In-Depth Clinical Review

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...
| 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 Two-centre study       |
| 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) |
| Roderick [15] 2002, UK | 1 June 1996–31 May 1997 | 361    | 4 months prior to RRT, 1 month prior to RRT | 35%              | Death within 6 months 16% | NA       | 10 days         | Differentiation unavoidable/avoidable                                          |
| Winkelmayer [50] 2001, USA | January 1991–June 1996 | 3014   | 3 months prior to RRT                 | 35%              | 32% 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, 6 months prior to RRT: ER 6–1 months: intermediate reference Less than 1 month: LR | 47%              | Death within 1 year after start of RRT | NA       | NA              | Single centre                                                                   |
| Wauters [70] 2004, France | November 1999–March 2001 | 279    | 1 month prior to RRT                  | 57%              | Survival rate: LR 69%, ER 87%; hazard ratio 2.77 | LR 2.8%, ER 5.1%; iPD LR 38.6%, ER 32.1% | NA              | Region wide, multi-centre study                                                |
| Sesso [71] 1996, Brazil | October 1992–March 1995 | 184    | 1 month prior to RRT                  | 57%              | 43% survival rate: LR 69%, ER 87%; hazard ratio 2.77 | LR 2.8%, ER 5.1%; iPD LR 38.6%, ER 32.1% | NA              |                                                                                  |
| Gorriz [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 | 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              |                                                                                  |
| Study                         | Location          | Study Period                  | Number of Patients | Time of Referral | Survival Rate | Mortality Rate | Late Versus Early Referrals |
|-------------------------------|-------------------|-------------------------------|--------------------|------------------|---------------|-----------------|----------------------------|
| Schmidt [74] 1998, USA        | USA               | January 1990–April 1997       | 238                | 1 month prior    | LR 35%        | ER 57%          | NA                        |
| Ifudu [75] 1999              | USA               | 1990–94                       | 220                | RRT              | LR 57%        | ER 35%          | NA                        |
| Sesso [40] 1996, Brazil      | Brazil            | October 1992–March 1995       | 184                | 1 month prior    | LR 57%        | ER 57%          | NA                        |
| Korevaar [76] 2001, The Netherlands |          | January 1997–May 1999         | 253                | 1 month prior    | LR 37%        | ER 25%          | NA                        |
| Astor [65] 2001, USA         | USA               | October 1995–June 1996        | 356                | 1 month prior    | LR 25%        | ER 35%          | NA                        |
| Lameire [77] 1997, Europe    | Europe            | January 1993–December 1995    | 184                | 1 month prior    | LR 29%        | ER 35%          | NA                        |
| Van Biesen [78] 1998, Europe | Europe            | January 1996–December 1997    | 253                | 1 month prior    | LR 29%        | ER 35%          | NA                        |
| Khan [79] 1994, UK           | UK                | March 2003–March 2005          | 304                | Referred and     | 2-year survival rate: 58.7% referred, 25% non-referred patients | NA                        |
|                              |                   |                               |                    | non-referral to   | 1-year survival rate: LR 18%, ER 9% | NA                        |
|                              |                   |                               |                    | specialist       |               | NA             | Socioeconomic implications |
| Navaneethan [80] 2007, USA    | USA               | March 2000–March 2005         | 204                | GFR <15 ml/min: | LR 22%        | NA             | NA                        |
|                              |                   |                               |                    | LR (CKD V), CKD 1- IV | NA           | NA             | NA                        |
| Obialo [9], 2005, USA        | USA               | 1999–2002                     | 460                | 3 months prior   | Mortality 40% LR and 26% ER | NA                        |
|                              |                   |                               |                    | to RRT: LR, under | NA        | NA             | NA                        |
|                              |                   |                               |                    | 1 month; ultra LR | NA        | NA             | Socioeconomic factors for LR |
|                              |                   |                               |                    | referred 37% LR   | NA        | NA             | Subgroup analysis: diabetes leading to ESRD |
|                              |                   |                               |                    | Referral 3 months | NA        | NA             | Analysis on vascular access |
|                              |                   |                               |                    | prior to RRT     | NA        | NA             | Includes only ER patients, analysis of multi-disciplinary clinic care |
| Steel [81] 2002, USA         | USA               | 1996–2000                     | 494                | 46% ultralate    | ER 40% on PD, | NA             | NA                        |
| Abderrahim [82] 2001, Tunisia |                  | 1990–96                       | 299                | referred, 37% LR | ER 49% on PD | NA             | NA                        |
| Bhan [83] 2007, Canada       | Canada            | 1 year                        | 93                 | 3 months prior   | Late versus early referrals (15.1 ± 16.0 versus 27.8 ± 23.7 days) | NA                        |
| Curtis [84,85] 2005, Canada/Italy |             | 1997–1998/1999–30 June 2002   | 288                | RRT              | NA            | NA             | NA                        |
Table 1. Continued.

| Reference          | Time period               | Number          | Definition of LR                                      | % of LR patients | Mortality                  | PD/HD | Hospitalization | Special remarks                                                                 |
|--------------------|---------------------------|------------------|------------------------------------------------------|-----------------|---------------------------|-------|-----------------|--------------------------------------------------------------------------------|
| Frimat [86]        | 1997–99                   | 508 / 148 patients with diabetes type II | 3 months prior to RRT                               | 27%             | Mortality: 75% HD, 25% PD |       | NA              | Subgroup analysis: type II diabetes leading to ESRD                          |
| Kazmi WH [85]      | 2004, USA                 | 2195             | 4 months prior to RRT                                | 33%             | Mortality: Hazard ratio 1.44 from LR death within 1 year |       | NA              | WAVE II study                                                                   |
| Lorenzo [87]       | 2004, USA                 | 538              | 3 months prior to RRT: planned presentation          | 281 planned patients (52%), 257 unplanned patients (48%) | NA            | Unplanned presentation hazard ratio (HR), 1.73 |       | All-cause hospitalization (incidence rate ratio, 1.56; 95% CI, 1.36 to 1.79; P < 0.001) |
| Riegel [88]        | 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]         | 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]         | 1998–97                   | 3014             | 3 months prior to RRT                                | 34.5%           | 37% increase in risk of death in the first year of dialysis | NA              | NA                                                                          |
| Castellano [90]    | 2003–04                   | 117              | Planned and unplanned                                | 44% unplanned, 56% planned | NA              | 6-month mortality 4.6% versus 11.5% | NA              | 23.6 days unplanned, 3 days                                                   |
| Gallego [91]       | 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]         | 1998–99                   | 1137             | 2 months prior to RRT                                | 45%             | Mortality: 44% ER, 9.1% LR | NA              | Multi-centre study                                                            |
| Goransson [93]     | 1984–98                   | 242              | 3 months prior to RRT                                | 27%             | Mortality: NA             | NA              | 31 days LR, 7 days ER                                                         |
| Lhotta [94]        | 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]           | February 1988–June 2001   | 115              | 6 months prior to RRT                                | 53%             | 5-year follow-up: ER: 72.4%; LR: 35.2% | NA              | Subgroup analysis of type II diabetes                                           |
| Pena [96]          | January 1990 to December 2001 | 178           | 4 months prior to RRT                                | 22%             | Mortality: NA             | NA              | NA                                                                          |
widely differing perceptions of indications for nephrology referral. A few residents chose nephrology referral for proteinuria (45%), uncontrolled hypertension (64%) or hyperkalaemia (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 m² 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 m² (59%), 18% would only do so when eGFR was <5 ml/min/1.73 m².

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 uremic 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 LR: 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’ (MDR) 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 hyperkalaemia, 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 multi-disciplinary 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 ± 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. Winkelmaier 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, in-patient 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 (~$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 multi-disciplinary 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, Thanamoooran 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 uremic complications, attenuation of comorbidity 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=11982809
8. Laneire N, Wauters JP, Teruel JH 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=10008710
9. Obialo CI, Ofili EO, Quanshie A et al. Ultrafiltration 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, Djurdjov 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=1858533
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: 322–328. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19092130
14. Mendelsohn 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.
21. Glassock RJ, Winearls C. The global burden of chronic kidney 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=16431256

22. 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

23. 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

24. MacGregor MS, Boag DE, Innes A. Chronic kidney disease: evolving strategies for detection and management of impaired renal function. *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=16682439

25. 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

26. 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

27. Glassock RJ, Winearls C. CKD in the elderly. *Am J Kidney Dis* 2008; 52: 803–804. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18805350

28. 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=18275457

29. 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

30. 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

31. 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

32. Schwenker 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=16369674

33. Visser A, Dijkstra GJ, Huiteman 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

34. Abdullah 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

35. Ajelbous 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=17650501

36. Van Biesen W, Laneire N, Veys N 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

37. Causer 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

38. 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

39. 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

40. 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

41. 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

42. Avaro J, Winkelmaier 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

43. 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

44. 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

45. 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

46. Sesso R, Bellosico 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, Alhouze 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. 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=15526911

43. Owen JE, Walker RJ, Edgell L et al. 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=14582048

44. Wang L, Deng 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, Mendelsohn DC, Barre PE et al. Predisialysis 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. Ravan P, Mariangeli 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, Glyn RN, Levin R et al. Late referral and mortality risk of death among hemodialysis patients. *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. Passant 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. Mendelsohn 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, Iversen P. How to start the late referred ESRD patient urgently on chronic APD. *Nephrol Dial Transplant* 2006; 21(Suppl 2): i56–i59. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16825263

55. Lobbezode 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, Eastace 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
LR of patients with end-stage renal disease

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 GL 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=10846623

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, Hedhi 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 Med 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, Martín 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. Fiegel W, Hahn K, Kreutz R et al. BENEFIT Kidney—significance of a nephrology screening at intervention outset and therapy success. Desch 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 EDTNA ERCA J 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, Zechl 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=12603509

96. Pena JM, Logrono JM, Permea R et al. Late nephrology referral influence 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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