

Pro and con arguments in using alternative dialysis regimens in the frail and elderly patients

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Abstract In the last decade, an increasing number of patients over 75 years of age are starting renal replacement therapy. Frailty is highly prevalent in elderly patients with end-stage renal disease (ESRD) in the context of the increased prevalence of some ESRD-associated conditions: protein–energy wasting, inflammation, anaemia, acidosis or hormonal disturbances. There are currently no hard data to support guidance on the optimal duration of dialysis for frail/elderly ESRD patients. The current debate is not about starting dialysis or managing conservatory frail ESRD patients, but whether a more intensive regimen once dialysis is initiated (for whatever reasons and circumstances) would improve patients' outcome. The most important issue is that all studies performed with extended/alternative dialysis regimens do not specifically address this particular

type of patients and therefore all the inferences are derived from the general ESRD population. Care planning should be responsive to end-of-life needs whatever the treatment modality. Care in this setting should focus on symptom control and quality of life rather than life extension. We conclude that, similar to the general dialysed population, extensive application of more intensive dialysis schedules is not based on solid evidence. However, after a thorough clinical evaluation, a limited period of a trial of intensive dialysis could be prescribed in more problematic patients.

Keywords Frail · Dialysis · Elderly

Introduction

Since the early 1960s, dialysis therapy sustains life of end-stage renal disease (ESRD) patients [1]. At least in industrialised countries, there is no limitation on access of this therapy based on age or underlying comorbidity. Due to a general increase in life expectancy, the changing epidemiology of cardiovascular disease [2] and, counterintuitively, the implementation of renoprotective strategies, the population of older ESRD patients is increasing. The frail elderly comprise an increasing proportion of the population with advanced kidney disease. They are subject to multiple complex geriatric problems, physical, cognitive and psychosocial. Consequently, the prevalence of frail and elderly patients on dialysis is escalating. Currently, elderly patients represent 16.6–27.4 % of the dialysis population in Japan and Europe, respectively [3].

Dialysis patients are considered as elderly usually when beyond 75 years of age [4, 5]. Frailty in dialysis patients has been defined as a combination of exhaustion, weakness, low physical activity and weight loss [6]

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and is associated with increased hospitalisation and death. Frailty compromises functional status and depletes reserves [27–30]. In a national cohort of incident dialysis patients, Johansen et al. reported that 2/3 of the patients met criteria for frailty, including over 40 % of the patients who were under 40 years of age and over 75 % of patients over age 60 [7]. In addition, these patients had more than a twofold higher risk of death than those who were not frail even multiple adjustments. Therefore, the presence of frailty has a huge impact on the decision whether or not to start renal replacement therapy (RRT) at all. In a recent review, Singh et al. [5] showed that when compared to conservative management a number of patients do not benefit from dialysis therapy in terms of life expectancy and quality of life (QoL). The recent CONSIDER study among nephrologists in Australia and New Zealand showed that patient comorbidities, more than age itself, are the key factor driving the nephrologist's advice to the patient regarding dialysis [8]. However, it is disconcerting that when specifically asked in a study published in 2010, many elderly regret their decision of starting RRT [9] and that dependency after dialysis start has been reported to be very high [10].

What are the goals of dialysis therapy in frail/elderly patients and how to meet them?

The objective of dialysis therapy in frail/elderly is to improve survival and maintain an optimal quality of life (QoL). To ensure QoL, it is important to avoid unpleasant symptoms such as cramps, intradialytic hypotension, headaches, nausea and vomiting and to provide a minimal recovery time after dialysis. To avoid further increase in frailty, adequate nutrition to avoid protein–energy wasting should be aimed for. When aiming at prolonging survival, the major concern is correction of fluid overload, as pulmonary oedema and congestive heart failure are important causes of mortality and morbidity in this patient group [11]. Other outcomes such as bone mineral disease or high blood pressure per se may be less a priority, as they have consequences on the longer term, at a time frame mostly not relevant to the frail and elderly.

Both sides of this pro–con debate agree that frail elderly ESRD patients who are reluctant to start dialysis should be offered the possibility of conservative care. For some frail elderly subgroups, especially those with high comorbidity, poor functional status and high dependency, the survival benefit of dialysis may be limited and, if present, achieved at the cost of increased intrusion, hospitalisation and reduced quality of life (QoL) [34–38]. This position paper deals with the question whether in this patient group we should provide as little dialysis as possible, aiming for prolonged survival, or whether we should initiate for more extended regimens, aiming for optimal dialysis parameters.

The discussion whether or not to start or to withhold dialysis is outside the scope of this paper. As a preliminary statement, it is necessary to underline that no data exist specifically addressing the benefits or drawbacks of extended or alternative dialysis strategies in this category of frail and/or elderly dialysis patients. Therefore, it was opted to compile available expert opinions in a pro–con debate.

Alternative (prolonged slow, daily, nocturnal) dialysis regimens: arguments pro

The rationale of alternative dialysis strategies?

Standard RRT schemes usually include 3 weekly sessions of 4 h, but in fact large differences in session time across countries and continents are reported [12]. Similarly, mortality rates largely differ across continents—higher in the USA and in Western Europe than in Japan [13]. Importantly, many intermediate relevant outcomes, such as tolerance of the dialysis sessions, hypertension, development of left ventricular hypertrophy (LVH) and congestive heart failure, bone mineral metabolism and vascular calcifications, are not altered by standard dialysis. It is hypothesised that many of these are attributable to insufficient removal of middle molecular and protein-bound uraemic toxins. This has led to the development of alternative dialysis strategies—mainly concerning time and frequency—to improve removal of these toxins and therefore patients' outcomes. Although hard data are lacking, it is conceivable that the risk of “underdialysis” is more important in the frail or elderly, because physicians are in fact attempting to prescribe shorter duration, lower blood flow and smaller dialyser area.

Indeed, an improvement in some intermediate outcomes has been reported in uncontrolled or small studies when patients were switched to extended or daily sessions [14]. More recently, the Frequent Haemodialysis Network (FHN) short daily dialysis randomised controlled trial reported better combined outcomes (death and left ventricular hypertrophy; death and physical health composite score) with daily short dialysis versus standard dialysis [15]. These positive effects were, however, counterbalanced by an increased risk of vascular access-related complications. In another case–control study, thrice-weekly nocturnal extended hours dialysis was also associated with a decrease in left ventricular hypertrophy, improved blood pressure control and survival [16]. Besides, there is evidence that increasing time and/or frequency of dialysis may improve patient's condition and well-being (Table 1). Although these studies were not specifically oriented to frail elderly ESRD patients, the rationale to avoid underdialysis could be even more applicable to frail elderly. Uraemic intoxication appears to be

Table 1 Summary of pros and cons of extended dialysis strategies in frail and elderly patients

Pro	Cons
Might reduce intradialytic side effects, mainly hypotension episodes	More time spent in the dialysis unit
Might improve appetite and protein–energy wasting	Longer dialysis recovery time ^b
Might help to maintain euvolaemia and avoid fluid overload	Can prolong the postdialysis recovery time if the number of session is reduced and intensity increased
Might improve cognitive functions and quality of life if the factors mentioned above are achieved	
Improves phosphate control ^a	
Improves blood pressure control ^b	

^a May not be considered by some as a priority because related with long-term outcomes outside the time frame of this patient group

^b Might be confounded by comorbidities as only observational data

proportionally more important in frail patients as the ratio between the metabolic compartment producing the toxins (the visceral mass) and the diffusion space of these toxins is higher in patients with low BMI [17].

Advantages and potential dangers of various dialysis regimens

Studies on session tolerance mostly focus on occurrence of intradialytic hypotension as parameter of interest. Mostly, no data are provided on cramps or gastrointestinal tolerance. Extending dialysis session by 1 h reduces the frequency of hypotension episodes [18]. Whereas the FHN short daily trial did not find a difference in the incidence of hypotension episodes [15], the FHN nocturnal trial and the case–control study by Ok et al. confirmed an improvement in hemodynamic stability with extending the duration of the session [16, 19]. Increasing session time or frequency may be necessary to remove fluid excess without side effects. It can therefore be postulated that extending session duration may improve hemodynamic stability and session comfort in the frail and elderly who are prone for these types of problems.

In a recent DOPPS cohort including 6040 patients, the subjective self-assessment of recovery time was related to both the physical and mental components of QoL and was longer in patients with older age, lower dialysate sodium and, counterintuitively, prolonged session duration [20]. Interpretation of these associations is challenging. For instance, the UF rate relationship with recovery time was

U-shaped with faster recovery in patients with larger UF rate. However, larger interdialytic weight gain and subsequently higher UF rate are observed in fitter patients. Moreover, (longer) duration of the dialysis session may be confounded by indication situation since it is usually prescribed for sicker or unstable patients. Regarding dialysis frequency, daily dialysis has been found to be associated with a significant drop of recovery time [21].

Frail and/or elderly patients are at high risk of protein–energy wasting. Dialysis dose appears important to support adequate nutrition, as sufficient clearance of uraemic toxins interfering with appetite is necessary. There is a linear relationship between protein intake as assessed from 7-day food records and dialysis dose as assessed from urea recovery in dialysate (to avoid mathematical coupling as seen with Kt/V and normalised protein catabolic rate) [22]. DOPPS data support the association between duration and/or frequency of dialysis session and appetite [23]. In a recent study in which the average session time was 6.7 h, age had no independent influence on the weight gain during the first year of haemodialysis therapy, implying that extending the duration of the dialysis session may help to improve nutritional status irrespective of age. In case–control studies comparing standard versus thrice-weekly long-hour treatment, serum albumin was significantly higher in patients treated with the alternative strategy [16, 24].

In the FHN daily trial, opposite to the FHN nocturnal trial [19], the physical health composite score was significantly better after 1 year in the intervention vs the standard group [15]. The Beck Depression Inventory score and the Trail Making Test exploring cognition were unchanged. Ok et al. [16] found an improvement in cognitive functions in nocturnal extended dialysis patients and a stability in QoL, whereas it deteriorated in the conventional treated group. Of note, the mean age in these three studies was much lower than in daily practice, and these improvements may thus not apply to frail and elderly patients. Jassal et al. reported improved cognitive function in elderly patients switched from thrice-weekly to nocturnal regimes [25, 56], though this was not replicated in the FHN studies [26], neither was objective physical performance improved [27]. Ting et al. [28] reported improvement in QoL in the 20 of 42 patients with high comorbidity who, after switching from thrice-weekly to daily treatments, maintained this for 12 months. It remains thus to be proven that more extended dialysis regimens can prevent deterioration, or restore, frailty and independency in elderly patients.

Conclusions—pro side

There are currently no hard data to support guidance on the optimal duration of dialysis for frail/elderly ESRD patients. In patients who tolerate their dialysis session well and

maintain a good appetite and euvoemia, extending duration of the session offers no additional benefit, as the positive effects, if any, of enhanced clearance will only pay off on a much longer time scale. More extended strategies have shown clear clinical advantages, especially for session tolerance, that may be even more present in elderly or frail patients. Extending rather than shortening duration of dialysis can be tried as a strategy to improve QoL, avoid recurrent hypotension episodes, persistent fluid overload or malnutrition in patients who still struggle with these problems after start of dialysis. A trial approach could be introduced for a limited period of time before discussing dialysis withdrawal and palliative care if unsuccessful.

Alternative (prolonged slow, daily, nocturnal) dialysis regimens: arguments against

Rationale of decreased dialysis regimens

Kidney function declines more slowly in older patients, and in those with late stage 4 and stage 5 CKD, the risk of dying exceeds that of surviving to require renal replacement therapy (RRT) [29–31]. For some, therefore, preparations for dialysis may be futile [29, 30]. Frailty increases the susceptibility to the harmful effects of stressors. For such patients, dialysis initiation is an added stressor and may contribute to the functional decline and high mortality typical of the early months of treatment [10, 32, 33]. Travelling for centre-based haemodialysis adds to the burden, reduces QoL and increases mortality risk [34].

Careful multidisciplinary assessment is essential to inform shared decision-making about treatment options [35, 36] and realistic dialysis regimens. Assessment should include measures to identify frailty and its constructs [37]. There is a strong case for carrying out a comprehensive geriatric assessment encompassing comorbidity, cognition, functional status, nutrition, medications and social support networks [38]. Prognostic scores may be informative [39].

Advantages and potential dangers of dialysis

The initiation of dialysis is a potentially dangerous time for elderly frail patients. Haemodialysis initiation is a potent stressor. Mortality is increased in the months following initiation [32], particularly in the more fragile [40]. Functional status is reduced in the more dependent [10]. The incidence of stroke is increased fourfold [41]. Traditionally dialysis practices are particularly intense at initiation. Probing for dry weight involves aggressive ultrafiltration to control blood pressure. This is likely to be poorly tolerated by the frail elderly. The number of sessions complicated

by hypotension can be as high as 15–20 % during the first 4 months [42]. Dialysis-induced myocardial stunning may have potential long-term consequences [43]. Gut hypoperfusion may cause endotoxemia [44]. There may be adverse neurological and cognitive consequences [45, 46]. Furthermore, intensive ultrafiltration can abolish residual kidney function (RKF) [47], which has many beneficial effects in haemodialysis patients [48]. We suggest that, in this patient group, there is a strong case for less intensive rather than more intensive dialysis, especially in the months following initiation. Twice-weekly regimes have been successfully deployed and shown to be associated with similar or improved survival compared with thrice-weekly treatments, probably due to their use in those with better RKF [49–51]. Nutritional status and QoL can be also well maintained [51, 52]. RKF may be better preserved on twice-weekly regimes [53, 54], more intensive regimes being associated with more rapid loss [55]. Twice-weekly regimes have been advocated in the period following dialysis initiation [56, 57] though RKF should be monitored. Likewise, the duration of dialysis schedules may be reduced if RKF is factored into the prescription [48]. Given the limited prognosis on dialysis of the frail elderly, given the adverse consequences of aggressive dialysis regimes in this group, given their lower urea generation rates and lower interdialytic weight gains [58] and given the known benefits of RKF, there is a strong case for less aggressive dialysis strategies in these patients.

There is a need to monitor progress in these patients against attainable treatment goals [59] by regular multidisciplinary review to ensure the benefits of dialysis continue to outweigh the burdens. Treatment plans should be formulated around individual patient-centred preferences and prognosis rather than being dictated by guideline-driven standards [59]. Where there is doubt or lack of consensus about the potential benefits of dialysis, a time-limited trial may be considered [4, 36, 60, 61], though the potential for ensuing loss of residual kidney function (RKF) risks this being a one-way ticket.

In this setting, palliative dialysis can be considered as an aspect of holistic patient care [59, 61, 62]. In this context, palliative dialysis should be understood as performing dialysis sessions only with the intent to alleviate symptoms of uraemia on a short-term basis.

Potential indications

Benefits of more frequent dialysis regimes have been demonstrated, though most studies included younger patients than those receiving conventional in-centre treatments. The mean age of patients in the FHN short hours daily trial was 50 years and in the nocturnal trial 53 years [63]. The

same is true for most reported observational studies [64–67]. Though potential benefits of such regimes have been postulated, the evidence base is slim [68]. There may be specific short-term roles for such therapies such as during periods of intensive rehabilitation [69] or during hospitalisation with intercurrent problems such as fluid overload. However, their role in maintenance therapy for this patient group is likely to be very limited, particularly as an in-centre treatment.

The need for advance care planning

Whatever their treatment modality, the prognosis of the elderly and frail is likely to be poor. Treatment should be tailored to the achievable goals of the patient and carefully monitored [59]. Most such patients have supportive care needs from the outset, which increase over time. It is important to identify, in a timely fashion, those who are approaching the end-of-life phase, whose need is for care rather than life extension. The trigger for this change in focus may be an acute event such as a stroke, multiple hospital admissions or gradual deterioration despite dialysis—often associated with weight loss, hypoalbuminaemia, and cognitive and functional decline. Sensitive discussions with the patient, its family and carers should ensue around advance care planning [70]. Such plans might include de-escalation of dialysis intensity or frequency—palliative dialysis [59, 62, 71]—and perhaps withdrawal from dialysis in favour of a purely palliative approach [72].

Other considerations

The difficulties for frail elderly patients in coping with in-centre haemodialysis regimens have been alluded to and would be amplified by enhanced sessional frequency. Treatment delivery in the patient's home could offset some difficulties, particularly the need to travel, though other problems—such as haemodynamic instability—would remain, and others may be exacerbated—especially those with resource implications. These may be addressed by family or friends helping carry out the treatments, though this is relatively unusual, particularly for extended treatments [73]. There are reports of staff-assisted home haemodialysis being offered to the frail elderly, albeit for brief periods of rehabilitation or end-of-life care [74, 75]. Such support is more common for peritoneal dialysis patients [76].

Recognising the role of healthcare funding and advances in technology

The analysis outlined above is provisional both geographically and temporally. Economic resources vary hugely

across the globe, and in many less developed areas, the availability of RRT is severely restricted for people of all ages—let alone the frail elderly. Treatment options depend on the available resources and the priorities given to their deployment [77]. Similarly, technological progress and innovations in the way technologies are deployed continue to shift the boundaries between what is possible and what is not [78].

Conclusion—con side

The role of alternative dialysis regimens in the treatment of the frail elderly is limited. Where there is difficulty or conflict surrounding therapy choice, a time-limited trial of dialysis may be considered. The belief that intensive HD may prevent the early loss of functionality and high mortality associated with dialysis initiation is difficult to justify. More gentle incremental initiation of dialysis, taking into account loss of residual renal function, and individualisation of treatment aims are likely to be more generally applicable in this population.

There are indications for short-term use of augmented schedules, which include management acute complications, especially fluid overload and support of intensive inpatient rehabilitation where appropriate.

Care planning should be responsive to end-of-life needs whatever the treatment modality. Care in this setting should focus on symptom control and quality of life rather than life extension. This approach might include a reduction in dialysis intensity and/or frequency (palliative dialysis) and dialysis withdrawal (see Fig. 1).

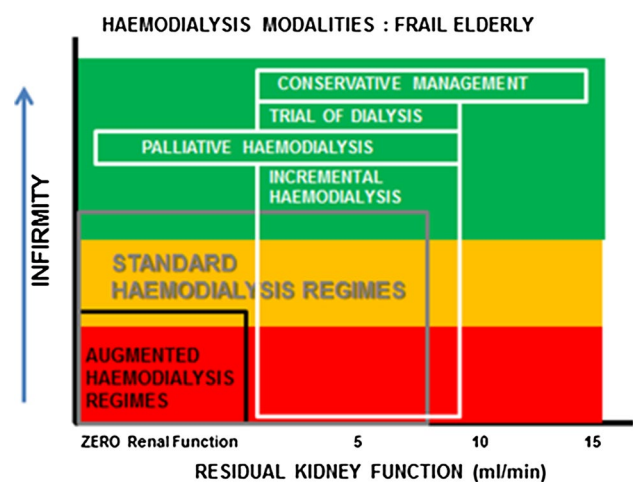


Fig. 1 Haemodialysis modalities most suitable for deployment in the frail elderly. Colours relate to the likelihood of deployment in this population. Green most likely and red least likely

Summary of the pro and con arguments and general discussion

In the last decade, an increasing number of patients over 75 years of age are starting renal replacement therapy [79, 80]. Up to one-third of elderly ESRD patients have four or more chronic health conditions [5], and frailty is common [7]. Frailty can be generally defined as a physiological state of increased vulnerability to stressors that results from decreased physiological reserves and dysregulation of multiple physiological systems [81]. Frailty is highly prevalent in elderly patients with end-stage renal disease (ESRD) in the context of the increased prevalence of some ESRD-associated conditions: protein–energy wasting, inflammation, anaemia, acidosis or hormonal disturbances [82].

As correctly acknowledged by the authors of the pro side, the current debate is not about starting dialysis or managing conservatory frail ESRD patients, but whether a more intensive regimen once dialysis is initiated (for whatever reasons and circumstances) would improve patients' outcome. The most important issue is that all studies performed with extended/alternative dialysis regimens do not specifically address this particular type of patients and therefore all the inferences are derived from the general ESRD population.

To date, data about the effects of intensive dialysis regimens obtained from observational studies are conflicting. The randomised controlled trials (RCT) designed to eliminate the inherent biases of observational studies showed also some inconclusive results.

The issues that arise are related to what we expect to improve in the long term in this elderly and frail population with a more intensive regimen. Improving phosphate control or reducing LVM may not be appropriate goals, as the life expectancy of such patients is too short to observe a beneficial impact of these changes. An improvement in perceived QoL or in cognitive function may be a better goal for these techniques. Although a better control of blood pressure could also be obtained, there is a current disagreement on what actually "normal" blood pressure is, in the elderly, particularly in those with ESRD, and an indication on this basis may not be a correct one. Attention should be also paid to an increase risk of vascular access interventions associated with a more intensive dialysis approach.

In agreement with a recent editorial [83], we conclude that, similar to the general dialysed population, extensive application of more intensive dialysis schedules is not based on solid evidence. However, after a thorough clinical evaluation, a limited period of a trial of intensive dialysis could be prescribed in more problematic patients.

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Compliance with ethical standards

Conflict of interest Charles Chazot, Hanneke Joosten, Daniel Teta and Dimitrie Siritopol have no relevant disclosures. Ken Farrington is the Co-Chair of ERBP Elderly Development Guideline Group. Wim Van Biesen is the Chair of ERBP. Ionut Nistor is a member of the Methods Support Team of ERBP. Adrian Covic is the Co-Chair of ERBP Elderly Development Guideline Group. ERBP is currently in the process of developing a clinical practice guideline on the diagnosis and treatment of frail and elderly patients with advanced chronic kidney disease.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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