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Novel conservative management of chronic kidney disease via dialysis-free interventions

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Purpose of review
In advanced chronic kidney disease (CKD) patients with progressive uremia, dialysis has traditionally been the dominant treatment paradigm. However, there is increasing interest in conservative and preservative management of kidney function as alternative patient-centered treatment approaches in this population.

Recent findings
The primary objectives of conservative nondialytic management include optimization of quality of life and treating symptoms of end-stage renal disease (ESRD). Dietetic-nutritional therapy can be a cornerstone in the conservative management of CKD by reducing glomerular hyperfiltration, uremic toxin generation, metabolic acidosis, and phosphorus burden. Given the high symptom burden of advanced CKD patients, routine symptom assessment using validated tools should be an integral component of their treatment. As dialysis has variable effects in ameliorating symptoms, palliative care may be needed to manage symptoms such as pain, fatigue/lethargy, anorexia, and anxiety/depression. There are also emerging treatments that utilize intestinal (e.g., diarrhea induction, colonic dialysis, oral sorbents, gut microbiota modulation) and dermatologic pathways (e.g., perspiration reduction) to reduce uremic toxin burden.

Summary
As dialysis may not confer better survival nor improved patient-centered outcomes in certain patients, conservative management is a viable treatment option in the advanced CKD population.

Keywords
conservative management, low-protein diet, palliative care, symptom management, uremia

INTRODUCTION

In advanced chronic kidney disease (CKD) patients with progressive uremia, dialysis has traditionally been the dominant treatment paradigm among those ineligible for or unlikely to receive kidney transplantation [1,2,3▪,4]. However, there has been increasing interest in *conservative management*, defined as the active medical management of kidney failure without dialysis, as an alternative patient-centered treatment approach in this population. Given that dialysis may not confer better survival nor improved outcomes in certain patients (i.e., elderly, high comorbidity burden, poor functional status) [5–8], conservative nondialytic management may indeed serve as a viable treatment option in these subgroups.

There has also been growing recognition of the importance of preservation of kidney function, known as preservative management, upon the health and survival of advanced CKD patients progressing to end-stage renal disease (ESRD) [3▪,4]. One of the integral components of *preservative management* includes nutritional interventions such as dietary protein restriction and prioritization of plant-based proteins to ameliorate kidney function decline in the CKD population [9,10,11▪,12▪]. As patients with advanced CKD experience a high burden of physical and mental symptoms that may adversely impact health-related quality of life [13–16], a core aspect of conservative and preservative management is the treatment of symptoms using nondialytic approaches, including palliative care

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KEY POINTS

- Conservative management require a multidisciplinary approach that includes dietetic nutritional therapy, medical interventions that preserve kidney function, proactive symptom management, uremia management without dialysis, and psychological support.
- While dietetic nutritional therapy, including dietary protein restriction and consumption of plant-based proteins, can ameliorate glomerular filtration rate decline and mitigate the symptoms of CKD in the conservative management, less than 10% of adults with CKD receive any dietary counseling prior to initiation of dialysis.
- Routine symptom assessment and nondialytic management approaches using palliative care should be integrated into the treatment of advanced CKD and ESRD patients.
- Emerging data suggest that intestinal and dermatologic pathways, including diarrhea induction, colonic dialysis, oral sorbents, gut microbiota modulation, and stimulation of perspiration, can be used to reduce uremic toxin burden in advanced CKD patients progressing to ESRD.

[1,3▪,13,17] as well as innovative interventions for uremia that utilize nonrenal pathways (i.e., intestinal, dermatologic) [18,19]. In this Review, we summarize the current evidence regarding nutritional interventions used to preserve kidney function, the concepts of preservative and conservative CKD management, symptom management and other palliative approaches in advanced CKD, and emerging and novel treatments for uremia.

CONSERVATIVE KIDNEY MANAGEMENT OF CHRONIC KIDNEY DISEASE

The primary objectives of conservative-dialytic management include optimization of patients' health-related quality of life, treating symptoms of ESRD without dialysis or transplant, and maintaining remaining kidney function as long as possible [1,4,20,21]. To this end, conservative management requires a multidisciplinary approach that provides nutritional care as described below, medical interventions that preserve kidney function, proactive symptom management, uremia management without dialysis, and psychological support.

In 2013, an international panel of experts convened for a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference in Supportive Care in CKD in which they summarized the current state of evidence with respect to conservative care [1]. The workgroup underscored the lack of a clear definition for conservative management that has hindered its broader implementation in the advanced CKD population, and thus proposed a detailed and specific definition of 'comprehensive conservative care' as 'planned holistic patient-centered care for patients with glomerular filtration rate category (G) 5 CKD that includes interventions to delay progression of kidney disease and minimize risk of adverse events or complications, shared decision making, active symptom management, detailed communication including advance care planning, psychological support, social and family support, and cultural and spiritual domains of care.' Whereas conservative care programs are more prevalent in parts of Europe, Australia, Asia, and Canada, nondialytic management for advanced CKD still remains underutilized because of inadequate training, financial systems that do not incentivize supportive care metrics, and misperceptions that conservative care equates to 'no care' or 'lack of care' [1,4,15]. Indeed, as a form of 'active medical management' and 'comprehensive' care, conservative dialysis-free management may warrant more attentive and frequent treatment of uremic, biochemical, and volume derangements as compared with dialysis and kidney transplantation.

While there are major knowledge gaps regarding the comparative effectiveness of conservative management vs. dialysis, a growing number of studies have examined the implementation of nondialytic treatment of CKD in parts of the world [5–8,22–30]. Although survival is expected to be longer for advanced CKD patients undergoing treatment with renal replacement therapy in the form of dialysis or kidney transplantation vs. conservative management, limited data suggest that the survival benefit of dialysis vs. conservative management is marginal or even reversed in certain subpopulations, such as those of elderly age, multimorbid conditions, and with underlying cardiovascular disease (Table 1) [5–8]. For example in a study of elderly patients with stage 5 CKD who underwent conservative management vs. dialysis in the United Kingdom, 1 and 2-year survival were greater for dialysis in the overall cohort; however, among patients with higher comorbidity scores or ischemic heart disease, the survival of those undergoing conservative management vs. dialysis were equivalent [7]. In another UK study of stage 5 CKD patients, the survival advantage of dialysis vs. conservative management was also mitigated in those of elder age (i.e., >75 years old) after accounting for age and comorbidity status [5]. In a more recent analysis of advanced CKD patients from the Netherlands, the survival advantage of dialysis was reduced or mitigated in elderly patients (≥ 70 and ≥ 80 years, respectively) and

Table 1. Selected epidemiologic studies of conservative nondialytic management vs. dialysis

Reference	Study population, *N*	Country	Outcomes	Key findings
Joly *et al.* [25]	≥80 years with CrCl < 10 ml/min, *N* = 146	France	Survival	Median survival of conservative management vs. dialysis: 8.9 vs. 28.9 months
Murtagh *et al.* [7]	>75 years with stage 5 CKD, *N* = 129	United Kingdom	Survival	Survival equivalent in patients with high comorbidity burden or ischemic heart disease
Carson *et al.* [23]	>70 years with ESRD, *N* = 202	United Kingdom	Survival and hospitalization	Median survival of conservative management vs. dialysis: 13.9 vs. 37.8 months Hospitalization rates higher for dialysis vs. conservative management
Chandna *et al.* [5]	Stage 5 CKD, *N* = 844	United Kingdom	Survival	Median survival of conservative management vs. dialysis: 21.2 vs. 67.1 months In patients >75 years of age, survival advantage of dialysis attenuated to ~4 months after accounting for differences in age and comorbidity burden
Da Silva-Gane *et al.* [24]	Late stage 4 and 5 CKD from 'Low Clearance Clinics,' *N* = 170	United Kingdom	Survival and HRQOL	Adjusted median survival of conservative management vs. dialysis: 913 vs. 1317 days HRQOL scores stable over time with conservative management, but declined with dialysis
Shum *et al.* [29]	≥65 years with stage 5 CKD, *N* = 199	China	Survival, ED visits, hospitalization, institutionalization	Survival of conservative management vs. PD: 2.35 vs. 3.75 years ED-hospitalization rate of conservative management vs. PD: 3.51 vs. 1.63 events per person-years Hospitalization days of conservative management vs. PD: 38.0 vs. 16.2 days per person-years No difference in institutionalization between conservative management vs. PD
Brown *et al.* [22]	Stage 4–5 CKD with renal supportive care without dialysis vs. planning or commencing dialysis, *N* = 567	Australia	Symptoms, HRQOL, and survival	Survival in renal supportive care patients: *Median survival 12 months* Symptoms: *No difference in symptom trajectory in renal supportive care or predialysis patients* HRQOL *No difference in trajectory of Physical or Mental Component Scores in renal supportive care or predialysis patients*
Teruel *et al.* [30]	Stage 5 CKD, *N* = 232	Spain	Survival	>70 years with ESRD, *N* = 202
Verberne *et al.* [8]	≥70 years with advanced CKD, *N* = 311	The Netherlands	Survival	Median survival of conservative management vs. dialysis: 1.5 vs. 3.1 years Survival advantage of dialysis attenuated in patients ≥80 years, with higher comorbidity burden, or cardiovascular disease
Kurella *et al.* [26]	Veterans with eGFR < 30 ml/min/1.73 m^2, *N* = 73 349	The United States	Survival	Among patients initiating dialysis at eGFR 9–<12 ml/min/1.73 m^2, difference in median life expectancy <1 year

CKD, chronic kidney disease; CrCl, creatinine clearance; ED, emergency department; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HRQOL, health-related quality of life; PD, peritoneal dialysis.

reduced in those with higher comorbidity burden or cardiovascular disease [8]. Finally, in a US study of elderly males with stage 3–5 CKD, the impact of nondialytic vs. dialytic management upon survival was found to be modified by age and estimated glomerular filtration rate (eGFR) by dialysis initiation [26]. Notably, among patients initiating dialysis at eGFRs 9 to less than 12 ml/min/1.73 m^2, the difference in median life expectancy was less than 1 year as compared with nondialytic treatment. While data examining the impact of nondialytic management upon patient-centered outcomes are sparse, one recent pooled analysis of 1718 patients across 11 observational studies suggested that conservative care has the potential to achieve similar health-related quality of life and symptoms as compared with dialysis [31▪].

Preservative management is also a critical adjunct of conservative nondialytic management (Fig. 1). In addition to the dietary interventions detailed below (e.g., dietary protein restriction), approaches used to delay the progression to ESRD and its uremic complications include cautious blood pressure (BP) management (i.e., averting hypertension and relative hypotension), avoidance of nephrotoxins, and utilization of traditional and novel pharmacotherapies that can avert life-threatening electrolyte complications (e.g., sodium bicarbonate, potassium binders). Appreciation of the potential benefits of conservative management also brings clarity to the misperception that patients with terminal kidney failure only have two dichotomous treatment options, that is, dialysis vs. hospice without dialysis [3▪]. For example, given the burdensome nature of thrice-weekly hemodialysis upon patients and their care partners, even among those who eventually pursue this life-prolonging pathway, delaying the progression to ESRD with conservative management provides an opportunity to enhance patients' overall well being and survival. In addition, utilizing conservative management in the treatment of the incident and prevalent ESRD

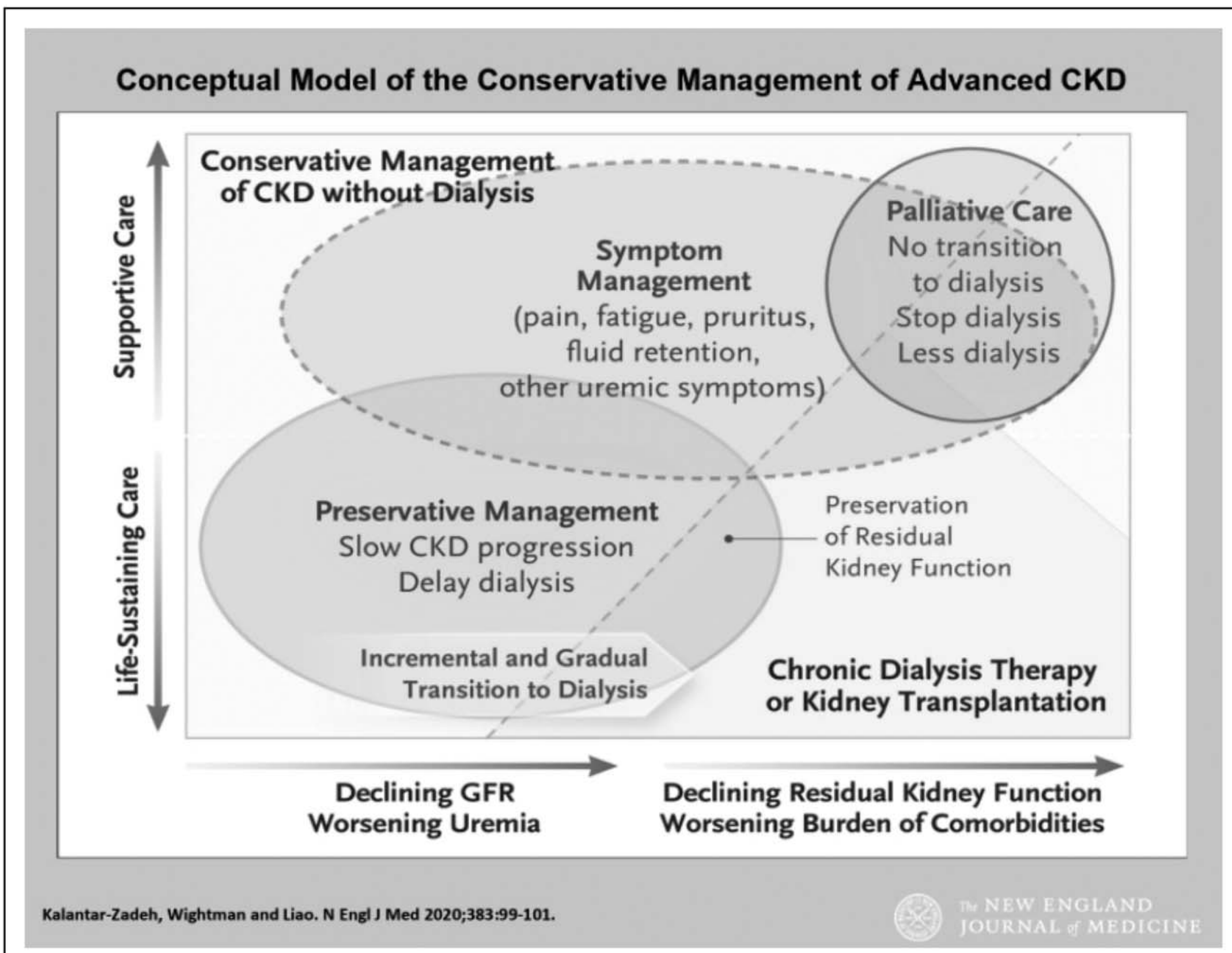

FIGURE 1. Conceptual model of the conservative management of advanced chronic kidney disease. GFR, glomerular filtration rate [38].

population may allow some patients to gradually transition to dialysis using an incremental approach (i.e., once or twice-weekly hemodialysis) [32,33]. Indeed, presence of residual kidney function and urine output has been associated with better health-related quality of life in dialysis patients, likely because of greater dietary liberalization, improved solute clearance (i.e., thus avoiding the development of uremic symptoms, and better fluid balance (i.e., averting large interdialytic weight gains, high ultrafiltration rates, and subsequent intradialytic hypotension and leg cramping) [32–37].

NUTRITIONAL ASPECTS TO PRESERVE KIDNEY FUNCTION

Over time, dietary change represents a low-cost and powerful means for prevention and management of CKD; in particular, the dietetic-nutritional therapy (DNT) is necessary to counteract clinical and metabolic alterations caused by CKD. Uncontrolled intake of nutrients and proteins promotes retention of phosphorus, fixed acids and uremic toxins leading to the onset of uremic state; this condition promotes the onset of protein–energy wasting syndrome, the progression of kidney damage with consequent impact on mortality [11▪,32,39,40]. DNT can also help to reduce the pill burden in the renal patient [11▪,40,41] and mitigate the symptoms of CKD in the conservative management [2,41]. On the contrary, less than 10% of adults with CKD receive any dietary counseling prior to initiation of dialysis [39].

The cornerstone of DNT is low-protein intake. Low-protein diet (LPD) has demonstrated a lower progression to ESRD and a lower rate of all-cause death [40]. However, increasing evidence shows that the protein type may be more important for kidney progression than the total amount of protein itself [12▪,39,42]. In fact, animal proteins, in particular those found in red meat, were associated with an increased risk of CKD and faster progression on ESRD [43,44]; on the other hand, higher intake of vegetable proteins was associated with a lower prevalence of CKD in patients with type 2 diabetes mellitus and a lower risk of developing CKD in the general population [45]; moreover, substitution analysis revealed that replacing one serving of red meat with legumes was associated with halved risk of ESRD in CKD patients [43]. Consumption of plant proteins also correlates with the reduction of mortality in CKD patients [46]. It is plausible to consider that plant proteins offer advantages over animal proteins in patients with CKD. Vegetable proteins are mostly acid-neutral, therefore generate a low amount of uremic toxins and advanced glycation end products (AGEs), and result in better lipidic control [43–45]. Moreover, vegetable proteins don't appear to induce renal hyperfiltration, and have a low-bioavailable phosphorus [39,45]. Finally, plant-proteins decrease the risk of kidney stones and reduce BP when compared with animal proteins [47,48].

For all the above-mentioned reasons, there is an increasing interest in the use of plant-based diets (PBDs) for prevention and treatment of CKD [42,43,45,48–51,52▪,53]. PBDs are those that emphasize the consumption of plant, low processed, foods (fruit, vegetables, nuts, seeds, oils, whole grains, legumes, and beans) and may or may not include small or moderate amounts of meat, fish, seafood, eggs, and dairy products [48]. The PBDs includes vegan and vegetarian diet, and, according to some authors, also the Mediterranean and Dietary Approaches to Stop Hypertension diet [45,53]. However, a widely accepted definition of PBD lacks, at the moment [44]. An increasing body of research shows that PBDs may lower the risk of CKD in the general population as well as renal disease progression [54–57]. In nephrology there are at least two types of PBD options: vegan LPD (0.6 g/kg/day) that is based on consumption of cereals and legumes as sources of complementary protein, and very LPD (VLPD) (0.3 g/kg/day) supplemented with essential amino acid and ketoacids and based on the combination of protein-free products and plant-based food [9]. Current PBD and no PBD options are described in Table 2.

Plant-based LPD options seem to offer potential benefits in counteracting the factors that correlate with progression of kidney damage and risk of death, like metabolic acidosis [58], uremic toxins [42], phosphate [52▪], inflammation, and oxidative stress [12▪] and may reduce the need for medications [41].

Adherence to PBD, rich in fruits and vegetables, as well as a supplemented VLPDs, are effective in correcting metabolic acidosis and improving insulin sensitivity [41,59,60]. VLPDs also result in reduced (or even normalised) urea levels, with consensual reduction of cyanates (that promote endothelial dysfunction) [41]. Furthermore, VLPDs are effective in beneficially modulating gut microbiota, reducing indoxyl sulfate and p-cresol sulfate (PCS) serum levels as well as trimethylamine N-oxide (TMAO) and restoring intestinal permeability; all this reduces systemic inflammation and may also improve adherence to the diet [49,52▪,61]. Moreover, a PBD decreases intestinal absorption of phosphate and VLPDs have been shown to improve serum phosphate levels and reduce fibroblast growth factor 23 [41,43]. Finally, a PBD ensures

Table 2. Current plant-based diet and omnivorous diet options for chronic kidney disease

	Omnivorous diet	Plant-based diet		
	Low-protein diet	Low-protein options		Normoproteic options
	LPD (traditional)	VLPD	Vegan LPD	PBD (vegan, vegetarian, Mediterranean or DASH diet)
Protein content quantity quality	0.6 g/kg/day >50% animal	0.3–0.4 g/kg/day 100% vegetable	0.7 g/kg/day 100% vegetable	0.8 g/kg/day 100% vegetable (vegan) or most vegetable (other options)
Necessary integrations	Protein-free products	AAE-KA Protein-free products Vitamin B12	Vitamin B12	Vitamin B12
CKD stage	3–4°	4–5°	3–4°	1–2–3°
General features	Protein-free products instead of cereals. Most of protein source are animal based	Based on consumption of fruit, vegetable, cereals, and protein-free products to reach the necessary caloric intake	Consumption of cereals and legumes as sources of complementary protein	High consumption of fruit, vegetable, cereals, legumes, and seeds (most whole and unrefined food)
Possible concerns	Animal protein are source of acid load and uremic toxins Fiber poor	Adequate caloric intake Compliance Fluid overload if diuresis reduction	Variability of diet Legumes tolerability	Excess of protein or hyperkalemia if use in advanced stages of CKD
Possible benefits	Reduction of protein leads to less acid load, uremic load and phosphorus load	Absence of animal protein and high intake of vegetable food may lead to: Less acid load, less uremic toxins (TMAO, PCS, IS), AGEs, and POPs Improve serum phosphate levels, insulin sensitivity, and lipidic profile High intake of antioxidants, micronutrients and fibers Beneficial effect on gut microbiota and reduction of systemic inflammation		
Role in preservative therapies	Protein reduction showed a lower progression to ESRD and a lower rate of all-cause death	Postpone dialysis Preserve remaining kidney function and diuresis	Improve metabolic status Improve appetite (less uremic toxins)	May lower the risk of CKD in the general population as well as renal disease progression
Role in conservative therapies	May reduce the uremic status and may improve nutritional status compared with normoproteic diet	May improve appetite May improve pruritus and constipation Better metabolic control may reduce the pills burden		

AAE-KA, essential, aminoacid-ketoacid; AGE, advanced glycation end product; CKD, chronic kidney disease; DASH, Dietary Approaches to Stop Hypertension; ESRD, end-stage renal disease; IS, indoxyl sulfate; LPD, low-protein diet; PBD, plant-based diet; PCS, p-cresol sulfate; POP, persistent organic pollutant; TMAO, trimethylamine N-oxide; VLPD, very low protein diet.

greater intake of fibers, that feed the gut microbiota and produce short chain fatty acids, that may improve kidney health by maintaining an intact mucosal barrier and reducing systemic inflammation [62]. Fibers reduce also the risk of constipation and hyperkalemia [63]. Additional potential benefits of a PBD can be higher intake of antioxidants and micronutrients (magnesium, zinc, vitamin K, and vitamin C) [45] and lower content in AGEs, persistent organic pollutants as well as phosphorus-based preservatives, that are often used for meat processing [12▪,41,42,49].

With regard to the possible concerns related to high intake of potassium with PBD, recent studies confirmed that plant-based LPDs are not associated with significantly higher prevalence of hyperkalemia [43,63]. Furthermore, PBDs result in nutritionally adequate dietary intake in CKD patients [41,47,64▪].

SYMPTOM MANAGEMENT AND OTHER PALLIATIVE APPROACHES IN CHRONIC KIDNEY DISEASE

Patients with advanced CKD experience a high symptom burden which may negatively impact their health-related quality of life [13–16]. These symptoms may be due to a constellation of uremia, advancing age, coexisting comorbidities (e.g., anemia, hypervolemia, cardiovascular disease), and medications prescribed to manage these conditions (Fig. 2) [13]. While there are several generic and disease-specific validated tools for symptom assessment

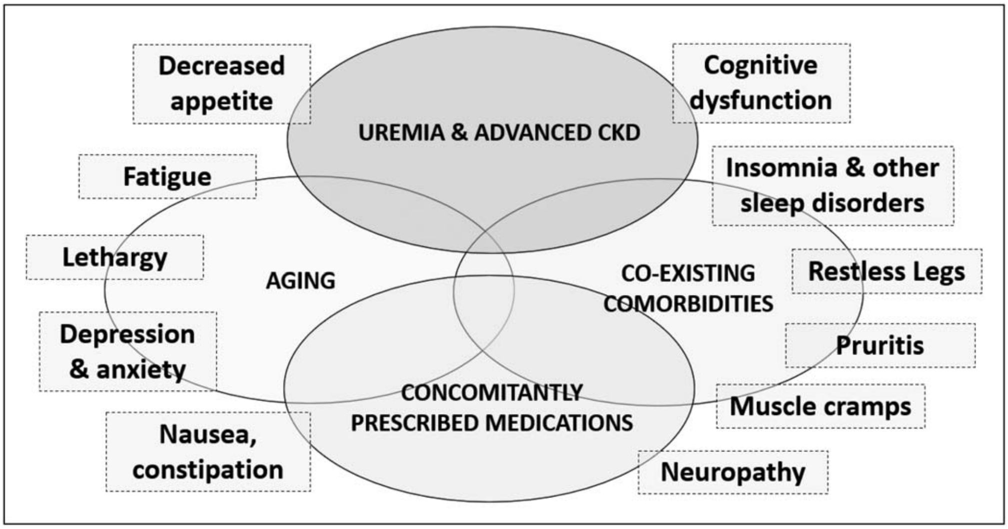

FIGURE 2. The constellation of symptoms with uremia, aging, coexisting comorbidities, and concomitantly prescribed medications in advanced chronic kidney disease.

(Table 3) [15,65], they are oftentimes underrecognized and undertreated in dialysis patients [15].

Some of the most frequent symptoms reported in advanced CKD and ESRD patients include fatigue and lethargy; anorexia and nausea; constipation; depression and anxiety; insomnia and other sleep disturbances; cognitive dysfunction; muscle cramps, neuropathy, and pain; and pruritis [1,13–16]. The effects of dialysis upon the prevention or reduction of the development, frequency, or intensity of uremic symptoms remains unclear due to sparse and mixed data. In one rigorous study that examined 99 ESRD and 87 advanced CKD patients who underwent a battery of symptom, depression, and health-related quality of life assessments [i.e., Dialysis Symptom Index (DSI), Patient Health Questionnaire-9, and Short Form 36, respectively], the burden of symptoms (defined by the overall number of symptoms or the total DSI symptom-severity score) and prevalence of depression

Table 3. Validated instruments used for symptom assessment

Instrument	Category	Description
Dialysis Symptom Index	Disease-specific (nephrology)	30-Item survey that assesses physical and emotional symptoms and their severity
Edmonton Symptom Assessment Revised: Renal	Disease-specific (nephrology)	Modified from original tool to specifically assess the physical and emotional symptoms of dialysis patients
Integrated Palliative Care Outcome Scale Renal	Disease-specific (nephrology)	Modified from original tool; 11-item survey that combines the most common symptoms renal patients experience and additional items such as information needs, practical issues, family anxiety, etc.
Kidney Disease Quality of Life Instrument	Disease-specific (nephrology)	134-Item instrument designed to assess generic and kidney-disease-targeted aspects of quality of life for individuals on dialysis
Memorial Symptom Assessment Scale	Disease-specific (oncology)	Instrument designed to assess physical and emotional symptoms experienced by diverse types of cancer patients
Rotterdam Symptom Checklist	Disease-specific (oncology)	Tool originally developed to measure the symptoms reported by cancer patients participating in clinical research
Symptom Distress Scale	Generic	One of the first scales developed to measure the construct of symptom distress (defined the degree of discomfort from the specific symptom being experienced as reported by the patient)

and impaired health-related quality of life were comparable in patients with ESRD and advanced CKD [66]. Furthermore, dialysis and its preparation may inadvertently lead to development of de-novo symptoms [13]. For example, hemodialysis patients may frequently experience symptoms of feeling 'washed-out,' light-headedness, or weakness after a dialysis treatment session, as well as pain ensuing from vascular access cannulation or leg cramping. Similarly, peritoneal dialysis patients may feel discomfort resulting from fullness related to large peritoneal fill volumes, peritonitis, exit site infections, and encapsulating peritoneal sclerosis. In addition to physical symptoms, dialysis patients commonly experience mental and emotional discomfort. In a study of 246 hemodialysis patients who underwent various assessments for anxiety and depression using the Beck Anxiety Inventory and Beck Depression Inventory, approximately one-third to half of the cohort reported anxiety when coming to dialysis, hearing an alarm sound during treatment, being connected to the dialysis machine by a new dialysis staff, or seeing paramedics in the dialysis unit [67].

Hence, to improve their quality of care, routine symptom assessment and management of symptoms should be integrated into the treatment of advanced CKD and ESRD patients [1,2,3▪,15]. As dialysis may be inadequate in treating symptoms, one of the mainstays of symptom management includes palliative care, defined by the WHO as 'an approach that improves the health-related quality of life of patients and their families through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of other problems, physical, psychosocial, and spiritual' [68]. However, a number of studies show that there is low utilization of palliative care resources among patients with advanced CKD and ESRD compared with other chronic disease populations, and hence a missed opportunity to better address symptom management using these nondialytic approaches. In addition, the Executive Summary of KDIGO Controversies Conference on Supportive Care has presented a list of symptoms most frequently experienced by CKD patients and a critical review of existing evidence summarizing their treatment options [1], and there are emerging nondialytic treatments used to ameliorate uremia as described below. Finally, greater prioritization of patients' self-reported symptoms by regulatory agencies in lieu of traditionally emphasized and more easily quantifiable laboratory parameters could lead to a paradigm shift in the health-related quality of life of advanced CKD and ESRD patients [13,14].

ALTERNATIVE TREATMENTS OF UREMIA

The main alternatives to dialysis that have been proposed to control uremia, are methods that use gut and skin, which are the two other organs, in addition to the kidney, normally predisposed to the elimination of fluids, electrolyte and toxins [18,19].

The idea to have the intestinal tract taking over kidney function comes from the evidence that the excretion of creatinine, urea, uric acid, phosphate, potassium is physiologically high in feces. The reduction of uremic toxins (which include PCS, indoxyl sulfate) can mitigate uremic symptom, while reduction of serum potassium and phosphorus can partially ease off the dietetic restriction; both of these effects may improve quality of life in the conservative treatment of uremia [2]. The most studied methods to enhance the gut capacity of excretion of uremic toxins are: the induction of diarrhea, the colonic dialysis, the use of oral sorbent and the modification of gut microbiota with prebiotics, probiotics, symbiotics, and diet.

In the literature there are a few, small, and dated experiences that support the use of nonabsorbable solutions taken orally, to induce diarrhea and increase the clearance of uremic toxins [19]. These studies show that this method seems to be well tolerated and can postpone, in uremic patients, the onset of dialysis, up to a maximum of 2 years. But, at the moment, there are a lack of randomized controlled trials, that might verify the safety and feasibility of this technique [19]. On the other hand, the colonic dialysis is an alternative method that use a modified dialysate solution administered through an anal catheter. In a retrospective study, 178 patients, affected by stage 3–5 CKD, received colonic dialysis three time per week. This method was able to slow down the progression of renal disease as well as postpone the need for dialysis or transplant [18,69].

The use of oral sorbents was also tested to reduce absorption of uremic toxins. AST-120 (KREMEZIN) is one of these sorbents, available in Japan since 1999 and now also in other Asian countries. AST-120 is a spherical carbon particle that adsorbs uremic toxins within the gastrointestinal tract, inducing their excretion in the stool [70]. However, while the study has shown that AST-120 effectively reduces indoxyl sulfate values, it is still debated whether it can also slow down disease progression and mortality in patients with CKD [70,71]. Another sorbent is the activated charcoal that comes from the incomplete combustion of organic matter, and it is then activated by the high-temperature gas flow on its surface to increase absorption capacity [72]. A randomized controlled study, including 97 patients with stage 3–4 CKD, showed that activated charcoal can delay the onset of hyperphosphatemia and vascular calcification [73]; it was also tested for the treatment of pruritus. The main problem is the nonselective absorption that can interfere with many drugs and nutrients [72]. Recently it was also tested 'Veverimer,' a hydrochloric acid binder; a preliminary study showed that a treatment course of 12 weeks can increase serum bicarbonate [74], but the effect on CKD progression is yet to be ascertained. In addition, the potassium binders, including calcium polystyrene sulfonate, sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate, can be useful to reduce the plasmatic potassium level as well as to relax the dietary restrictions, even though there is no evidence, at the moment, that they can modify the health-related quality of life [75,76]. With regards to the use of prebiotic, pro-biotic and symbiotic intake in CKD, a recent systematic review and meta-analysis showed that their use correlates with improvement of inflammation and oxidative stress, as well as lipid profiles [77]. In addition, the use of a prebiotic fructooligosaccharide (12 g/day) was tested to reduce uremic toxins and it showed a decreased level of PCS [78], while a dietary supplement containing 3 g of oat β-glucan per day for 12 weeks was efficacious in lowering serum concentrations of the uremic toxin TMAO in patients with CKD stages 3–4 [79]. Moreover, the intake of prebiotic inulin (19 g/day), associated with LPD, showed a favorable increase in Bifidobacteriacea and reduction of C-reactive protein [80]. Among the different probiotics, a relevant role seems to be played by *Streptococcus thermophilus*, that has been shown to reduce indoxyl sulphate [81]. Furthermore, the diet itself can modify the intestinal function; in fact, high intake of fibers increases fecal bacterial mass and nitrogen excretion and reduced serum levels of urea and creatinine [62]. Moreover, low protein to fiber ratio, as well as VLPD, reduces the levels of PCS and indoxyl sulfate [41,44,57].

Finally, as mentioned above, there is the possibility to use the skin, through the sweat to remove fluids, electrolytes, and toxins, but for this technique, studies are currently scarce. The methods most commonly used to induce perspiration in CKD are dry (Finnish) sauna and the water immersion. The proven effects are: fluid loss (about 0.5–1 l for hour), reduction of serum potassium, improvement of pruritus, while the possible beneficial effect on urea removal is still unclear [18].

CONCLUSION

DNT, routine symptom assessment and management, and palliative care approaches are core components of conservative nondialytic care. While limited data suggest that nondialytic treatment approaches are associated with equivalent trajectories of health-related quality of life vs. dialysis in selected advanced CKD patients, further research is needed to determine the comparative effectiveness of conservative management vs. dialysis upon symptom burden and patient-centered outcomes in advanced CKD patients, as well as which patient subgroups will most benefit from these treatment strategies. Lastly, future studies are needed to determine the effectiveness and safety of emerging, innovative nondialytic uremia treatment approaches, such as diarrhea induction, colonic dialysis, oral sorbents, gut microbiota modulation, and stimulation of perspiration, in delaying or averting the need for dialysis in this population.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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