Supportive care in advanced chronic kidney disease: Withholding and withdrawing dialysis therapy

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ABSTRACT

Over the latest few decades, dialysis has been offered to older and more complex patients. This treatment can increase the symptom burden and also add new symptoms that can have a profound impact in frail and/or elderly patients with multiple comorbidities. A quality of life approach may be more desirable than a quantity of life approach in these cases. Around the world, some countries have endorsed programs of shared decision-making process and advanced care planning for end-stage renal disease, with creation of goal-directed protocols. Alignment with palliative care programs to develop structured approaches is the key to successful outcomes. Reforms in medical education are needed to address current necessities in these areas. This article summarizes current knowledge regarding decision making and palliative care in end-stage renal disease.

Keywords: dialysis withdraw, time-limited trial, renal palliative care

INTRODUCTION

The prevalence of end-stage kidney disease continues to increase, along with life expectancy. International data shows a high mortality in elderly patients initiating dialysis therapy and the majority had severe chronic illnesses1-4. These patients will probably benefit more from an integrated individual approach prioritizing quality of life instead of a disease approach of prolonging life, frequently with more hospice use and interference with social and family spheres. Adequate shared decision-making process and advanced care planning with proper assessment and management of symptoms are fundamental. In this article, we will discuss the principles and issues related to decisions to forgo dialysis and palliative care of ESRD patients.

ETHICAL PRINCIPLES REGARDING DECISIONS TO FORGO DIALYSIS

The ethical principles of beneficence, non-maleficence, autonomy, justice and professional integrity must undergo all clinical decisions. Considering these principles, the Renal Physicians Association (RPA) published a group of practice guidelines1 that identified some conditions in which is ethical to withhold or withdraw dialysis, many of which were further incorporated in the KDIGO 2015 conference2 on supportive care in CKD:

1. Patients with decision-making capacity who, being fully informed and making voluntary choices refuse dialysis or request discontinuation of therapy.
2. Patients who no longer possess decision-making capacity who have previously indicated refusal of dialysis therapy in an advance oral or written directive.

3. Patients who no longer possess decision-making capacity and whose properly appointed legal agents/surrogates refuse dialysis therapy or request to be discontinued.

4. Patients with irreversible profound neurologic impairment such that they lack signs of though, sensation, purposeful behavior, and awareness of self and environment.

5. It is reasonable to consider not initiating or withdrawing dialysis for patients with acute renal failure or ESRD who have a terminal illness (life expectancy ≤ 6 months) from a nonrenal cause or whose medical condition precludes the technical process of dialysis.

Specifically, nephrologists can only provide treatments that offer reasonable expectation of benefit without unacceptable harm and center them on patient autonomy, implying that the patient (or his legal substitute) is the best person to make his own health care decisions. Dialysis should only be provided if it meets individual goals and if it doesn’t, care should focus on treating symptoms and quality of life. For those requiring dialysis with an uncertain prognosis or for whom a consensus cannot be reached about providing dialysis, nephrologist should consider offering a time-limited trial of dialysis. Regarding withdrawal from dialysis, KDIGO states that this “is ethically and clinically acceptable after a process of shared decision making” but before this, all potentially remedial factors contributing to this decision such as depression, pain or other symptoms, should be addressed as well as the potentially reversible social factors.

### CULTURAL, ETHNIC AND RELIGIOUS CONCERNS

End-of-life care preferences can vary according ethnicity, cultural practices and religious beliefs. A family-centered model of decision making may be preferred and some patients may desire that their community receive and disclose information before a decision is made, even when the patient is competent. Alternatively, resistance to forgo dialysis despite reduced benefit may reflect patient’s need to extend life to fulfill moral duties. In some religions, not starting dialysis may represent a lack of faith in divine intervention. For this, it may be difficult to discuss illness course and prognosis in some cases. Nephrologist and other health care professionals will need to determine how the patient wishes to receive and discuss information and make decisions. Discussions and decisions should occur in a culturally appropriate context and with a cultural appropriate decision-making team.

### LEGAL ASPECTS

Competent patients have the right to consent to or decline a medical treatment. The decision should only be made after a full explanation of diagnosis, prognosis and all treatment options to each patient. According to RPA guidelines, explanation of treatment options should include: (1) available dialysis modalities; (2) not starting dialysis and continuing conservative management which should include end-of-life care; (3) a time-limited trial of dialysis; and (4) stopping dialysis and receiving end-of-life care. Final decision should be informed and voluntary and the medical team must ensure that the patient or his legal agent understand the consequences of the decision. In several countries, an official document with expression of informed consent or refusal must be signed by the patient or his legal agent. In Portugal, the Directorate-General for Health (in Portuguese, Direção-Geral da Saúde) norm 017/2011 includes the Portuguese version of this document that must be signed by all patients with advanced kidney disease, after being properly informed.

Informed consent is a process prescribed by law which has seven elements:

- Threshold elements (preconditions): decision-making capacity, voluntariness
- Information elements: disclosure of material information, recommendation of a plan, understanding the information and recommendation
- Consent elements: decision in favor a plan, authorization of a plan.

Currently, there is concerning discrepancy between legal and current practice. A US study which evaluated older patients on hemodialysis revealed that most of them lacked sufficient understanding of their clinical circumstances. Also, in a group of observation studies, only a minority reported that dialysis initiation was their choice. In a Canadian study, 61% of patients regretted commencing dialysis and 52% of them reported that
it was their physician’s wish and 14% said that is was their family’s wish. Clarifying this issue is of crucial importance to avoid suffer and waste of health resources. If the nephrologist is not sure of a patient’s capacity to make informed consent, this should be confirmed with a formal assessment or referral.

**PRACTICE PATTERNS**

There is a lack of evidence regarding the patterns and frequency of withholding dialysis therapy. The DOPPS (Dialysis Outcomes and Practice Patterns Study) showed a great variance in nephrologist’s practices. According to the Dialysis and Transplant Registration of the Spanish Society of Nephrology, about 60% of the patients with CKD stage 5 do not receive renal replacement therapy due to one of the following reasons: death, lack of clinical suitability for dialysis or the unawareness of the disease. In different Spanish studies, prevalence of CKD stage 5 patients on conservative treatment varied between 8 to 65%, with a mean of 39%.

Recently, in a large USA survey of views and practices patterns of dialysis medical directors towards end-of-life decision-making in ESRD, the majority of respondents felt “very prepared” (66%) or “somewhat prepared” (29%) and most (80%) endorsed a model of shared decision making. If asked to do so, 70% of the respondents provided prognostic information “often” or “nearly always”. For patients with a poor prognosis, 36% of respondents would offer withdrawal from dialysis if patients were already receiving their therapy due to one of the following reasons: death, lack of clinical suitability for dialysis or the unawareness of the disease. In different Spanish studies, prevalence of CKD stage 5 patients on conservative treatment varied between 8 to 65%, with a mean of 39%.

A TLT of dialysis has been considered an acceptable option when there is doubt if the patient will benefit from dialysis, if the patient’s prognosis or response to treatment is uncertain and persistence with burdensome life-prolonging treatments in terminally ill patients was allowed. Only 7% of the respondents reported the occurrence of withdrawal in their dialysis unit and 56% perceived life-prolonging treatments in terminally ill patients was allowed. Only 7% of the respondents reported the occurrence of withdrawal in their dialysis unit and 56% perceived life-prolonging treatments in terminally ill patients was allowed. Only 7% of the respondents reported the occurrence of withdrawal in their dialysis unit and 56% perceived life-prolonging treatments in terminally ill patients was allowed.

**TIME-LIMITED TRIAL OF DIALYSIS**

Time-limited trials (TLT) can be defined as “An agreement between clinicians and patient/surrogate decision-makers to use medical therapies such as mechanical ventilation, enteral feeding, or dialysis over a defined period of time to determine if the patient improves or deteriorates according to agreed-upon clinical outcomes.”

A TLT of dialysis has been considered an acceptable option when there is doubt if the patient will benefit from dialysis, if the patient’s prognosis or response to treatment is uncertain and persistence with burdensome therapies seems undesirable and when a lack of consensus among the medical team and family exists. There are other additional advantages such as alleviating some of the burden experienced by families when asked to choose a treatment in face of uncertainty or offering an opportunity for forecasting a poor prognosis, giving families time to emotionally prepare before the death of a love one and helping to avoid professional conflicts between the medical team and patient/family. However, a TLT is appropriate only when there is a reasonable chance that dialysis therapy will have a net benefit for patient and that patient’s goals are achieved.

When a trial is implemented, it is necessary to establish clear parameters and timelines in order to determine at the end of the trial if dialysis therapy should be continued or not. Quill and Holloway proposed a five-step framework for the management of a time-limited trial (Table 1). To be effective, a written contract between both the physician and the patient/legal agent should be drawn up and signed. In this document should list the patient’s current clinical condition and the duration of TLT with clear goals that must be met for dialysis to be continued. If the goals are not reached, dialysis is discontinued and aggressive palliative care is provided. This document, despite the difficulty
of achievement in clinical practice, helps to overcome possible conflicts between dysfunctional families with non-adherence to TLT or families who “want everything done” and the nephrologist and when there is no consensus in medical team15,16.

### When to start and when to stop the Trial

Deciding when to begin the trial is a complex and difficult decision. Although previously there was a trend to start dialysis early (eGFR > 10 ml/min/1.73 m²), evidence from recent years including the IDEAL (Initiating Dialysis Early and Late) trial showed no benefit of an early start4,18. Rosansky et al18 suggested that the severity of CKD may be overdiagnosed in elderly or very ill patients based on inaccuracies in eGFR estimation and this may result in unnecessary dialysis initiation. O’Hare et al19, using data from the Veterans Administration population, reported that elderly have slower progression of CKD and most are more likely to die than progress to end-stage kidney disease (ESRD). This mortality competing risk becomes more notable with ageing, with <1% of elderly with CKD progressing to a final state and subsequent dialysis each year4. Some authors have suggested that elderly patients with CKD will benefit more from an individualized approach with maximization of quality of life instead the traditional disease approach2-4.

### Table 1

<table>
<thead>
<tr>
<th>Key - Elements</th>
<th>Major Issues</th>
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<tbody>
<tr>
<td>Define clinical problems and prognosis</td>
<td>Achievement of consensus</td>
</tr>
<tr>
<td>Identify the patient’s goals and life values</td>
<td>Establishment of limits to invasive treatments</td>
</tr>
<tr>
<td>Clarify clinical measures of improvement or treatment failure</td>
<td>Previous advanced care planning decisions</td>
</tr>
<tr>
<td>Defining a Time Frame</td>
<td>Schedule regular meetings for update</td>
</tr>
<tr>
<td>Identify possible consequences at the conclusion of the time-limited trial</td>
<td>Consider a written contract signed by all parties and list symptoms, functional status, nutritional parameters, and comorbid conditions at initiation.</td>
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### Table 2

<table>
<thead>
<tr>
<th>Issue</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Nutritional issues</td>
<td>Poor appetite, weight loss, sarcopenia and fatigue may improve initially after dialysis start</td>
<td>Sarcopenia may posteriorly worsen and post-dialysis fatigue may be disabling.</td>
</tr>
<tr>
<td>Cognitive impairment and Depression</td>
<td>May initially improve with clearance of uremic toxins and reduction of drug burden</td>
<td>Incepient dementia and isquemic leukoencephalopathy will worsen with treatment.</td>
</tr>
<tr>
<td>Frailty and Falls</td>
<td>May initially improve with clearance of uremic toxins and reduction of drug burden. Intradialytic exercise programs can improve muscle strength.</td>
<td>Worsening of inflammatory state, sarcopenia and fatigue augments the risk of falls. There is loss of independence and functional status.</td>
</tr>
<tr>
<td>Hypervolemia</td>
<td>Refractory fluid overload related with heart and liver failure may improve with earlier dialysis start</td>
<td>Risk of hypotension and its’s isquemic consequences. Loss of RRF. No survival benefit.</td>
</tr>
<tr>
<td>Residual Renal Function (RRF)</td>
<td>RRF is associated with survival benefits superior to dialysis, even at levels below 5 ml/min/1.73m²</td>
<td>About 10% loss of endogenous renal function per month after dialysis start.</td>
</tr>
<tr>
<td>Vascular Access</td>
<td>Fistula is the best access for avoiding life-threatening complications, especially infections</td>
<td>Acquisition of a puncturable fistula may be a prolonged process with multiple surgical procedures. Catheter for a short period of time can be considered.</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Both PD and HD have similar results regarding quality of life, with no proven benefit of one technique over another.</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>No survival benefit for early start (eGFR &gt; 10 ml/min/1.73m²) or worse survival by delaying until eGFR 5 to 8 ml/min/1.73m², even if development of symptoms. Life expectancy can be estimated with several prognostic tools.</td>
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Moreover, when forthcoming the decision to start dialytic therapy and TLT, some aspects should be provided and pondered before reaching a decision (Table 2). Regular symptom assessment using scales and prognostic tools may help to estimate trajectory illness and find the point in which the benefit of dialysis will overcome the risks\(^2\). Adhesion to medical regime is also essential for proper management\(^2-4\).

The usual duration of a TLT in context of acute deterioration of renal function is few days to 2 weeks and 1-3 months for ESRD. Specific pause point for clinical re-evaluation are important to check for accomplishment of goals and identification of burdens and sentinel events that may indicate more benefit to specialized services such palliative care, with an eventually early termination of trial. If at the completion of the first trial the treatment outcomes remain uncertain and/or if doubt is regarding the achievement of patient’s goals, is licit to perform another trial\(^16\). Unfortunately, there is no information about the frequency or outcomes of TLT.

### Choice of dialysis modality

Patients who reach TLT are usually older and/or with greater number of comorbidities, risk of cognitive dysfunction and higher levels of frailty\(^4,20\). There are few studies who addressed dialysis outcomes in this group of patients. Given the social burden of and propensity for functional limitations, the self-care dialysis treatment options are most limited\(^20\). In the United States, only 2.5% of patients aged >65 years are on PD\(^21\). The numbers are better in Europe, about 10 – 15%\(^20,21\).

HD is challenging for these patients especially because of hypotension and negative impact on myocardial and cerebral functioning, risks of increasing inflammatory markers, the complexity of creating and maintaining a vascular access, post-dialysis recovery time and the risk of falls after dialysis\(^20\). Transportation issues may interfere with social and family life. However, there is also a social structure related to dialysis unit, with regular medical review when attending treatments and the procedure is done by others. Other advantages of HD are related with efficient solute and volume removal particularly in anuric patients, limited time spent of dialysis and freedom for the patient and his family form involvement with dialysis procedure itself\(^20\). Otherwise, the main advantage of PD is the possibility of home-based therapies, with flexibility of treatments especially if there is some RRF left and avoidance of multiple visits to hospital or clinic regardless of whether and how the patient is feeling\(^20\). Assisted PD can overcome functional and sensorial impairment barriers. With planning and appropriate information there is no evidence of PD-related complications being more common in these patients\(^20\). PD seems to confer less risk for dementia, hemorrhagic stroke and subdural hematomas, despite equivalent risk of falls. Outcomes of survival and quality of life are similar between two techniques at least at 6 and 12 months\(^20,22,23\).

Considering this, the optimal modality for TLT is individualized according to patient and family characteristic and wishes.

### Dialysis dosage

The amount of dialysis that should be prescribed for patients on TLT has not yet been defined. The updated KDOQI guidelines\(^24\) generally suggest a minimal target of Kt/V urea of 1.2 per HD treatment given 3 times per week. More frequent treatments (5-7 per week) have been shown to reduce recovery time, respiratory distress and sleep disorders and to improve cardiovascular function and quality of life but in a long-term way (12 months)\(^25\). In short-term, more frequent treatments may enable better rehabilitation. However, treatment burden and access issues must be balanced\(^20\). For patients with RRF, a customized approach with shorter periods of treatment time or only 2 times per week as part of an incremental hemodialysis regime has been shown to improve results\(^20\). Calculation of PD clearance already includes RRF, enabling also an incremental increase in PD prescription as renal function declines, besides flexibility of treatment (automatic versus continuous ambulatory PD)\(^20\). Like the modality chosen, the optimal dialytic regimen for TLT is individualized and upgraded according to patient characteristics and results.

### THE CONCEPT OF PALLIATIVE DIALYSIS

A palliative approach to dialysis can be defined as a transition from a disease-oriented focus on dialysis as rehabilitative treatment to an approach prioritizing comfort and alignment with patient’s preferences and goals to improve quality of life and reduce symptom burden for maintenance dialysis patients in their final year of life. This transition aligns generally with palliative care. Table 3 summarizes the major sentinel events signalizing this period\(^26-31\).
A central venous catheter can be acceptable, as also lower clearances if changes in dialysis prescription increase demands inconsistent with patient preference. Hypertension can be tolerated to avoid symptoms, no indication for dyslipidemia treatment. Reduction of dietary restrictions (with more permissive hyperphosphatemia) can have a major impact in quality of life. Laboratory monitoring should be the minimal necessary.26

It is important to note that palliative dialysis is not equivalent to less dialysis or a precursor to withdrawal of dialysis because this alone will not reduce symptoms or suffering of patients. Less dialysis rarely provides benefits and can aggravate symptoms and post-dialysis fatigue, especially if greater ultrafiltration is needed. Also, alterations in dosing and timing of dialysis session can affect the patient. For example, stress associated with rushing for an earlier or later dialysis session or change in eating patterns when attending dialysis. Engaging families in frequent discussions will help to identify conditions that can be optimized. Even minor issues like small changes in dialysis schedule or location may improve wellbeing and dialysis tolerance.27

### Table 3

<table>
<thead>
<tr>
<th>Major sentinel signs of end-of-life period26-31</th>
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<tr>
<td>Poor appetite and weight loss &gt; 10% in 6 months</td>
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<tr>
<td>Hypoalbuminemia</td>
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<tr>
<td>Total dependency for daily live activities</td>
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<tr>
<td>Unplanned dialysis</td>
</tr>
<tr>
<td>Increased hypertensive episodes</td>
</tr>
<tr>
<td>Increased intolerance to dialysis</td>
</tr>
<tr>
<td>Two or more non elective admissions in last 3 months</td>
</tr>
<tr>
<td>Active malignancy</td>
</tr>
</tbody>
</table>

Figure 1
Spectrum of symptoms in ESRD28

(A) – Conservative Treatment and Dialysis; (B) – When withdraw from dialysis
PALLIATIVE/SUPPORTIVE CARE

Palliative care should be offered to all patients with ESRD, despite decision to withhold or withdraw from dialysis. The evolving concept of palliative care is the providence of support through the course of a person’s chronic disease rather just at the end of life.

Symptom burden and management in ESRD

The symptom burden is similar to that of patients with terminal heart failure or cancer. Figure 1 presents the prevalence of major symptoms in renal disease. Figure 2 resumes the non-pharmacologic and pharmacologic approaches to major symptoms (made by the authors).

Fatigue is frequent and disabling in ESRD patients. Usually is described as a complex and poor defined constellation of symptoms like physical sleepiness, lack of energy, lethargy and weakness, being closely related with depressive symptoms. Causes that may contribute to fatigue are anemia, inadequate dialysis, post-dialysis fatigue and efforts associated with attending dialysis sessions or hospital visits. Other modifiable contributing factors are vitamin D deficiency, metabolic acidosis, tertiary hyperparathyroidism, hypothyroid, mood disorders; sleep disorders, malnutrition and polypharmacy.

Evidence regarding treatment is driven from palliative studies in other settings, since ESRD patients are usually excluded. Evidence from cancer literature suggests a benefit with use of methylphenidate 5 mg per day (can be increased up to 20 mg per day). However, adverse effects related with appetite reduction may increase malnutrition and lead to further frailty. Some authors recommend fluoxetine 20 mg or sertraline 50 mg orally per day. More safe approaches are psychotherapy, correction of modifiable factors, reduction of post-dialysis fatigue (e.g. increased frequency).

Figure 2

Nonpharmacological (blue) and pharmacological treatment of major symptoms in ESKD.
Pruritus and itchy skin are also one of the most bothersome symptoms, with significant impact in quality of life and related with poor sleep and depression. The causes are multifactorial: anemia, iron deficiency, hypercalcemia, hyperphosphatemia and other uremic toxins, xerosis, allergies, drug sensitivities and contact dermatitis. The highest levels of evidence for efficacy are for topical agents, oral medications and ultraviolet B therapy. Topical emollients are first-line therapies; they should be water-based and be fragrance and additive free. They should be applied 2-3 times daily. Agents that help to cool skin such as a fan or topical camphor/menthol, especially at night, also have good results. Other topical therapies such as gamma-linolenic acid 2.2% cream applied twice daily, capsaicin 0.025% or 0.03% applied 2-4 times daily may be valuable adjuncts. Oral medications should be considered if the above is not effective and pruritus is affecting quality of life. Low-dose gabapentin starting at 50-100 mg post-dialysis or second-line doxepin 10 mg nightly are good options. Mirtazapine reduces central sensitization to itch and is also an option, starting dose of 15 mg daily. Antihistamines do not reduce uremic pruritus; however, the sedative effect may help with sleep disturbance. There is some evidence for ondansetron 4 mg orally every 8 hours or naloxone 50 mg orally per day31. Other therapies with less evidence include UVB phototherapy 3 times per week and acupuncture2,27,28.

Breathlessness/shortness of breath is very distressful for ESRD patients. Major causes are anemia, hypervolemia with pulmonary edema and metabolic acidosis. Correction of these modifiable factors with medical therapy (erythropoiesis-stimulating agents, diuretics and sodium bicarbonate) or adjustment in dialysis prescription with ultrafiltration intensification may be needed. Encouragement of physical activity in selected cases might be helpful2,27,28. If anxiety is a significant component, low-dose benzodiazepines such as lorazepam or diazepam may be helpful. Domiciliary oxygen may be needed, especially in cases of advanced pulmonary disease27. Low dose opioids can also be given, but should be chosen carefully and monitored to avoid toxicity2,28.

Sleep disorders are common and mostly secondary to restless leg syndrome (RLS), pruritus, pain, dyspnea, mood disorders, obstructive sleep apnea and certain medications. Non-pharmacologic treatment should be considered first, like relaxation therapy or cognitive behavioral therapies, promotion of sleep hygiene (avoid napping during the day, reduce stimulants such as caffeine, alcohol and nicotine). If those are unsuccessful, consider low-dose gabapentin post-dialysis, melatonin, zolpidem 5-10 mg nightly, doxepin 10 mg nightly or temazepam 15 mg orally at bedtime28,31. Management of secondary causes is fundamental.

Restless leg syndrome (RLS) is particularly common in dialysis patients, reaching a prevalence of 10-20%. About 80% of affected patients also have the sleep disorder periodic limb movements. Besides reducing quality of life, RLS is also associated with increased cardiovascular morbidity and mortality. Specific cause is unknown2,27-32. Modifiable contributing factors have been identified: anemia, iron deficiency, hyperphosphatemia and medications such as dopamine antagonists, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, calcium channel blockers, opioids. Consider nonpharmacologic therapy first, like intradialytic aerobic exercise, removal of stimulants and dopamine antagonists, good sleep hygiene, pneumatic compression devices and correction of modifiable factors. If unsuccessful, low-dose gabapentin or pregabalin (25 mg) after dialysis may help and second-line options include dopamine agonists such as levodopa 50-200 mg nightly, ropinirole 0.25-3 mg/day and pramipexole 0.125-0.5 mg nightly. Clonazepam 0.5-2 mg/day nightly can also improve symptoms, mainly because of a sedative effect27-31.

Refractory Cramps, also common in these patients, can be managed with quinine sulphate 200-300 mg nightly31.

Depressive symptoms occur frequently along the entire spectrum of CKD. Lifetime risk of depression in these patients is about 39% compared with 7% in general population27. Depression augments the risk of hospitalization, mortality and withdrawal from dialysis. Usually is associated with other symptoms like pain, poor sleep and pruritus that have to be managed. More frequent dialysis, cognitive behavioral therapy and exercise programs are the major nonpharmacological options. Antidepressants like fluoxetine 20-40 mg, sertraline 50-100 mg, paroxetine10-40 mg, escitalopram 10-20 mg daily can be effective drugs in these patients27,31. Tricyclic antidepressants are usually poorly tolerated and abuse of benzodiazepines increases mortality risk.
Gastrointestinal symptoms like anorexia, nausea, vomiting, constipation and diarrhea are also frequent in ESRD patients. Uremia is a powerful nausea inductor and contributes to gastrointestinal hypomotility, which can be aggravated by diabetes mellitus. Many drugs used commonly in CKD like phosphate binders, iron, vitamin D analogues, antibiotics or antidepressants can induce gastrointestinal intolerance. Good oral hygiene and smaller but frequent meals cooked simply without excessive grease, spice and sweetness can improve symptoms. Applying a cool, damp cloth to forehead or nape of neck and loose-fitting clothing can also help. Useful drugs are metoclopramide 2.5 mg PO/SC 4/4 hours, domperidone orally 10 mg 2-3 times daily if intolerance to metoclopramide, ondansetron 4 mg orally 8/8 hours, haloperidol 0.5 mg PO/SC 4/4 hours, olanzapine 2.5 mg PO 4/4hours. If usual antiemetics are ineffective, levopromazine 6 mg PO/SC once daily may be tried.27-31.

Anorexia has been associated with malnutrition, weight loss, fatigue and falls, with greater hospitalization rates and mortality. Adequate dialysis should be ensured, dry mouth (salivix pastilles) and gastroparesia treatment should be managed. Consider mirtazapine 15 – 50 mg/day, dronabinol 2.5 mg orally before meals, megestrol 400 mg or prednisolone 10 mg orally per day29-32.

### Figure 3
Nonpharmacological (blue) and pharmacological treatment of major symptoms in ESKD

| 1) Paracetamol 1 g 8/8 hours (Ben-U-Ron ®) |
| 2) Weak Opiods |
| ➢ Tramadol 50 mg 12/12 hours (Tramal ®) |
| ➢ Buprenorphine Patch 5 µ/hr (max. 15µ/hr) to change/titulate every 4 - 7 days (Transtec ®; Ramatrix ®) |
| 3) Strong Opiods |
| ➢ Hydromorphone (Jurnista ®) 1.3 mg orally, titrate 4/4 – 8/8 hr. |
| If continuous pain administer 1.3 mg hourly. |
| ➢ Oxycodone (Targin ®) 1 mg orally 12/12hours, titrate to 5 mg 8/8 hr. |

If tolerated over at least 24 hours, then convert to or add fentanyl patch 12 µg/hr to change every 3 days and titrate up. For breakthrough pain, administer hydromorphone 1.3 mg, oxycodon 1 mg, bucal/sublingual fentanil 200 mcg (Abstral ®, Actiq ®), with a second dose separated for 30 minutes if necessary.

| ADJUVANT AGENTS |
| Can be used at any stage of the WHO ladder according to specific type of pain |

| Musculoskeletal pain |
| NSAIDs - should be avoided in patients with some renal function left, except if is the only way of symptom control |

| Colic |
| Hyoscine Butylbromide (Buscopan ®) start with 20 mg and up to 240 mg/24 hr |

| Neuropathic Pain |
| Clonazepam (Rivotril ®) - 0.5 mg per 12/12hr |
| Amitriptyline (Adt ®) - start with 10 mg, titrate up according to tolerance (maximum 150 mg) |
| Gabapentin - start with 25 mg and titrate up according to tolerance (maximum 300 mg) |
| Pregabalin - start with 50 mg, titrate up according to tolerance (maximum 150 - 300 mg) |
Pain is well documented in more than 50\% of CKD patients. There are five types of pain: renal-specific pain (polycystic kidneys, amyloid, and calciphylaxis), dialysis-specific pain (steel syndrome, headache, fistula problems, and abdominal pain from PD), musculoskeletal pain (renal osteodystrophy, muscle spasms and cramps, carpal tunnel syndrome), neuropathic pain (renal or diabetic neuropathy) and ischemic pain (peripheral vascular disease, vasculitis). Exercise, cognitive and psychological approaches can minore pain sensation. A step-wise approach to analgesics such as outlined in World Health Organization (WHO) Analgesic Ladder is recommended. Analgesic selection, initial dosing and titration must be individualized and according to type of pain\textsuperscript{27,32} (Figure 3 – proposed by the authors, based on WHO Analgesic Ladder and Gloucestershire NHS Foundation Hospitals – Guidelines for End of Life Care in Advanced Kidney Disease). Before starting chronic opioid therapy (moderate to severe pain), risks of substance abuse, misuse or addiction should be addressed. Morphone, codeine, meperidine and propoxyphene have neurotoxic metabolites that are excreted by the kidneys and that accumulate in CKD with a high likelihood of toxicity, and are not recommended as a first line\textsuperscript{27-32}.

\section*{Last days of life}

Patients should be given the choice to die at home with hospice care or wherever they prefer, if there is sufficient and appropriate support to enable this option. When a patient decides to withdraw from dialysis, it is important to prepare him and his family that survival average is 7.4 days (range 0 – 40). A specialist in palliative care is fundamental in this process. Agitation and confusion are best managed using a combination of haloperidol and a benzodiazepine. Pain is better addressed with intravenous or subcutaneous opioids. Dyspnea can be relieved with oxygen, bronchodilators and a combination of low dose opioids and short-acting benzodiazepines like midazolam to decrease respiratory effort. Respiratory tract secretions can be reduced with use of hyoscine butylbromide and glycopyrronium. Haloperidol can be used to treat myoclonus, nausea and vomiting, ondansetron is also effective for nausea and uremic pruritus. Bereavement support should also be offered to patients’ families\textsuperscript{27,28-32}.

\section*{CONCLUSIONS}

The scenario of withholding and withdrawing dialysis will become increasingly more frequent in the near future, since the ESRD patient is now typically elderly with multiple comorbidities and life expectancy is increasingly growing. Nephrologists are poorly prepared to deal with end of life decisions and to engage in shared decision making and advanced care planning. Efforts in medical education and creation of specialized programs and protocols with palliative care team are essential towards a better medical care and fulfillment of patient, family and also the doctor’s goals and perspectives.

\section*{Acknowledgments}

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\section*{Disclosure of potential conflicts of interest}

The authors disclose no conflicts of interest.

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\begin{enumerate}
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