossibility

of creating a fistula, reflecting a higher comorbidity. It should also be kept in mind that in LR patients, vascular access possibilities are often destroyed as no preservation of the 'venous assets' has been implemented.

Once more, focussing only on the narrow, time to dialysis dependent, definition of LR will probably not be much of help to improve problems related to modality choice or access-related morbidity. In the multi-disciplinary programme in Toronto, predialysis access creation was achieved in 86.3% of patients, demonstrating that a planned approach can be helpful [45,53].

Although HD is by far the most often chosen modality of RRT for LR patients, Povlsen *et al*. [54] demonstrated that in their centre, acute start of PD is possible, and gives good short- and long-term results. Lobbedez *et al*. [55] compared the outcome of unplanned PD and HD patients. After correcting for differences in comorbidity, the initial hospitalization duration was similar in HD versus PD patients, as was long-term patient and technique survival. PD was started 8.6 $\pm$ 10 days after catheter insertion. As this strategy might prevent patients starting on a non-tunnelled central venous line, this approach could be considered in all patients. However, an 'acute start of PD' programme needs careful planning and dedication from the complete team, from the trainee at the emergency ward, to the nurses and the person placing the Tenckhoff catheter.

LR not only influences modality choice between HD and PD but also impacts on the chances of transplantation. Cass *et al*. [32,56] demonstrated that late referred patients had a twice lower likelihood of being waitlisted for transplantation and a 35% lower likelihood of being transplanted during the first 2 years of their RRT. Winkelmayer *et al*. [49] found a 5-fold lower transplantation rate in LR patients, even after correction for differences in comorbidity and socioeconomic status. Kessler *et al*. [35] found similar results in a 2-year prospective community-based study.

Efficacy and cost-effectiveness of (multi-disciplinary) programmes to fight LR

RRT is expensive and the arising costs are additionally increased by the already existing comorbidity of patients with ESRD and the chosen modality of RRT. LR also results in a lower utilization of cost-saving strategies, such as PD, home-based HD and transplantation.

Lee [57] calculated the costs, including outpatient dialysis care, inpatient care and physician claims, in 166 patients on dialysis therapy for longer than 6 months and found a nearly 50% reduction of cost for PD ($\sim$\$27 000) in comparison to in-patient HD care (\$51 000). These savings come to effect even after switching of dialysis modality from initial therapy with HD to PD [58].

A second cost impact results out of hospitalization [59], its 'intensity' and duration. Costs increase sharply in the last 6 months prior to initiation of dialysis, and hospitalization is a major component of this. As hospitalization is longer in LR patients, and increases with comorbidity, these costs could potentially be avoided by timely management of CKD.

Whereas it is clear that LR increases costs of treatment, it should also not be forgotten that 'early referral' and its related treatment costs are also substantial.

Up to now, it has not been investigated weather costs of management of comorbidities such as renal anaemia and secondary hyperparathyroidism and bone mineral disease will prove to be cost-effective. Whereas there is little doubt about improved outcome by their apt management, their management is expensive [60]. According to the data from the DOPPS, anaemia has proven to be a risk factor independent of comorbid conditions and is associated with higher risks of both hospitalization and death. Collins [61] found that early epoetin treatment to correct renal anaemia appears to be associated with improved survival of ESRD patients in the first year after the start of dialysis and reduced cost of treatment.

There is also indirect evidence that referral to a nephrology unit results in a slowing down of the progression of renal failure [62], thus potentially delaying the start of renal replacement, and thus resulting in substantial cost savings, as renal replacement is itself an expensive treatment. Levin *et al*. [63] reported about the outcomes of two multidisciplinary predialysis programmes in two major Canadian cities, aiming at a reduction of urgent dialysis starts, improvement of preparedness for dialysis and improvement of resource utilization. The studies demonstrated fewer urgent dialysis starts (13% versus 35%), more outpatient training (76% versus 43%) and less hospital days in the first month of dialysis (6.5 days versus 13.5 days) as well as a success in access creation (86.3% of patients), with estimated cost savings of \$4000 (Canadian dollars) per patient. Goldstein *et al*. [64] describe a better control of blood pressure, renal anaemia, acid–base metabolism and serum albumin in a group of predialysis patients seen by a multi-disciplinary team, resulting in significant superior clinical outcomes.

In a retrospective analysis of 340 patients, Thanamyooran *et al*. demonstrated an improvement in metabolic and blood pressure control, and an increase in the prevalence of PD by the implementation of a multi-disciplinary model [66]. As is demonstrated above, early referral is not sufficient, as also a multi-disciplinary approach [46] is needed to achieve an improvement in functioning vascular access [65] and quality of life [31].

Thanks to a structured predialysis education programme, Goovaerts *et al*. [67] report that 31% of their patients start on PD, 16% on self-care HD and 9% on home HD as initial RRT modality.

However, health economic evaluation of all these interventions is lacking as up till now, and further research is certainly warranted.

The major problems relate to a lack of evidence on the natural evolution of renal function and outcome in this group. The majority of CKD stage 3 patients are far more likely to die from cardiovascular disease than to end up on RRT [11], and even in CKD 4, only 25–30% will need renal replacement. The situation becomes even more complex if one takes into account the normal decline of renal function with age. Taken together, it might be that a lot of effort is invested in 'preparing' patients who never will need RRT. There is an urgent need for a large registry of CKD 4 patients, so that more epidemiologic data on this patient group

become available. Without this information, all efforts to claim cost-effectiveness of pre-ESRD care and by extension early referral will remain inaccurate and vague.

Conclusions/suggestions

Although Obrador *et al*. [68] summarized an optimal pre-ESRD care with early detection of progressive renal disease, intervention to retard its progression, prevention of uraemic complications, attenuation of comorbid conditions, adequate preparation for ESRD therapy and timely initiation of RRT already 10 years ago, the numbers of LR patients remain high and unchanged over the past 20 years. This implicates a tremendous socioeconomic impact on the medical systems all over the world.

Several international, national and local initiatives opted to define the point of time of referral as linked to the GFR (broad definition of referral), as the more 'narrow' definition (4 months before start of RRT) is too restrictive and leads too many missed opportunities for intervention in the earlier stages of kidney disease.

Undoubtedly, the sheer number of stage 3 CKD patients would by far overwhelm the existing nephrology care facilities. The management of these numbers will imply a change in paradigm; specialists in nephrology will have to delegate responsibilities to other trained care providers to participate in the care for a growing number of CKD patients. This would also mean a change from the personal 'one-to one' relationship between nephrologist and patient to a more programme-based/clinical pathway-orientated surveillance and care for CKD patients.

With the help of well-informed and well-supported primary care providers as 'screening and detection' agents, the CKD patient could easily be followed up and only be referred to a multi-disciplinary team of a nephrological centre when appropriate and needed. Secondly, the short communication channels within such a team make 'informal information' between caregivers easy and effective, with a minimum of information loss.

The choice of the RRT in the 'late referred' setting has long-lasting consequences for the patient, but the situation does not yield much time for considerations, neither for the medical staff nor for the patient and his or her relatives. The planning and processing of a chronic dialysis access is imperative. Preparation for late start RRT should include a strong encouragement for initiation on PD to avoid unnecessary use of central lines, and the discussion of pre-emptive transplantation of live donors when available.

The goal should be a reduction of LR patients when analysing the single centre's situation, and hereby the differentiation between 'avoidable' and 'unavoidable' LR is crucial. A large-scale registry on the fate of CKD 4 patients is urgently warranted to provide evidence for initiatives taken in the field of pre-ESRD care.

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References

1. Collins AJ, Foley R, Herzog C *et al*. Excerpts from the United States Renal Data System 2007 annual data report. *Am J Kidney Dis* 2008; 51: S1–S320. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18086389
2. Ratcliffe PJ, Phillips RE, Oliver DO. Late referral for maintenance dialysis. *Br Med J (Clin Res Ed)* 1984; 288: 441–443. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6419957
3. Lameire N, Van Biesen W. The pattern of referral of patients with end-stage renal disease to the nephrologist—a European survey. *Nephrol Dial Transplant* 1999; 14(Suppl 6): 16–23. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10528708
4. Jungers P. Late referral: loss of chance for the patient, loss of money for society. *Nephrol Dial Transplant* 2002; 17: 371–375. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11865079
5. Arora P, Obrador GT, Ruthazer R *et al*. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 1999; 10: 1281–1286. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10361866
6. Key SM. Optimizing dialysis modality choices around the world: a review of literature concerning the role of enhanced early pre-ESRD education in choice of renal replacement therapy modality. *Nephrol Nurs J* 2008; 35: 387–394; quiz 395. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18783001
7. Navaneethan SD, Aloudat S, Singh S. A systematic review of patient and health system characteristics associated with late referral in chronic kidney disease. *BMC Nephrol* 2008; 9: 3. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18298850
8. Lameire N, Wauters JP, Teruel JL *et al*. An update on the referral pattern of patients with end-stage renal disease. *Kidney Int Suppl* 2002; 80: 27–34. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11982809
9. Obialo CI, Ofili EO, Quarshie A *et al*. Ultralate referral and presentation for renal replacement therapy: socioeconomic implications. *Am J Kidney Dis* 2005; 46: 881–886. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16253728
10. Pisoni RL, Arrington CJ, Albert JM *et al*. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: an instrumental variable analysis. *Am J Kidney Dis* 2009; 53: 475–491. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19150158.
11. Levin A, Djurdjev O, Beaulieu M *et al*. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis* 2008; 52: 661–671. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18805347
12. Johnson ES, Thorp ML, Platt RW *et al*. Predicting the risk of dialysis and transplant among patients with CKD: a retrospective cohort study. *Am J Kidney Dis* 2008; 52: 653–660. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18585833
13. Agrawal V, Ghosh AK, Barnes MA *et al*. Perception of indications for nephrology referral among internal medicine residents: a national online survey. *Clin J Am Soc Nephrol* 2009; 2: 323–328. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19092130.
14. Mendelssohn DC, Toffelmire EB, Levin A. Attitudes of Canadian nephrologists toward multidisciplinary team-based CKD clinic care. *Am J Kidney Dis* 2006; 47: 277–284. Available at http://www.ncbi.

nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16431256
15. Roderick P, Jones C, Drey N *et al*. Late referral for end-stage renal disease: a region-wide survey in the south west of England. *Nephrol Dial Transplant* 2002; 17: 1252–1259. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12105249
16. Roderick P, Jones C, Tomson C *et al*. Late referral for dialysis: improving the management of chronic renal disease. *Q J Med* 2002; 95: 363–370. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12037244
17. MacGregor MS, Boag DE, Innes A. Chronic kidney disease: evolving strategies for detection and management of impaired renal function. *Q J Med* 2006; 99: 365–375. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16682439
18. Van Biesen W, Vanholder R, Veys N *et al*. The importance of standardization of creatinine in the implementation of guidelines and recommendations for CKD: implications for CKD management programmes. *Nephrol Dial Transplant* 2006; 21: 77–83. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation& list_uids=16221704
19. Noble E, Johnson DW, Gray N *et al*. The impact of automated eGFR reporting and education on nephrology service referrals. *Nephrol Dial Transplant* 2008; 23: 3845–3850. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18632591
20. Glassock RJ, Winearls C. CKD in the elderly. *Am J Kidney Dis* 2008; 52: 803; author reply 803–804. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18805350
21. Glassock RJ, Winearls C. The global burden of chronic kidney disease: how valid are the estimates? *Nephron Clin Pract* 2008; 110: c39–c46; discussion c47. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18689986
22. Wetzels JF, Willems HL, den Heijer M. Age- and gender-specific reference values of estimated glomerular filtration rate in a Caucasian population: results of the Nijmegen Biomedical Study. *Kidney Int* 2008; 73: 657–658. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18274547
23. Van Biesen W, De Vecchi A, Dombros N *et al*. The referral pattern of end-stage renal disease patients and the initiation of dialysis: a European perspective. *Perit Dial Int* 1999; 19(Suppl 2): S273–S275. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10406531
24. White SL, Chadban SJ, Jan S *et al*. How can we achieve global equity in provision of renal replacement therapy? *Bull World Health Organ* 2008; 86: 229–237. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18368211
25. Ward MM. Medical insurance, socioeconomic status, and age of onset of endstage renal disease in patients with lupus nephritis. *J Rheumatol* 2007; 34: 2024–2027. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17696272
26. Schwenger V, Morath C, Hofmann A *et al*. Late referral—a major cause of poor outcome in the very elderly dialysis patient. *Nephrol Dial Transplant* 2006; 21: 962–967. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16396974
27. Visser A, Dijkstra GJ, Huisman RM *et al*. Differences between physicians in the likelihood of referral and acceptance of elderly patients for dialysis-influence of age and comorbidity. *Nephrol Dial Transplant* 2007; 22: 3255–3261. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17595178
28. Abdulkader RC, Zanetta DM, Oliveira GM *et al*. Risk factors for hospital death of patients with end-stage renal disease without previous diagnosis of severe chronic renal failure arriving in an emergency situation at the hospital. *Ren Fail* 2003; 25: 631–638. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12911168
29. Alebiosu CO. Detrimental effects of late referral for dialysis. *Afr J Health Sci* 2001; 8: 89–92. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17650051
30. Van Biesen W, Lameire N, Veys N *et al*. From curing to caring: one character change makes a world of difference. Issues related to withholding/withdrawing renal replacement therapy (RRT) from patients with important co-morbidities. *Nephrol Dial Transplant* 2004; 19: 536–540. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14767005
31. Caskey FJ, Wordsworth S, Ben T *et al*. Early referral and planned initiation of dialysis: what impact on quality of life? *Nephrol Dial Transplant* 2003; 18: 1330–1338. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12808170
32. Cass A, Cunningham J, Arnold PC *et al*. Delayed referral to a nephrologist: outcomes among patients who survive at least one year on dialysis. *Med J Aust* 2002; 177: 135–138. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12149081
33. Chow KM, Szeto CC, Law MC *et al*. Impact of early nephrology referral on mortality and hospitalization in peritoneal dialysis patients. *Perit Dial Int* 2008; 28: 371–376. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18556379
34. Jander A, Nowicki M, Tkaczyk M *et al*. Does a late referral to a nephrologist constitute a problem in children starting renal replacement therapy in Poland?—a nationwide study. *Nephrol Dial Transplant* 2006; 21: 957–961. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16339164
35. Kessler M, Frimat L, Panescu V *et al*. Impact of nephrology referral on early and midterm outcomes in ESRD: EPidemiologie de l'Insuffisance REnale chronique terminale en Lorraine (EPIREL): results of a 2-year, prospective, community-based study. *Am J Kidney Dis* 2003; 42: 474–485. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12955675
36. Avorn J, Winkelmayer WC, Bohn RL *et al*. Delayed nephrologist referral and inadequate vascular access in patients with advanced chronic kidney failure. *J Clin Epidemiol* 2002; 55: 711–716. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12160919
37. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 2003; 41: 310–318. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12552491
38. Goncalves EA, Andreoli MC, Watanabe R *et al*. Effect of temporary catheter and late referral on hospitalization and mortality during the first year of hemodialysis treatment. *Artif Organs* 2004; 28: 1043–1049. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15504120
39. Levin A. Consequences of late referral on patient outcomes. *Nephrol Dial Transplant* 2000; 15(Suppl 3): 8–13. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11032351
40. Sesso R, Belasco AG. Late diagnosis of chronic renal failure and mortality on maintenance dialysis. *Nephrol Dial Transplant* 1996; 11: 2417–2420. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9017615

41. Jungers P, Zingraff J, Albouze G *et al*. Late referral to maintenance dialysis: detrimental consequences. *Nephrol Dial Transplant* 1993; 8: 1089–1093. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8272221
42. Lin CL, Chuang FR, Wu CF *et al*. Early referral as an independent predictor of clinical outcome in end-stage renal disease on hemodialysis and continuous ambulatory peritoneal dialysis. *Ren Fail* 2004; 26: 531–537. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15526911
43. Roubicek C, Brunet P, Huiart L *et al*. Timing of nephrology referral: influence on mortality and morbidity. *Am J Kidney Dis* 2000; 36: 35–41. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10873869
44. Wang L, Dong J, Gan HB *et al*. Empowerment of patients in the process of rehabilitation. *Perit Dial Int* 2007; 27(Suppl 2): S32–S34. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17556325
45. Devins GM, Mendelssohn DC, Barre PE *et al*. Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up. *Am J Kidney Dis* 2005; 46: 1088–1098. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16310575
46. Owen JE, Walker RJ, Edgell L *et al*. Implementation of a pre-dialysis clinical pathway for patients with chronic kidney disease. *Int J Qual Health Care* 2006; 18: 145–151. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16396939
47. Ravani P, Marinangeli G, Tancredi M *et al*. Multidisciplinary chronic kidney disease management improves survival on dialysis. *J Nephrol* 2003; 16: 870–877. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14736015
48. Vonesh EF, Snyder JJ, Foley RN *et al*. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. *Kidney Int* 2004; 66: 2389–2401. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15569331
49. Winkelmayer WC, Owen WF, Jr., Levin R *et al*. A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003; 14: 486–492. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12538751
50. Winkelmayer WC, Glynn RJ, Levin R *et al*. Late referral and modality choice in end-stage renal disease. *Kidney Int* 2001; 60: 1547–1554. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11576371
51. Arnold WP. Improvement in hemodialysis vascular access outcomes in a dedicated access center. *Semin Dial* 2000; 13: 359–363. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11130256
52. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. *Kidney Int* 2002; 62: 620–626. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12110026
53. Mendelssohn DC. Pre end-stage renal disease care: opportunities and challenges. *Perit Dial Int* 1999; 19: 113–114. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10357179
54. Povlsen JV, Ivarsen P. How to start the late referred ESRD patient urgently on chronic APD. *Nephrol Dial Transplant* 2006; 21(Suppl 2): ii56–ii59. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16825263
55. Lobbedez T, Lecouf A, Ficheux M *et al*. Is rapid initiation of peritoneal dialysis feasible in unplanned dialysis patients? A single-centre experience. *Nephrol Dial Transplant* 2008; 23: 3290–3294. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18424817
56. Cass A, Cunningham J, Snelling P *et al*. Late referral to a nephrologist reduces access to renal transplantation. *Am J Kidney Dis* 2003; 42: 1043–1049. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14582048
57. Lee CP, Zenios SA, Chertow GM. Cost-effectiveness of frequent in-center hemodialysis. *J Am Soc Nephrol* 2008; 19: 1792–1797. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18614773
58. Shih YC, Guo A, Just PM *et al*. Impact of initial dialysis modality and modality switches on Medicare expenditures of end-stage renal disease patients. *Kidney Int* 2005; 68: 319–329. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15954923
59. Arora P, Kausz AT, Obrador GT *et al*. Hospital utilization among chronic dialysis patients. *J Am Soc Nephrol* 2000; 11: 740–746. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10752533
60. Tonelli M, Wiebe N, Culleton B *et al*. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007; 22: 2856–2866. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17906326
61. Collins AJ, Kasiske B, Herzog C *et al*. Excerpts from the United States Renal Data System 2003 Annual Data Report: atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 2003; 42: A5–A7, S1–S230. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14655179
62. Jones C, Roderick P, Harris S *et al*. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. *Nephrol Dial Transplant* 2006; 21:2133–2143. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16644779
63. Levin A, Lewis M, Mortiboy P *et al*. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. *Am J Kidney Dis* 1997; 29: 533–540. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9100041
64. Goldstein M, Yassa T, Dacouris N *et al*. Multidisciplinary predialysis care and morbidity and mortality of patients on dialysis. *Am J Kidney Dis* 2004; 44: 706–714. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15384022
65. Astor BC, Eustace JA, Powe NR *et al*. Timing of nephrologist referral and arteriovenous access use: the CHOICE Study. *Am J Kidney Dis* 2001; 38: 494–501. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11532680
66. Thanamayooran S, Rose C, Hirsch DJ. Effectiveness of a multidisciplinary kidney disease clinic in achieving treatment guideline targets. *Nephrol Dial Transplant* 2005; 20: 2385–2393. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16046506
67. Goovaerts T, Jadoul M, Goffin E. Influence of a pre-dialysis education programme (PDEP) on the mode of renal replacement therapy. *Nephrol Dial Transplant* 2005; 20: 1842–1847. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15919693
68. Obrador GT, Pereira BJ. Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. *Am J Kidney Dis* 1998; 31: 398–417. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9506677
69. Nakamura S, Nakata H, Yoshihara F *et al*. Effect of early nephrology referral on the initiation of hemodialysis and survival in patients

with chronic kidney disease and cardiovascular diseases. *Circ J* 2007; 71: 511–516. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17384451

70. Wauters JP, Bosson JL, Forneris G *et al*. Patient referral is influenced by dialysis centre structure in the Diamant Alpin Dialysis cohort study. *Nephrol Dial Transplant* 2004; 19: 2341–2346. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15252154
71. Del Vecchio L, Locatelli F, Martins Prata M *et al*. The QUEST initiative anemia study in ESRD: rationale and study protocol. *J Nephrol* 2007; 20: 547–553. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17918139
72. Gorriz JL, Sancho A, Pallardo LM *et al*. Prognostic significance of programmed dialysis in patients who initiate renal substitutive treatment. Multicenter study in Spain. *Nefrologia* 2002; 22: 49–59. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11987685
73. Metcalfe W, Khan IH, Prescott GJ *et al*. Can we improve early mortality in patients receiving renal replacement therapy? *Kidney Int* 2000; 57: 2539–2545. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10844623
74. Schmidt RJ, Domico JR, Sorkin MI *et al*. Early referral and its impact on emergent first dialyses, health care costs, and outcome. *Am J Kidney Dis* 1998; 32: 278–283. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9708613
75. Ifudu O, Dawood M, Iofel Y *et al*. Delayed referral of black, Hispanic, and older patients with chronic renal failure. *Am J Kidney Dis* 1999; 33: 728–733. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10196016
76. Korevaar JC, Jansen MA, Dekker FW *et al*. National Kidney Foundation-Dialysis Outcomes Quality Initiative. Evaluation of DOQI guidelines: early start of dialysis treatment is not associated with better health-related quality of life. *Am J Kidney Dis* 2002; 39: 108–115. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11774109
77. Lameire N, Van Biesen W, Dombros N *et al*. The referral pattern of patients with ESRD is a determinant in the choice of dialysis modality. *Perit Dial Int* 1997; 17(Suppl 2): S161–S166. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9163820
78. Van Biesen W, Wiedemann M, Lameire N. End-stage renal disease treatment: a European perspective. *J Am Soc Nephrol* 1998; 9: S55–S62. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11443769
79. Khan IH, Catto GR, Edward N *et al*. Chronic renal failure: factors influencing nephrology referral. *Q J Med* 1994; 87: 559–564. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7953505
80. Navaneethan SD, Nigwekar S, Sengodan M *et al*. Referral to nephrologists for chronic kidney disease care: is non-diabetic kidney disease ignored? *Nephron Clin Pract* 2007; 106: c113–c118. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17522473
81. Steel J, Ellis P. Do demographic variables affect the timing of referral to the nephrologist? *EDTNA ERCA J* 2002; 28: 185–187. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12638936
82. Abderrahim E, Zouaghi K, Hedri H *et al*. Renal replacement therapy for diabetic end-stage renal disease. Experience of a Tunisian hospital centre. *Diabetes Metab* 2001; 27: 584–590. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd = Retrieve&db = PubMed&dopt=Citation&list_uids=11694858
83. Bhan V, Soroka S, Constantine C *et al*. Barriers to access before initiation of hemodialysis: a single-center review. *Hemodial Int* 2007; 11: 349–353. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17576301
84. Curtis BM, Barrett BJ, Djurdjev O *et al*. Evaluation and treatment of CKD patients before and at their first nephrologist encounter in Canada. *Am J Kidney Dis* 2007; 50: 733–742. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17954286
85. Kazmi WH, Obrador GT, Khan SS *et al*. Late nephrology referral and mortality among patients with end-stage renal disease: a propensity score analysis. *Nephrol Dial Transplant* 2004; 19: 1808–1814. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15199194
86. Frimat L, Loos-Ayav C, Panescu V *et al*. Early referral to a nephrologist is associated with better outcomes in type 2 diabetes patients with end-stage renal disease. *Diabetes Metab* 2004; 30: 67–74. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15029100
87. Lorenzo V, Martn M, Rufino M *et al*. Predialysis nephrologic care and a functioning arteriovenous fistula at entry are associated with better survival in incident hemodialysis patients: an observational cohort study. *Am J Kidney Dis* 2004; 43: 999–1007. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15168379
88. Riegel W, Hahn K, Kreutz R *et al*. BENEFIT Kidney—significance of a nephrology screening at intervention outset and therapy success. *Dtsch Med Wochenschr* 2005; 130: 792–796. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15789300
89. Ellis PA, Reddy V, Bari N *et al*. Late referral of end-stage renal failure. *Q J Med* 1998; 91: 727–732. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10024934
90. Castellano I, Gallego S, Labrador PJ *et al*. The start of renal replacement therapy in a Spanish department. *Nefrologia* 2006; 26: 445–451. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17058856
91. Gallego E, Lopez A, Lorenzo I *et al*. Influence of early or late referral to nephrologist over morbidity and mortality in hemodialysis. *Nefrologia* 2003; 23: 234–242. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12891938
92. Paris V, Ballerini L. Patient flow analysis and referrals—how 1,137 ESRD patients started dialysis during 1998–1999. *EDTNA ERCA J* 2002; 28: 160–163, 169. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12638927
93. Goransson LG, Bergrem H. Consequences of late referral of patients with end-stage renal disease. *J Intern Med* 2001; 250: 154–159. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11489065
94. Lhotta K, Zoebl M, Mayer G *et al*. Late referral defined by renal function: association with morbidity and mortality. *J Nephrol* 2003; 16: 855–861. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14736013
95. Lin CL, Wu MS, Hsu PY *et al*. Improvement of clinical outcome by early nephrology referral in type II diabetics on hemodialysis. *Ren Fail* 2003; 25: 455–464. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12803509
96. Pena JM, Logrono JM, Pernaute R *et al*. Late nephrology referral influences on morbidity and mortality of hemodialysis patients. A provincial study. *Nefrologia* 2006; 26: 84–97. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16649429

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