**Name of Journal:** *World Journal of Nephrology*

**Manuscript NO:** 66246

**Manuscript Type:** REVIEW

**Hidden risks associated with conventional short intermittent hemodialysis: A call for action to mitigate cardiovascular risk and morbidity**

Canaud B *et al*. Dialysis sickness and dialysis related morbidity

Bernard Canaud, Jeroen P Kooman, Nicholas M Selby, Maarten Taal, Andreas Maierhofer, Pascal Kopperschmidt, Susan Francis, Allan Collins, Peter Kotanko

**Bernard Canaud, Allan Collins,** Global Medical Office, Fresenius Medical Care, Bad Homburg 61352, Germany

**Bernard Canaud,** Department of Nephrology, Montpellier University, Montpellier 34000, France

**Jeroen P Kooman,** Department of Internal Medicine, Maastricht University, Maastricht 6229 HX, Netherlands

**Nicholas M Selby, Maarten Taal,** Centre for Kidney Research and Innovation, Academic Unit for Translational Medical Sciences, School of Medicine, University of Nottingham, Derby DE22 3DT, United Kingdom

**Andreas Maierhofer, Pascal Kopperschmidt,** Global Research Development, Fresenius Medical Care, Schweinfurt 97424, Germany

**Susan Francis,** Sir Peter Mansfield Imaging Centre, University of Nottingham, Nottingham NG7 2RD, United Kingdom

**Peter Kotanko,** Renal Research Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10065, United States

**Author contributions:** All authors contributed equally to concept, writing, and revising of the manuscript.

**Corresponding author: Bernard Canaud, MD, PhD, Emeritus Professor,** Global Medical Office, Fresenius Medical Care, 1 Else Kroner Str, DE-61352, Bad Homburg 61352, Germany. bernard.canaud@fmc-ag.com

**Received:** March 26, 2021

**Revised:** October 30, 2021

**Accepted: March 23, 2022**

**Published online:**

**Abstract**

The development of maintenance hemodialysis (HD) for end stage kidney disease patients is a success story that continues to save many lives. Nevertheless, intermittent renal replacement therapy is also a source of recurrent stress for patients. Conventional thrice weekly short HD is an imperfect treatment that only partially corrects uremic abnormalities, increases cardiovascular risk, and exacerbates disease burden. Altering cycles of fluid loading associated with cardiac stretching (interdialytic phase) and then fluid unloading (intradialytic phase) likely contribute to cardiac and vascular damage. This unphysiologic treatment profile combined with cyclic disturbances including osmotic and electrolytic shifts may contribute to morbidity in dialysis patients and augment the health burden of treatment. As such, HD patients are exposed to multiple stressors including cardiocirculatory, inflammatory, biologic, hypoxemic, and nutritional. This cascade of events can be termed the dialysis stress storm and sickness syndrome. Mitigating cardiovascular risk and morbidity associated with conventional intermittent HD appears to be a priority for improving patient experience and reducing disease burden. In this in-depth review, we summarize the hidden effects of intermittent HD therapy, and call for action to improve delivered HD and develop treatment schedules that are better tolerated and associated with fewer adverse effects.

**Key Words:** End stage kidney disease; Cardiovascular mortality; Dialytic morbidity; Circulatory stress; Biologic storm; Dialysis sickness; Personalized medicine

Canaud B, Kooman JP, Selby NM, Taal M, Maierhofer A, Kopperschmidt P, Francis S, Collins A, Kotanko P. Hidden risks associated with conventional short intermittent hemodialysis: A call for action to mitigate cardiovascular risk and morbidity. *World J Nephrol* 2022; In press

**Core Tip:** In this in-depth review, we summarize the hidden effects of intermittent hemodialysis (HD) therapy, namely, dialysis sickness and dialysis related morbidity. We call for action to improve delivered HD and develop treatment schedules that are better tolerated and associated with fewer adverse effects. The final aim is to reduce cardiovascular burden and improve patient outcomes.

**INTRODUCTION**

Conventional hemodialysis (HD) is a mature treatment that sustains life in almost 3 million patients with end stage kidney disease (ESKD) worldwide and provides a valuable bridging solution to kidney transplant[1-4]. However, by nature intermittent HD is an imperfect treatment that only partially corrects uremic abnormalities, increases cardiovascular risk, and is associated with a high disease burden[5-11]. The high treatment costs of renal replacement therapy represent in addition a significant health economic burden[12-14].

Recent evidence indicates that conventional high efficiency thrice-weekly intermittent HD schedules may be harmful to patients by provoking alternating cycles of fluid loading associated with cardiac stretching during the interdialytic period and fluid unloading that contribute to cardiac and vascular damage. This unphysiologic loading and unloading phenomenon combined with cyclical disturbances including osmotic and electrolytic shifts may contribute to dialytic morbidity and augment the health burden associated with the treatment of uremia[15-17].

Over past few years, several studies have emphasized the importance of ensuring optimal fluid volume and arterial pressure control, as well as adequately dosed and better tolerated dialysis therapy to improve patient outcomes[18]. The benefits of a dry weight first policy approach has been reinforced by interventional studies[19-21]. Fluid volume guidance has also been facilitated by means of supportive tools[22-24]. On the other hand, prospective clinical studies not only have documented that intermittent treatment might cause significant circulatory stress depending on treatment time and schedule[10,25-27], but have also shown that guided interdialytic and/or specific dialysis-based interventions might be able to reduce this risk[10,28,29].

However, few reports have focused on all aspects of dialysis patient management in a comprehensive way[30-32]. In this in-depth review, we summarize potential harmful effects of intermittent HD and propose solutions for achieving more cardioprotective and tolerable treatment.

**INTERMITTENT EXTRACORPOREAL RENAL REPLACEMENT THERAPY IS THE SOURCE OF PERMANENT STRESS IN MAINTENANCE HD PATIENTS**

***Cardiocirculatory stress***

The ‘unphysiology’ of intermittent HD is recognized as a leading cause of dialysis intolerance and multiorgan morbidity[33,34]. This phenomenon was exacerbated by operational changes that resulted in shortening of dialysis treatment schedules and increasing dialysis efficiency[35]. As such, intermittent HD generates periodic changes in volume and blood pressure, osmotic shifts, and variation in circulating levels of compounds and electrolytes. Treatment-induced disturbances are in complete contrast with strictly regulated and stable conditions of the internal milieu in healthy subjects[32,36,37] (Figure 1).

During the interdialytic period, anuric HD patients tend to accumulate sodium and fluid according to fluid and diet intake, leading to chronic fluid overload[38]. In this condition, fluid overload has two components: The first, resulting from cyclic changes imposed by intermittent treatment marked by weight gain and progressive increase of systemic arterial pressure and pulmonary arterial pressure with cardiac stretching occurring between two treatment sessions; and the second, which reflects chronic fluid overload that has accumulated over time, exposing patients to chronic cardiac stretching and structural cardiac remodeling[39] (Figure 1).

During the intradialytic period, sodium and fluid removal resulting from ultrafiltration (intradialytic weight loss) and the patient to dialysate sodium gradient contributes to reducing circulating blood volume and triggering an adaptative hemodynamic response[40,41]. In response to ultrafiltration provoking a reduction in blood volume and cardiac stroke volume, arterial pressure and tissue perfusion are maintained by an increase in vascular tone, mainly through vasoconstriction of alpha-adrenoceptor territories, and an increase of vascular refilling and in venous return[42,43]. Recent intradialytic imaging studies have shown that reductions in myocardial perfusion and contractility (myocardial stunning) are linked to ultrafiltration rate that happens even without ischemic cardiac disease[17,44,45]. Several observational studies have reported a strong association between mortality and high ultrafiltration rate or volume changes, drop in blood pressure, and end-organ ischaemic insult[10]. The systemic response is more complex than a simple reaction to hypovolemia, since it incompasses others factors such as vascular refilling capacity, thermal balance, electrolyte fluxes, nutrient losses, as well as the individual patient’s baseline cardiac reserve and neurohormonal stress responses[45,46]. Interesting, this response may be mitigated by various factors (*e.g.,* age, gender, comorbidity, and medication) explaining individual or temporal variations in hemodynamic response[38,47]. The hemodynamic stress induced by dialysis must be considered as a potent disease modifier in highly susceptible patients[48] (Figure 1).

Whatever the exact contribution of these phenomena, dialysis-induced cyclical volemic changes (hyper- and hypo-volemia) provoke alternating cardiac loading and unloading. This volemia variation cycle is responsible for repetitive myocardial stretching, a mechanism that leads to release of inflammatory mediators and promotes cardiac fibrosis and arrhythmias[49,50] (Figure 1).

***Inflammatory stress***

Bio-incompatibility (or more specifically, hemo-incompatibility) of the extracorporeal blood circuit and its systemic effects is a well identified issue associated with several aspects of dialysis related morbidity[51,52]. In brief, the activation of a cascade of serum proteins and blood cells is induced upon contact with foreign material in the extracorporeal circuit[53,54], and endothelial damage may further induce a vascular endothelial breach[55]. This process is further modified by the geometry, design (*e.g.,* blood air interface and dead space), and nature of blood tubing (*e.g.,* type of polymer and plasticizer) or dialyzer membrane (*e.g.,* cellulosic and synthetic), and may be amplified by microbial-derived products from dialysis fluid (*e.g.,* lipopolysaccharide, endotoxins, and bacterial DNA)[56-59]. As a result, endothelial cells and circulating blood cells (*e.g.,* platelets, leukocytes, and monocytes) are primed and activated to release pro-inflammatory mediators (*e.g.,* platelet activating factor 4, beta-thromboglobulin, granulocytes proteinases, anaphylatoxins, and cytokines) and activate protein cascades (*e.g.,* clotting cascades, complement activation, surface contact, and kallikrein-kinin system)[60-66]. Activation of the innate immune and coagulation systems amplifies and propagates this reaction[67]. Platelets and endothelial cell activation trigger coagulation, endothelial damage, vascular reactivity, and pulmonary trapping of cells. Mononuclear leukocyte activation results in the release of enzymes (*e.g.,* granulocyte neutral proteinase and elastase)[60,68-70], and increases their reactivity and adhesiveness that may cause obstruction at the microcirculatory level. In the lungs, this may contribute to hypoxemia[71-73]. Activation of monocytes and macrophages induces release of proinflammatory cytokines [interleukin (IL)-1, IL-6, and tumor necrosis factor-α][74,75]. In addition, acute inflammatory reactions are amplified by oxidative stress in an amplifying loops contributing to a vicious circle[74]. Seminal studies performed in various HD settings (*e.g.,* cellulosic *vs* synthetic dialyzers and contaminated *vs* ultrapure dialysate) have documented the importance of this “biologic storm” and provided evidence of its damaging effects (*e.g.,* allergic reaction, lung dysfunction, thrombocytopenia, and inflammation)[67,76] (Figure 1).

Despite significant improvements in extracorporeal circuit biocompatibility and wide-spread use of ultrapure dialysis fluid, systemic hemobiological reactions periodically induced by extracorporeal treatment[77,78] are likely to contribute to a micro-inflammatory state in chronic HD patients that amplifies long-term deleterious effects[30,75,79] (Figure 1).

***Biological stress***

In the absence of significant kidney function, internal metabolic processes and dietary intake produce metabolites during the interdialytic phase that steadily accumulate over 48 h and lead to classical biologic uremic abnormalities[80]. During dialysis, biologic disorders are usually corrected, at least partially, within 4 h. Biologic gradients between the dialysate and blood may be large, resulting in high amplitude changes of body composition during each session[32,76,81,82]. This gradient stress may be easily quantitated by dialysate-blood gradient concentrations and time averaged deviations for various solutes that are exchanged during the dialysis session[81]. Solutes exchange in HD follows negative or positive gradients, knowing that solute gradient is conventionally defined as dialysate-plasma concentration difference. Uremic retention toxins (*e.g.,* urea, creatinine, uric acid, potassium, and phosphate) are removed according to a negative gradient from blood to dialysate, while selected electrolytes (*e.g.,* bicarbonate, calcium, and magnesium) or nutritional compounds (*e.g.,* glucose) may move in the opposite direction. Unwanted removal of essential nutrients (*e.g.,* amino acids, peptides, and water soluble vitamins such vitamin D) and albumin may occur, contributing to a nutritional stress. The description of biochemical changes during dialysis is beyond the scope of this review. Through this remark we emphasize the fact that dialysis patients are challenged by various and large osmotic changes due to movements of urea and uraemic metabolites, water shift from extra- to intra-cellular space, acid-base changes moving the patient from metabolic acidosis to mixed alkalosis, potassium swings from hyper- to hypo-kalemia, and divalent ion alterations moving from hyper- to hypo-phosphatemia and from hypo- to hyper-calcemia, while at the same time patients are losing amino acids and other important nutrients[83-86]. Clinical manifestations of these metabolic derangements range from none, through minor to severe symptoms (fatigue, headache, and cognitive impairment), with the most extreme manifestation being dialysis disequilibrium syndrome[87,88] (Figure 1).

***Hypoxemic stress***

During dialysis, in addition to circulatory stress and impaired tissue perfusion[89-91], hypoxemia may occur, which can be particularly marked in the early phase of a dialysis session, likely related to hemoincompatibility reactions inducing leukocyte trapping within the lungs. This observation suggests the occurrence of an additional respiratory stress resulting from impaired pulmonary gas exchange[92,93]. Prolonged intradialytic hypoxemia is likely to play an aggravating role in end organ damage by reducing further tissue oxygen delivery. We can speculate that this is a pathophysiologic link that explains the increased mortality observed in patients presenting with prolonged hypoxemia during HD[92] (Figure 1).

During the interdialytic phase, sleep apnea syndrome (SAS) and nocturnal hypoxemia have emerged as important additional cardiovascular risk factors in HD patients[80]. SAS marked by repetitive pause of breathing during sleep resulting in hypoxemia and hypercapnia is highly prevalent in HD patients[80,94]. In addition, SAS is associated with profound changes in cardiac loading conditions, lung arterial pressure, and autonomic activation, all factors that have been associated with significant cardiovascular morbidity such as left ventricular hypertrophy or arrhythmias and sudden cardiac death[95-98]. Although uremic abnormalities contribute to the development of SAS, the role of fluid overload exacerbating upper airways obstruction should not be neglected as recently pointed out by a study exploring fluid displacement into nuchal and peripharyngeal soft tissues in healthy subjects[99]. It is therefore tempting to speculate that chronic fluid overload is partly responsible for an edema of upper airway especially during sleep while in the supine position, thereby contributing to the occurrence of SAS (Figure 1).

In brief, whatever mechanisms are associated with impaired pulmonary gas exchange in HD patients, occurring either during intradialytic or interdialytic phases, prolonged periods of hypoxemia are likely to represent an additional stressor[34] (Figure 1).

***Nutritional stress***

Loss of muscle mass is common in HD patients and represents one of the most important predictors of mortality[100,101]. Sarcopenia is the main component of the protein-energy wasting syndrome that results from complex uremic abnormalities and the adverse effects of HD treatment[102-104] (Figure 1).

On one hand, acute studies assessing muscle and whole body protein turnover conducted in stable patients have consistently demonstrated an imbalance in protein synthesis and degradation during HD sessions[105-108]. It has been also shown that losses of amino acids during HD, ranging between 8 and 10 g per session, contributed significantly to the net protein catabolism[85,109-111]. Interestingly, this amino acid loss leads to reprioritization of protein metabolism during HD sessions. Amino acid loss during HD stimulates muscle and liver protein catabolism in order to preserve plasma and intra-cellular amino acid concentrations. Furthermore, amino acid utilization for protein synthesis either by the liver or muscle is impaired in HD patients, mainly through activation of cytokine pathways (IL-6) rather than because of amino acid depletion[112-114]. Remarkably, amino acid repletion by IV administration during HD tends to increase muscle protein synthesis but does not decrease muscle protein breakdown[115]. It is also interesting to note that dextrose depletion (when dextrose-free dialysate is used)[116] and other aspects of HD including type of membrane (cellulosic *vs* synthetic)[117,118] and dialysate microbiologic purity[119,120] may modulate this muscle protein catabolism phenomenon[121] (Figure 1).

On the other hand, long-term precise nutritional studies conducted in stable patients under strict metabolic conditions have shown that HD-induced imbalance in protein metabolism[122,123] might be compensated for by dietary protein and caloric supplements[124,125]. As shown, the net negative protein metabolic imbalance observed on dialysis days might be compensated for by increasing dietary protein and caloric intake (about 25%) during non-dialysis days, leading to a neutral protein and caloric balance on a weekly basis[124,126]. However, in practice, this can be hard to achieve.

In brief, intermittent HD treatment is associated with repetitive nutritional stress conditions due to reprioritization of protein metabolism within the muscle and liver (Figure 1).

***Dialysis sickness and dialysis related morbidity***

Dialysis sickness (DS) refers to the concept that inter-, peri-, and intra-dialytic morbidity resulting from the hemodynamic, inflammatory, biological, hypoxemic, and nutritional stresses discussed above, and can result in the long-term in end organ damage as summarized in Figure 2.

Dialysis-related morbidity (intra- and peri-dialytic symptomatology) has a negative impact on patients’ perception and on their quality of life (QoL)[16,48,93,127,128]. This can be measured by scoring scales according to patient reported outcomes measures (PROM) or patient reported experience measures (PREM)[129-131]. Intra- and inter-dialytic symptoms that include hypotensive episodes, cramps, headache, fatigue, pruritus, and sleep disorders are the most frequently reported[132]. PROMs, PREMs, and most domains of health related QoL are significantly reduced in patients treated by conventional HD and tend to be improved by daily or extended treatment schedules[133-135]. Furthermore, dialysis symptom burden has been shown to be associated with increased mortality and hospitalization risks. Indeed, these clinical performance indicators are strongly recommended to assess dialysis adequacy and patient experience[129,136-139] (Figure 1).

End organ damage results from exposure to hemodynamic and pulmonary stressors leading to poor tissue perfusion and oxygen delivery, which are further aggravated by biological and cytokine “storms”. Multifactorial and repetitive systemic stressors induced by intermittent HD treatment are likely to have harmful long-term effects on the function and structural modeling of vital organs (*e.g.,* cardiac stunning, leukoaraiosis, gut ischemia, and hepato-splanchnic changes). Some of these cardiovascular effects are enhanced by chronic low-grade inflammation acting on endothelial dysfunction and contributing to poor outcomes[10,28,140-142]. The combination of cardiocirculatory stress, hypovolemia, and electrolyte changes occurring during HD sessions creates pro-arrhythmogenic conditions that may contribute to clinically significant cardiac arrhythmias during the interdialytic phase[143-147]. Cardiac structural changes following myocardial stunning and remodeling in response to cyclical dialysis-induced phenomenon, such as fibrotic scarring and loss of segmental contractile function with irregular electrical conductivity, are plausibly increasing the risk of sudden cardiac death[44,146,148-151]. These findings mimick the intense physiologic demands endured by healthy subjects under extreme conditions[152]. In order to mitigate dialysis-induced organ damage, we propose that conventional HD treatment schedule may be adapted and personalized, as a new treatment paradigm.

**CALL FOR DESIGNING AND APPLYING A MORE CARDIOVASCULAR PROTECTIVE HD TREATMENT**

***Optimizing hemodynamic management***

The inevitable sodium and fluid accumulation that occurs during the interdialytic phase in anuric HD patients is responsible for chronic extracellular fluid overload with its adverse effects[153,154]. Hypertension is part of this constellation of disorders being recognized as the leading cause of cardiac and vascular disease in HD patients[19,20]. Management of fluid volume has been identified as a specific cardiovascular risk factor: On one hand, persistence of chronic fluid overload is independently associated with increased cardiovascular risk[155]; on the other hand, overly-rapid fluid volume reduction (*i.e.,* ultrafiltration rate) and hypovolemia are also associated with an increased risk of cardiovascular mortality[10,156] (Figure 3).

In other words, sodium and fluid volume homeostasis and blood pressure need to be managed more precisely during the interdialytic phase to achieve suitable targets. Additionally, hemodynamic stress secondary to volume contraction should be mitigated during dialysis by the use of appropriate tools and adjustment of the treatment schedule. Better monitoring of blood pressure and hemodynamics that are applicable to the clinical setting are also needed. This is a fundamental challenge of intermittent HD (Figure 3).

**Improving sodium, fluid volume, and pressure management during the interdialytic phase:** Salt and fluid management of the dialysis patient represents a major challenge for clinicians.A combined approach is needed that includes clinical management (a dry weight probing policy, *e.g.,* ultrafiltration, dialysate sodium prescription, and diet education) supported by assessment tools (*e.g.,* multifrequency bioimpedance and lung ultrasound)[157], cardiac biomarkers [*e.g.,* B-type natriuretic peptide (BNP) and NTproBNP], HD technical options (*e.g.,* sodium control module), and algorithms (*e.g.,* artificial intelligence) using advanced analytics in the future[38,158] (Figure 3).

**Reducing hemodynamic stress induced by HD:** Intradialytic morbidity (*i.e.,* fatigue, headache, cramps, hypotension, and alteration of cognitive function) is largely dependent on fluid removal (*i.e.,* ultrafiltration) and dialysis efficiency (*i.e.,* osmotic and solute concentration changes, and electrolytes shifts). The intensity and frequency of these symptoms also depend on patient characteristics (*e.g.,* age, gender, and anthropometrics), metabolism, and body composition, and on the HD treatment schedule (*e.g.,* treatment time and frequency). It is well recognized that longer and more frequent dialysis treatment schedules are better tolerated with reduced circulatory stress and slower osmotic and electrolytic changes, as compared to short and less frequent dialysis schedules[159,160]. In that respect, ultrafiltration rate, reflecting fluid volume removed per time unit, is a well-recognized cardiac risk factor in dialysis patients that also associates with mortality risk[40]. In addition, it reflects the fact that biochemical gradients and solute fluxes are reduced per time unit, as well as osmotic changes and water shifts occurring within the central nervous system (Figure 3).

In a stepwise approach, increasing treatment time and/or dialysis frequency should ideally represent the first and most rational step to reduce risks associated with ultrafiltration rate and osmotic changes in non-compliant or fragile patients[161]. As a next step, modulating patients’ hemodynamic responses through various tools embedded in the HD machine is another appealing option[162]. Monitoring blood volume during dialysis sessions is useful to identify critical volemia, to estimate remaining fluid in the interstitium, or to quantify vascular refilling capacity[163], but it is not sufficient to manage patient hemodynamic response[164]. Instead, surveillance of central venous oxygen saturation (ScvO2) in patients with central venous catheters may indicate critical changes in organ perfusion before they result in clinical symptomatology. Interestingly, the decline in ScvO2 during dialysis has been correlated to ultrafiltration volume[165,166]. With arterio-venous fistula, near infrared spectroscopy, a non-invasive method, could be of interest to estimate tissue oxygenation[167]. Feedback controlled ultrafiltration system relying on blood volume changes has improved hemodynamic stability in selected studies, but so far has not improved patient outcomes and intradialytic morbidity[168,169]. Some studies have shown that using dialysate sodium and ultrafiltration profiling, with or without blood volume monitoring, may preserve intradialytic hemodynamic status but at the expense of an increased risk of subclinical salt loading, thirst, high interdialytic weight gain, and chronic fluid overload[170]. Adjusting dialysis thermal balance to preserve peripheral vascular resistance and cardiac output is also a simple strategy to improve hemodynamic tolerance that has been proven effective in several studies[171]. The main objective is to deliver isothermic or better, hypothermic dialysis, to prevent thermal gain during a dialysis session which is associated with an inappropriate hemodynamic response (vasodilation, tachycardia, and drop in ejection fraction)[172]. Hypothermic HD could be manually achieved by setting dialysate temperature 0.5-1 °C below the patient’s core temperature. Automated thermal control of dialysis sessions requires the use of an online blood temperature monitor that can control precisely the thermal balance of patients to a preset target[173]. Both approaches reduce hypotension incidence (Figure 3).

Another important component of intradialytic morbidity relates to biochemical stress as reflected by the magnitude of dialysate-plasma solute gradient, a major determinant of solute fluxes[170,174-176]. Reducing instantaneous solute fluxes while keeping solute mass removal constant during dialysis session may be an interesting approach to reduce intradialytic morbidity. This issue could be easily addressed by reducing blood flow and increasing treatment time and/or frequency to slow instantaneous solute fluxes. This is a usual practice in Japan but it is not the most popular nor the most appealing in Western countries[177]. Another approach within the current short dialysis treatment schedule would be to continuously adjust flow parameters to reduce instantaneous solute fluxes while keeping solute mass transfer constant. Advanced technology will facilitate such an approach in the future, relying on microsensors positioned on dialysate side, feeding specific algorithms, and then providing feedback control to the HD monitor to adjust relative flows and gradients (Figure 3).

In summary, one should consider that fluid volume removal and solute fluxes (dependent in part on blood-dialysate concentration gradients) are potentially modifiable factors of the dialysis prescription (Figure 3).

***Enhancing renal care efficacy***

The limited efficiency of contemporary HD in restoring the internal milieu composition and in controlling circulating levels of middle and large molecular sized uremic toxins, has stimulated use of convective-based therapies (*e.g.,* hemodiafiltration) and more porous membranes (*i.e.,* high cut-off)[36]. Therefore, the so-called ‘residual syndrome’, reflecting incomplete removal of uremic toxins, is another potential contributor to patient morbidity and mortality[178,179] (Figure 3).

Enhancing treatment efficiency by combining high efficiency hemodiafiltration and extended treatment time has been shown in recent studies to be able to address most remaining issues in adults. In brief, extended on-line hemodiafiltration (HDF) treatment has been associated with tight control of fluid volume and blood pressure without antihypertensive medications, normalization of phosphate levels while phosphate binders were stopped, correction of anemia while erythropoietic stimulating agent consumption was reduced by 50%, and a significant improvement of nutritional status and physical activity[180,181]. Interestingly, in a pediatric population, extended HDF has been also shown to improve intermediary outcomes (*i.e.,* fluid volume, blood pressure, inflammation, phosphate, and nutrition), to reduce cardiovascular disease progression, and to promote catch-up growth[182-184] (Figure 3).

Preserving residual kidney function is an important feature in dialysis patients since it is associated with a reduced disease and treatment burden and mortality[185-187]. Fluid volume and blood pressure control are usually better achieved with less dietary restriction[188]. Circulating levels of uremic toxins are significantly reduced, particularly for middle and large molecular weight substances but also for protein-bound uremic toxins[189]. In brief, all dialysis conditions, but particularly those ensuring a better hemodynamic stability, should be considered to prevent the repetitive ischemic kidney insults during HD[190] (Figure 3).

Acting on the gut to reduce protein-bound uremic toxin production has been recently suggested as a potential way of reducing circulating levels of protein bound uremic toxins (PBUT) such as indoxyl sulfate and paracresyl sulfate[191]. A few studies have confirmed positive effects of this option using either probiotics or adsorbers (AST120) administered orally in reducing plasma PBUT concentrations[192,193]. Unfortunately, published interventional studies have not confirmed potential long-term clinical benefits on patient outcomes[194] but further studies with better design and greater statistical power are warranted (Figure 3).

***Personalizing renal replacement treatment schedule***

**Treatment schedule adaptation:** A ‘one–size–fits-all’ approach is unlikely to work, and this should be kept in mind for optimizing renal replacement therapies in the future. Accordingly, dialysis prescription including treatment schedule (time and frequency), modality, dose, and efficiency[134,195,196], and electrolyte prescription should be tailored to patient profile, needs, and tolerance[197,198]. Furthermore, treatment prescription should be adapted over time to an individual patient’s results in a personalized way to follow patient metabolic changes, treatment tolerance, and symptoms. Dialysis prescription should return to physiologic principles; it should not be the patient who must adapt to a fixed treatment, but the treatment should fit to the patient needs and tolerance instead.

In this context, the treatment schedules offered to patients should be expanded and become more flexible. It is not our intent to develop this concept further but to highlight recent interesting findings (Figure 3).

Incremental dialysis is an interesting concept that deserves more attention in particular in incident ESKD patients and in emerging countries[199]. It relies on the fact that HD acts as a complement to residual kidney function. In other words, the number of dialysis sessions and/or treatment time per week is inversely related to the glomerular filtration rate. Recent comprehensive reviews have addressed this issue to which we refer the interested reader for more details on clinical benefits and implementation[200]. In brief, incremental dialysis has the capacity to facilitate treatment implementation in new patients by reducing treatment burden, but also potentially to mitigate a shortage of renal replacement therapy resources in low and middle income countries (Figure 3).

Extended HD schedules (*i.e.,* long and nocturnal dialysis, alternate day dialysis, and daily HD) appear particularly attractive in terms of improving outcomes[181]. Extended treatment schedules must be viewed from two aspects: On one hand, outcomes are favorable including with kidney transplant[195,201-204]; on the other hand, they increase treatment burden and cost, except if home HD is chosen[205]. In this context, to solve both logisitical and cost issues, it is therefore proposed to develop extended treatment schedules at home or in self-care facilities[206] (Figure 3).

**Use of new tools for monitoring and adapting treatment prescription:** A whole body bioimpedance cardiography (BIC) non-invasive device has been assessed in HD patients. BIC has interesting features to measure the hemodynamic response to fluid removal (*e.g.,* cardiac output and total peripheral vascular resistance) during dialysis. Based on these findings, it has been suggested that dialysis patients might be clustered into various categories defined as low or high cardiac output, low or high total peripheral vascular resistance, or normal hemodynamics[207,208]. BIC has the potential to support physicians to individualize dialysis treatment, although this would need to be tested in interventional studies[208]. Approaches using BIC warrant further studies to validate measurements and explore impact on patient outcomes[209] (Figure 3).

More recently, lung ultrasononography (LUS) has been proposed as a point-of-care tool to complete physical examination[24,210,211]. Lung ultrasound is a noninvasive method to estimate extravascular lung water easily mastered by nephrologists that help to quantify lung congestion by counting B-lines per lung area unit (Comet line scoring). The “Lung water by ultrasound guided treatment to prevent death and cardiovascular complications in high risk ESRD patients with cardiomyopathy” study has shown the clinical value of LUS in the management of HD patients at high cardiovascular risk[212,213] (Figure 3).

A further tool to reduce intradialytic hemodynamic stress is the development of wearable non-pervasive methods for continuous blood pressure monitoring. This would allow detection of subtle changes in blood pressure to prompt interventions such as reduction of ultrafiltration rate to prevent hypotension. Recent work using additional pressure sensors placed on dialysis lines to derive blood pressure without the need for additional equipment attached to the patient, shows promise in this regard[214,215]. Considering the high cardiac mortality risk of HD patients (10 to 100 times greater than the general population)[216], it appears of utmost importance to pay closer attention to cardiovascular monitoring to ensure early and appropriate intervention for improving outcomes[49]. Interestingly, new remote technologies or so-called connected iHealth devices offer convenient new tools for monitoring high risk HD patients during the interdialytic period in a fully automated and ambulatory mode[217]. Detection of clinical significant arrhythmias would be one important functionality, as shown in recent studies[146,218] (Figure 3).

**FUTURE DEVELOPMENT OF HD AND RENAL REPLACEMENT THERAPY**

In order to reduce dialysis associated morbidity and to improve patient experience, three main approaches should be proposed and explored.

***Designing and adapting HD treatment schedule to individual patient needs, tolerance, and risks***

Aside from the introduction of more flexible treatment schedules, recent studies have also shown the potential interest of stratifying patients according to their risks at short or medium term outcomes[219,220]. A better understanding of patient risks could help physicians to prescribe more appropriate and individualized therapy. Also, scoring systems could be tested as supports to alter specific treatment prescription features in an attempt to reduce early mortality of ESKD patients transitioning to dialysis.

***Using automated systems embedded in intelligent dialysis machines***

The technology relies on the combination of patient biologic sensors coupled to a feedback control loop and governed by adaptive algorithms embedded in the dialysis machine. The first example is the sodium control module that has been assessed and validated in clinical trials[72,221]. Using continuous conductivity cell measurements on inlet and outlet dialysate flow, an embedded algorithm controls plasma sodium concentration changes (*i.e.,* tonicity) and allows precise monitoring of plasma sodium concentration and sodium mass removal occurring within dialysis session. Interestingly, sodium mass transfer and plasma tonicity rely on an automated and self-adapting function that follows medical prescription setting. Further outcome based studies are needed to establish clinical benefits to patients and the device’s clinical added value[222].

***Combined use of connected iHealth devices, advanced analytics, and artificial intelligence will be able to support medical decision making and to predict future outcome***

Personalized medicine relying on iHealth trackers, advanced analytics, and artificial intelligence (artificial neuronal networks and machine learning) may allow identification of patients at increased risk. In this respect, the use of such tools will be able to support physician decision-making for individual patients to select the most appropriate treatment modality or suitable technical approach (*i.e.,* ultrafiltration rate and dialysate sodium) to reduce cardiovascular burden[223,224]. Furthermore, iHealth trackers and machine learning support may also be applied to continuous vital signs monitoring and other intra-dialytic hemodynamic variables. The ultimate goal is to detect or predict the occurrence of future clinical events with sufficient precision and time to intervene. Such iHealth trackers seem particularly attractive to monitor arrythmias and maybe to help prevent sudden cardiac death[217]. In brief, the paradigm of precision medicine appears particularly relevant to renal replacement therapy for designing a personalized, more effective, better tolerated, and more acceptable HD treatment[225].

**CONCLUSION**

In this in-depth review, we have summarized factors that are implicated in the cardiovascular and multi-organ morbidity associated with conventional short intermittent HD treatment schedules. Hidden risks result mainly from the conjunction of two main phenomena: First, the intermittent nature of the treatment that is responsible for an unphysiologic profile (illustrated by peaks and troughs reflecting fluctuation of internal milieu composition) and a multifactorial systemic stress; second, the incomplete correction of uremic metabolic abnormalities that may be summarized as “residual syndrome”. Such systemic stress induced by HD treatment is likely implicated in the poor dialysis tolerance and end-organ injury contributing to the DS syndrome. We summarize this cascade of events as the dialysis stress storm and sickness syndrome (D4S) and propose that D4S may act as a negative disease modifier of patient outcome.

Mitigating cardiovascular burden in HD requires further concerted actions to change the treatment paradigm. Such an approach will have multiple targets that should ideally include optimizing hemodynamic management both during the inter- and intra-dialytic phase, enhancing renal replacement therapy efficacy, and personalizing treatment schedule with use of new monitoring tools.

**REFERENCES**

1 **Thomas B**, Wulf S, Bikbov B, Perico N, Cortinovis M, Courville de Vaccaro K, Flaxman A, Peterson H, Delossantos A, Haring D, Mehrotra R, Himmelfarb J, Remuzzi G, Murray C, Naghavi M. Maintenance Dialysis throughout the World in Years 1990 and 2010. *J Am Soc Nephrol* 2015; **26**: 2621-2633 [PMID: 26209712 DOI: 10.1681/ASN.2014101017]

2 **Liyanage T**, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, Lv J, Garg AX, Knight J, Rodgers A, Gallagher M, Kotwal S, Cass A, Perkovic V. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; **385**: 1975-1982 [PMID: 25777665 DOI: 10.1016/S0140-6736(14)61601-9]

3 **Jain D**, Haddad DB, Goel N. Choice of dialysis modality prior to kidney transplantation: Does it matter? *World J Nephrol* 2019; **8**: 1-10 [PMID: 30705867 DOI: 10.5527/wjn.v8.i1.1]

4 **Himmelfarb J**, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. *Nat Rev Nephrol* 2020; **16**: 573-585 [PMID: 32733095 DOI: 10.1038/s41581-020-0315-4]

5 **Robinson BM**, Akizawa T, Jager KJ, Kerr PG, Saran R, Pisoni RL. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet* 2016; **388**: 294-306 [PMID: 27226132 DOI: 10.1016/S0140-6736(16)30448-2]

6 **Lopes AA**, Bragg-Gresham JL, Satayathum S, McCullough K, Pifer T, Goodkin DA, Mapes DL, Young EW, Wolfe RA, Held PJ, Port FK; Worldwide Dialysis Outcomes and Practice Patterns Study Committee. Health-related quality of life and associated outcomes among hemodialysis patients of different ethnicities in the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2003; **41**: 605-615 [PMID: 12612984 DOI: 10.1053/ajkd.2003.50122]

7 **Couillerot-Peyrondet AL**, Sambuc C, Sainsaulieu Y, Couchoud C, Bongiovanni-Delarozière I. A comprehensive approach to assess the costs of renal replacement therapy for end-stage renal disease in France: the importance of age, diabetes status, and clinical events. *Eur J Health Econ* 2017; **18**: 459-469 [PMID: 27146313 DOI: 10.1007/s10198-016-0801-6]

8 **Rayner HC**, Pisoni RL, Bommer J, Canaud B, Hecking E, Locatelli F, Piera L, Bragg-Gresham JL, Feldman HI, Goodkin DA, Gillespie B, Wolfe RA, Held PJ, Port FK. Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004; **19**: 108-120 [PMID: 14671046 DOI: 10.1093/ndt/gfg483]

9 **USRDS**. Annual Data Report. In: Chapter 5: Mortality. United States: NIDDK, 2018;2: 411-426

10 **McIntyre CW**. Recurrent circulatory stress: the dark side of dialysis. *Semin Dial* 2010; **23**: 449-451 [PMID: 21039872 DOI: 10.1111/j.1525-139X.2010.00782.x]

11 **McIntyre C**, Crowley L. Dying to Feel Better: The Central Role of Dialysis-Induced Tissue Hypoxia. *Clin J Am Soc Nephrol* 2016; **11**: 549-551 [PMID: 26936947 DOI: 10.2215/CJN.01380216]

12 **Eriksson JK**, Neovius M, Jacobson SH, Elinder CG, Hylander B. Healthcare costs in chronic kidney disease and renal replacement therapy: a population-based cohort study in Sweden. *BMJ Open* 2016; **6**: e012062 [PMID: 27855091 DOI: 10.1136/bmjopen-2016-012062]

13 **Vanholder R**, Davenport A, Hannedouche T, Kooman J, Kribben A, Lameire N, Lonnemann G, Magner P, Mendelssohn D, Saggi SJ, Shaffer RN, Moe SM, Van Biesen W, van der Sande F, Mehrotra R; Dialysis Advisory Group of American Society of Nephrology. Reimbursement of dialysis: a comparison of seven countries. *J Am Soc Nephrol* 2012; **23**: 1291-1298 [PMID: 22677554 DOI: 10.1681/ASN.2011111094]

14 **Vanholder R**, Annemans L, Brown E, Gansevoort R, Gout-Zwart JJ, Lameire N, Morton RL, Oberbauer R, Postma MJ, Tonelli M, Biesen WV, Zoccali C; European Kidney Health Alliance. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol* 2017; **13**: 393-409 [PMID: 28555652 DOI: 10.1038/nrneph.2017.63]

15 **Shoji T**, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 2004; **66**: 1212-1220 [PMID: 15327420 DOI: 10.1111/j.1523-1755.2004.00812.x]

16 **Flythe JE**, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol* 2015; **26**: 724-734 [PMID: 25270068 DOI: 10.1681/ASN.2014020222]

17 **Assimon MM**, Wang L, Flythe JE. Cumulative Exposure to Frequent Intradialytic Hypotension Associates With New-Onset Dementia Among Elderly Hemodialysis Patients. *Kidney Int Rep* 2019; **4**: 603-606 [PMID: 30993235 DOI: 10.1016/j.ekir.2019.01.001]

18 **Maduell F**, Ramos R, Varas J, Martin-Malo A, Molina M, Pérez-Garcia R, Marcelli D, Moreso F, Aljama P, Merello JI. Hemodialysis patients receiving a greater Kt dose than recommended have reduced mortality and hospitalization risk. *Kidney Int* 2016; **90**: 1332-1341 [PMID: 27780586 DOI: 10.1016/j.kint.2016.08.022]

19 **Agarwal R**, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and management of hypertension in patients on dialysis. *J Am Soc Nephrol* 2014; **25**: 1630-1646 [PMID: 24700870 DOI: 10.1681/ASN.2013060601]

20 **Agarwal R**, Weir MR. Dry-weight: a concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. *Clin J Am Soc Nephrol* 2010; **5**: 1255-1260 [PMID: 20507951 DOI: 10.2215/CJN.01760210]

21 **Agarwal R**, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension* 2009; **53**: 500-507 [PMID: 19153263 DOI: 10.1161/HYPERTENSIONAHA.108.125674]

22 **Moissl U**, Arias-Guillén M, Wabel P, Fontseré N, Carrera M, Campistol JM, Maduell F. Bioimpedance-guided fluid management in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; **8**: 1575-1582 [PMID: 23949235 DOI: 10.2215/CJN.12411212]

23 **Wabel P**, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009; **27**: 75-80 [PMID: 19169022 DOI: 10.1159/000167013]

24 **Zoccali C**. Lung Ultrasound in the Management of Fluid Volume in Dialysis Patients: Potential Usefulness. *Semin Dial* 2017; **30**: 6-9 [PMID: 28043083 DOI: 10.1111/sdi.12559]

25 **McIntyre CW**. Effects of hemodialysis on cardiac function. *Kidney Int* 2009; **76**: 371-375 [PMID: 19516249 DOI: 10.1038/ki.2009.207]

26 **Assa S**, Hummel YM, Voors AA, Kuipers J, Westerhuis R, Groen H, Bakker SJ, Muller Kobold AC, van Oeveren W, Struck J, de Jong PE, Franssen CF. Hemodialysis-induced regional left ventricular systolic dysfunction and inflammation: a cross-sectional study. *Am J Kidney Dis* 2014; **64**: 265-273 [PMID: 24364893 DOI: 10.1053/j.ajkd.2013.11.010]

27 **Buchanan C**, Mohammed A, Cox E, Köhler K, Canaud B, Taal MW, Selby NM, Francis S, McIntyre CW. Intradialytic Cardiac Magnetic Resonance Imaging to Assess Cardiovascular Responses in a Short-Term Trial of Hemodiafiltration and Hemodialysis. *J Am Soc Nephrol* 2017; **28**: 1269-1277 [PMID: 28122851 DOI: 10.1681/ASN.2016060686]

28 **McIntyre CW**, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CS, Camici PG. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 2008; **3**: 19-26 [PMID: 18003765 DOI: 10.2215/CJN.03170707]

29 **Eldehni MT**, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol* 2015; **26**: 957-965 [PMID: 25234925 DOI: 10.1681/ASN.2013101086]

30 **Freemont AJ**. The pathology of dialysis. *Semin Dial* 2002; **15**: 227-231 [PMID: 12191022 DOI: 10.1046/j.1525-139X.2002.00065.x]

31 **Cambi V**, Arisi L, Bignardi L, Garini G, Rossi E, Savazzi G, Migone L. Preliminary results obtained with short dialysis schedules. *Ateneo Parmense Acta Biomed* 1975; **46**: 349-358 [PMID: 1232995]

32 **Kjellstrand CM**, Evans RL, Petersen RJ, Shideman JR, von Hartitzsch B, Buselmeier TJ. The "unphysiology" of dialysis: a major cause of dialysis side effects? *Kidney Int Suppl* 1975: 30-34 [PMID: 1057690]

33 **Kjellstrand CM**, Evans RL, Petersen RJ, Shideman JR, Von Hartitzsch B, Buselmeier TJ. The "unphysiology" of dialysis: a major cause of dialysis side effects? *Hemodial Int* 2004; **8**: 24-29 [PMID: 19379398 DOI: 10.1111/j.1492-7535.2004.00083.x]

34 **Canaud B**, Kooman JP, Selby NM, Taal MW, Francis S, Maierhofer A, Kopperschmidt P, Collins A, Kotanko P. Dialysis-Induced Cardiovascular and Multiorgan Morbidity. *Kidney Int Rep* 2020; **5**: 1856-1869 [PMID: 33163709 DOI: 10.1016/j.ekir.2020.08.031]

35 **Cambi V**, Savazzi G, Arisi L, Bignardi L, Bruschi G, Rossi E, Migone L. Short dialysis schedules (SDS)--finally ready to become routine? *Proc Eur Dial Transplant Assoc* 1975; **11**: 112-120 [PMID: 1197243]

36 **Ledebo I**. Does convective dialysis therapy applied daily approach renal blood purification? *Kidney Int Suppl* 2001; **78**: S286-S291 [PMID: 11169028 DOI: 10.1046/j.1523-1755.2001.59780286.x]

37 **Modell H**, Cliff W, Michael J, McFarland J, Wenderoth MP, Wright A. A physiologist's view of homeostasis. *Adv Physiol Educ* 2015; **39**: 259-266 [PMID: 26628646 DOI: 10.1152/advan.00107.2015]

38 **Canaud B**, Chazot C, Koomans J, Collins A. Fluid and hemodynamic management in hemodialysis patients: challenges and opportunities. *J Bras Nefrol* 2019; **41**: 550-559 [PMID: 31661543 DOI: 10.1590/2175-8239-JBN-2019-0135]

39 **Kjellström B**, Braunschweig F, Löfberg E, Fux T, Grandjean PA, Linde C. Changes in right ventricular pressures between hemodialysis sessions recorded by an implantable hemodynamic monitor. *Am J Cardiol* 2009; **103**: 119-123 [PMID: 19101241 DOI: 10.1016/j.amjcard.2008.08.038]

40 **Flythe JE**, Brunelli SM. The risks of high ultrafiltration rate in chronic hemodialysis: implications for patient care. *Semin Dial* 2011; **24**: 259-265 [PMID: 21480996 DOI: 10.1111/j.1525-139X.2011.00854.x]

41 **Flythe JE**, Assimon MM, Wang L. Ultrafiltration Rate Scaling in Hemodialysis Patients. *Semin Dial* 2017; **30**: 282-283 [PMID: 28387031 DOI: 10.1111/sdi.12602]

42 **Levin NW**, de Abreu MHFG, Borges LE, Tavares Filho HA, Sarwar R, Gupta S, Hafeez T, Lev S, Williams C. Hemodynamic response to fluid removal during hemodialysis: categorization of causes of intradialytic hypotension. *Nephrol Dial Transplant* 2018; **33**: 1643-1649 [PMID: 29669016 DOI: 10.1093/ndt/gfy048]

43 **McGuire S,** Horton EJ, Renshaw D, Jimenez A, Krishnan N, McGregor G. Hemodynamic Instability during Dialysis: The Potential Role of Intradialytic Exercise. *Biomed Res Int* 2018; **2018**: 8276912 [PMID: 29682559 DOI: 10.1155/2018/8276912]

44 **Burton JO**, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; **4**: 914-920 [PMID: 19357245 DOI: 10.2215/CJN.03900808]

45 **Baldamus CA**, Ernst W, Frei U, Koch KM. Sympathetic and hemodynamic response to volume removal during different forms of renal replacement therapy. *Nephron* 1982; **31**: 324-332 [PMID: 7177269 DOI: 10.1159/000182675]

46 **Baldamus CA**, Ernst W, Kachel HG, Lysaght M, Koch KM. Hemodynamics in hemofiltration. *Contrib Nephrol* 1982; **32**: 56-60 [PMID: 7128163 DOI: 10.1159/000406905]

47 **Jefferies HJ**, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol* 2011; **6**: 1326-1332 [PMID: 21597028 DOI: 10.2215/CJN.05200610]

48 **Chou JA**, Kalantar-Zadeh K, Mathew AT. A brief review of intradialytic hypotension with a focus on survival. *Semin Dial* 2017; **30**: 473-480 [PMID: 28661565 DOI: 10.1111/sdi.12627]

49 **Chirakarnjanakorn S**, Navaneethan SD, Francis GS, Tang WH. Cardiovascular impact in patients undergoing maintenance hemodialysis: Clinical management considerations. *Int J Cardiol* 2017; **232**: 12-23 [PMID: 28108129 DOI: 10.1016/j.ijcard.2017.01.015]

50 **Herum KM**, Choppe J, Kumar A, Engler AJ, McCulloch AD. Mechanical regulation of cardiac fibroblast profibrotic phenotypes. *Mol Biol Cell* 2017; **28**: 1871-1882 [PMID: 28468977 DOI: 10.1091/mbc.E17-01-0014]

51 **Mollahosseini A,** Abdelrasoul A, Shoker A. A critical review of recent advances in hemodialysis membranes hemocompatibility and guidelines for future development. *Mater Chem Phys* 2020; **248**: 122911 [DOI: 10.1016/j.matchemphys.2020.122911]

52 **Wagner S,** Zschätzsch S, Erlenkoetter A, Rauber L, Stauss-Grabo M, Gauly A. Hemocompatibility of Polysulfone Hemodialyzers - Exploratory Studies on Impact of Treatment Modality and Dialyzer Characteristics. *Kidney360* 2020; **1**: 25-35 [DOI: 10.34067/KID.0000342019]

53 **Weber M**, Steinle H, Golombek S, Hann L, Schlensak C, Wendel HP, Avci-Adali M. Blood-Contacting Biomaterials: *In Vitro* Evaluation of the Hemocompatibility. *Front Bioeng Biotechnol* 2018; **6**: 99 [PMID: 30062094 DOI: 10.3389/fbioe.2018.00099]

54 **Doyle AJ**, Hunt BJ. Current Understanding of How Extracorporeal Membrane Oxygenators Activate Haemostasis and Other Blood Components. *Front Med (Lausanne)* 2018; **5**: 352 [PMID: 30619862 DOI: 10.3389/fmed.2018.00352]

55 **Martens RJH**, Broers NJH, Canaud B, Christiaans MHL, Cornelis T, Gauly A, Hermans MMH, Konings CJAM, van der Sande FM, Scheijen JLJM, Stifft F, Wirtz JJJM, Kooman JP, Schalkwijk CG. Relations of advanced glycation endproducts and dicarbonyls with endothelial dysfunction and low-grade inflammation in individuals with end-stage renal disease in the transition to renal replacement therapy: A cross-sectional observational study. *PLoS One* 2019; **14**: e0221058 [PMID: 31408493 DOI: 10.1371/journal.pone.0221058]

56 **Schaefer RM**, Heidland A, Hörl WH. Effect of dialyzer geometry on granulocyte and complement activation. *Am J Nephrol* 1987; **7**: 121-126 [PMID: 3496792 DOI: 10.1159/000167446]

57 **Taylor JE**, McLaren M, Mactier RA, Henderson IS, Stewart WK, Belch JJ. Effect of dialyzer geometry during hemodialysis with cuprophane membranes. *Kidney Int* 1992; **42**: 442-447 [PMID: 1405328 DOI: 10.1038/ki.1992.307]

58 **Cheung AK**. Biocompatibility of hemodialysis membranes. *J Am Soc Nephrol* 1990; **1**: 150-161 [PMID: 2104259 DOI: 10.1681/ASN.V12150]

59 **Schindler R**, Beck W, Deppisch R, Aussieker M, Wilde A, Göhl H, Frei U. Short bacterial DNA fragments: detection in dialysate and induction of cytokines. *J Am Soc Nephrol* 2004; **15**: 3207-3214 [PMID: 15579524 DOI: 10.1097/01.ASN.0000145049.94888.26]

60 **Hörl WH**, Jochum M, Heidland A, Fritz H. Release of granulocyte proteinases during hemodialysis. *Am J Nephrol* 1983; **3**: 213-217 [PMID: 6351616 DOI: 10.1159/000166713]

61 **Muñoz de Bustillo E**, Alvarez Chiva V. Leukocyte--endothelial cell interactions in haemodialysis-induced neutropenia. *Nephrol Dial Transplant* 1996; **11**: 572-574 [PMID: 8671842 DOI: 10.1093/oxfordjournals.ndt.a027343]

62 **Windus DW,** Atkinson R, Santoro S. The effects of hemodialysis on platelet activation with new and reprocessed regenerated cellulose dialyzers. *Am J Kidney Dis* 1996; **27**: 387-393 [DOI: 10.1016/S0272-6386(96)90362-5]

63 **Schoorl M**, Schoorl M, Nubé MJ, Bartels PC. Platelet depletion, platelet activation and coagulation during treatment with hemodialysis. *Scand J Clin Lab Invest* 2011; **71**: 240-247 [PMID: 21303224 DOI: 10.3109/00365513.2011.558106]

64 **Coppo R**, Amore A, Cirina P, Scelfo B, Giacchino F, Comune L, Atti M, Renaux JL. Bradykinin and nitric oxide generation by dialysis membranes can be blunted by alkaline rinsing solutions. *Kidney Int* 2000; **58**: 881-888 [PMID: 10916114 DOI: 10.1046/j.1523-1755.2000.00238.x]

65 **Krishnan A**, Vogler EA, Sullenger BA, Becker RC. The effect of surface contact activation and temperature on plasma coagulation with an RNA aptamer directed against factor IXa. *J Thromb Thrombolysis* 2013; **35**: 48-56 [PMID: 23054460 DOI: 10.1007/s11239-012-0778-7]

66 **Marney AM**, Ma J, Luther JM, Ikizler TA, Brown NJ. Endogenous bradykinin contributes to increased plasminogen activator inhibitor 1 antigen following hemodialysis. *J Am Soc Nephrol* 2009; **20**: 2246-2252 [PMID: 19628666 DOI: 10.1681/ASN.2009050505]

67 **Hakim RM**. Clinical implications of hemodialysis membrane biocompatibility. *Kidney Int* 1993; **44**: 484-494 [PMID: 8231020 DOI: 10.1038/ki.1993.272]

68 **Heidland A**, Hörl WH, Heller N, Heine H, Neumann S, Heidbreder E. Proteolytic enzymes and catabolism: enhanced release of granulocyte proteinases in uremic intoxication and during hemodialysis. *Kidney Int Suppl* 1983; **16**: S27-S36 [PMID: 6376917]

69 **Hörl WH**, Feinstein EI, Wanner C, Frischmuth N, Gösele A, Massry SG. Plasma levels of main granulocyte components during hemodialysis. Comparison of new and reused dialyzers. *Am J Nephrol* 1990; **10**: 53-57 [PMID: 2343881 DOI: 10.1159/000168054]

70 **Schaefer RM**, Heidland A, Hörl WH. Release of leukocyte elastase during hemodialysis. Effect of different dialysis membranes. *Contrib Nephrol* 1985; **46**: 109-117 [PMID: 3874043 DOI: 10.1159/000410773]

71 **Craddock PR**, Fehr J, Dalmasso AP, Brighan KL, Jacob HS. Hemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes. *J Clin Invest* 1977; **59**: 879-888 [PMID: 856872 DOI: 10.1172/JCI108710]

72 **Ságová M**, Wojke R, Maierhofer A, Gross M, Canaud B, Gauly A. Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis. *Artif Organs* 2019; **43**: 1002-1013 [PMID: 30939213 DOI: 10.1111/aor.13463]

73 **Hörl WH**, Schaefer RM, Heidland A. Effect of different dialyzers on proteinases and proteinase inhibitors during hemodialysis. *Am J Nephrol* 1985; **5**: 320-326 [PMID: 2414989 DOI: 10.1159/000166956]

74 **Morena M**, Delbosc S, Dupuy AM, Canaud B, Cristol JP. Overproduction of reactive oxygen species in end-stage renal disease patients: a potential component of hemodialysis-associated inflammation. *Hemodial Int* 2005; **9**: 37-46 [PMID: 16191052 DOI: 10.1111/j.1492-7535.2005.01116.x]

75 **Cobo G**, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transplant* 2018; **33**: iii35-iii40 [PMID: 30281126 DOI: 10.1093/ndt/gfy175]

76 **Saha M**, Allon M. Diagnosis, Treatment, and Prevention of Hemodialysis Emergencies. *Clin J Am Soc Nephrol* 2017; **12**: 357-369 [PMID: 27831511 DOI: 10.2215/CJN.05260516]

77 **Koga Y**, Fujieda H, Meguro H, Ueno Y, Aoki T, Miwa K, Kainoh M. Biocompatibility of Polysulfone Hemodialysis Membranes and Its Mechanisms: Involvement of Fibrinogen and Its Integrin Receptors in Activation of Platelets and Neutrophils. *Artif Organs* 2018; **42**: E246-E258 [PMID: 30239013 DOI: 10.1111/aor.13268]

78 **Kohlová M**, Amorim CG, Araújo A, Santos-Silva A, Solich P, Montenegro MCBSM. The biocompatibility and bioactivity of hemodialysis membranes: their impact in end-stage renal disease. *J Artif Organs* 2019; **22**: 14-28 [PMID: 30006787 DOI: 10.1007/s10047-018-1059-9]

79 **Eswari JS,** Naik S. A critical analysis on various technologies and functionalized materials for manufacturing dialysis membranes. *Mater Sci Energy Technol* 2020; **3**: 116-126 [DOI: 10.1016/j.mset.2019.10.011]

80 **Chan CT**. Sleep apnea with intermittent hemodialysis: time for a wake-up call!. *J Am Soc Nephrol* 2006; **17**: 3279-3280 [PMID: 17093070 DOI: 10.1681/ASN.2006101110]

81 **Lopot F**, Válek A. Mathematical Concept of Dialysis Unphysiology. *Home Hemodial Int (1997)* 1998; **2**: 18-21 [PMID: 28466530 DOI: 10.1111/hdi.1998.2.1.18]

82 **Lopot F**, Nejedlý B, Sulková S. Physiology in daily hemodialysis in terms of the time average concentration/time average deviation concept. *Hemodial Int* 2004; **8**: 39-44 [PMID: 19379400 DOI: 10.1111/j.1492-7535.2004.00073.x]

83 **Burmeister JE**, Scapini A, da Rosa Miltersteiner D, da Costa MG, Campos BM. Glucose-added dialysis fluid prevents asymptomatic hypoglycaemia in regular haemodialysis. *Nephrol Dial Transplant* 2007; **22**: 1184-1189 [PMID: 17272314 DOI: 10.1093/ndt/gfl710]

84 **Abe M**, Kalantar-Zadeh K. Haemodialysis-induced hypoglycaemia and glycaemic disarrays. *Nat Rev Nephrol* 2015; **11**: 302-313 [PMID: 25848881 DOI: 10.1038/nrneph.2015.38]

85 **Chazot C**, Shahmir E, Matias B, Laidlaw S, Kopple JD. Dialytic nutrition: provision of amino acids in dialysate during hemodialysis. *Kidney Int* 1997; **52**: 1663-1670 [PMID: 9407515 DOI: 10.1038/ki.1997.500]

86 **Raimann JG**, Kruse A, Thijssen S, Kuntsevich V, Dabel P, Bachar M, Diaz-Buxo JA, Levin NW, Kotanko P. Metabolic effects of dialyzate glucose in chronic hemodialysis: results from a prospective, randomized crossover trial. *Nephrol Dial Transplant* 2012; **27**: 1559-1568 [PMID: 21940484 DOI: 10.1093/ndt/gfr520]

87 **Sahani MM**, Daoud TM, Sam R, Andrews J, Cheng YL, Kjellstrand CM, Ing TS. Dialysis Disequilibrium Syndrome Revisited. *Hemodial Int* 2001; **5**: 92-96 [PMID: 28452440 DOI: 10.1111/hdi.2001.5.1.92]

88 **Zepeda-Orozco D**, Quigley R. Dialysis disequilibrium syndrome. *Pediatr Nephrol* 2012; **27**: 2205-2211 [PMID: 22710692 DOI: 10.1007/s00467-012-2199-4]

89 **Romaldini H**, Rodriguez-Roisin R, Lopez FA, Ziegler TW, Bencowitz HZ, Wagner PD. The mechanisms of arterial hypoxemia during hemodialysis. *Am Rev Respir Dis* 1984; **129**: 780-784 [PMID: 6426356 DOI: 10.1164/arrd.1984.129.5.780]

90 **Cardoso M,** Vinay P, Vinet B, Léveillée M, Prud'homme M, Téjédor A, Courteau M, Gougoux M, St-Louis G, Lapierre L, Piette Y. Hypoxemia during hemodialysis: a critical review of the facts. *Am J Kidney Dis* 1988; **11**: 281-297 [DOI: 10.1016/S0272-6386(88)80133-1]

91 **Campos I**, Chan L, Zhang H, Deziel S, Vaughn C, Meyring-Wösten A, Kotanko P. Intradialytic Hypoxemia in Chronic Hemodialysis Patients. *Blood Purif* 2016; **41**: 177-187 [PMID: 26765143 DOI: 10.1159/000441271]

92 **Meyring-Wösten A**, Zhang H, Ye X, Fuertinger DH, Chan L, Kappel F, Artemyev M, Ginsberg N, Wang Y, Thijssen S, Kotanko P. Intradialytic Hypoxemia and Clinical Outcomes in Patients on Hemodialysis. *Clin J Am Soc Nephrol* 2016; **11**: 616-625 [PMID: 26936946 DOI: 10.2215/CJN.08510815]

93 **Chou JA**, Streja E, Nguyen DV, Rhee CM, Obi Y, Inrig JK, Amin A, Kovesdy CP, Sim JJ, Kalantar-Zadeh K. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrol Dial Transplant* 2018; **33**: 149-159 [PMID: 28444336 DOI: 10.1093/ndt/gfx037]

94 **Forni Ogna V**, Ogna A, Pruijm M, Bassi I, Zuercher E, Halabi G, Phan O, Bullani R, Teta D, Gauthier T, Cherpillod A, Mathieu C, Mihalache A, Cornette F, Haba-Rubio J, Burnier M, Heinzer R. Prevalence and Diagnostic Approach to Sleep Apnea in Hemodialysis Patients: A Population Study. *Biomed Res Int* 2015; **2015**: 103686 [PMID: 26229952 DOI: 10.1155/2015/103686]

95 **Kerns ES**, Kim ED, Meoni LA, Sozio SM, Jaar BG, Estrella MM, Parekh RS, Bourjeily G. Obstructive Sleep Apnea Increases Sudden Cardiac Death in Incident Hemodialysis Patients. *Am J Nephrol* 2018; **48**: 147-156 [PMID: 30110675 DOI: 10.1159/000489963]

96 **Ito K,** Ookawara S, Fueki M, Imai S, Hattori T, Kiryu S, Sugai Y, Wada N, Shindo M, Ohnishi Y, Iino N, Tabei K, Morishita Y. Sleep apnea syndrome caused lowering of cerebral oxygenation in a hemodialysis patient: a case report and literature review. *Ren Replace Ther* 2018; **4**: 54 [DOI: 10.1186/s41100-018-0194-3]

97 **Zoccali C**, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 2002; **13**: 729-733 [PMID: 11856778 DOI: 10.1681/ASN.V133729]

98 **Zoccali C**, Benedetto FA, Tripepi G, Cambareri F, Panuccio V, Candela V, Mallamaci F, Enia G, Labate C, Tassone F. Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. *Kidney Int* 1998; **53**: 1078-1084 [PMID: 9551420 DOI: 10.1111/j.1523-1755.1998.00853.x]

99 **Chiu KL**, Ryan CM, Shiota S, Ruttanaumpawan P, Arzt M, Haight JS, Chan CT, Floras JS, Bradley TD. Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. *Am J Respir Crit Care Med* 2006; **174**: 1378-1383 [PMID: 16998093 DOI: 10.1164/rccm.200607-927OC]

100 **Stenvinkel P**, Carrero JJ, von Walden F, Ikizler TA, Nader GA. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. *Nephrol Dial Transplant* 2016; **31**: 1070-1077 [PMID: 25910496 DOI: 10.1093/ndt/gfv122]

101 **Canaud B**, Ye X, Usvyat L, Kooman J, van der Sande F, Raimann J, Wang Y, Kotanko P. Clinical and predictive value of simplified creatinine index used as muscle mass surrogate in end-stage kidney disease haemodialysis patients-results from the international MONitoring Dialysis Outcome initiative. *Nephrol Dial Transplant* 2020; **35**: 2161-2171 [PMID: 32830264 DOI: 10.1093/ndt/gfaa098]

102 **Carrero JJ**, Chmielewski M, Axelsson J, Snaedal S, Heimbürger O, Bárány P, Suliman ME, Lindholm B, Stenvinkel P, Qureshi AR. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr* 2008; **27**: 557-564 [PMID: 18538898 DOI: 10.1016/j.clnu.2008.04.007]

103 **Sabatino A**, Cuppari L, Stenvinkel P, Lindholm B, Avesani CM. Sarcopenia in chronic kidney disease: what have we learned so far? *J Nephrol* 2021; **34**: 1347-1372 [PMID: 32876940 DOI: 10.1007/s40620-020-00840-y]

104 **Kopple JD,** Massry SG, Kalantar-Zadeh K. Nutritional Management of Renal Disease. In: Workeneh B, Mitch WE. The Influence of Kidney Disease on Protein and Amino Acid Metabolism. Amsterdam: Elsevier, 2013: 1-16 [DOI: 10.1016/B978-0-12-391934-2.00001-1]

105 **Garibotto G**, Russo R, Sofia A, Sala MR, Robaudo C, Moscatelli P, Deferrari G, Tizianello A. Skeletal muscle protein synthesis and degradation in patients with chronic renal failure. *Kidney Int* 1994; **45**: 1432-1439 [PMID: 8072256 DOI: 10.1038/ki.1994.187]

106 **Lim VS**, Ikizler TA, Raj DS, Flanigan MJ. Does hemodialysis increase protein breakdown? Dissociation between whole-body amino acid turnover and regional muscle kinetics. *J Am Soc Nephrol* 2005; **16**: 862-868 [PMID: 15716333 DOI: 10.1681/ASN.2004080624]

107 **Lim VS**, Kopple JD. Protein metabolism in patients with chronic renal failure: role of uremia and dialysis. *Kidney Int* 2000; **58**: 1-10 [PMID: 10886544 DOI: 10.1046/j.1523-1755.2000.00135.x]

108 **Almushayt SJ**, Hussain S, Wilkinson DJ, Selby NM. A Systematic Review of the Acute Effects of Hemodialysis on Skeletal Muscle Perfusion, Metabolism, and Function. *Kidney Int Rep* 2020; **5**: 307-317 [PMID: 32154452 DOI: 10.1016/j.ekir.2019.12.012]

109 **Gil HW**, Yang JO, Lee EY, Lee EM, Choi JS, Hong SY. The effect of dialysis membrane flux on amino acid loss in hemodialysis patients. *J Korean Med Sci* 2007; **22**: 598-603 [PMID: 17728495 DOI: 10.3346/jkms.2007.22.4.598]

110 **Hynote ED**, McCamish MA, Depner TA, Davis PA. Amino acid losses during hemodialysis: effects of high-solute flux and parenteral nutrition in acute renal failure. *JPEN J Parenter Enteral Nutr* 1995; **19**: 15-21 [PMID: 7658594 DOI: 10.1177/014860719501900115]

111 **Hendriks FK**, Smeets JSJ, Broers NJH, van Kranenburg JMX, van der Sande FM, Kooman JP, van Loon LJC. End-Stage Renal Disease Patients Lose a Substantial Amount of Amino Acids during Hemodialysis. *J Nutr* 2020; **150**: 1160-1166 [PMID: 32006029 DOI: 10.1093/jn/nxaa010]

112 **Raj DS**, Moseley P, Dominic EA, Onime A, Tzamaloukas AH, Boyd A, Shah VO, Glew R, Wolfe R, Ferrando A. Interleukin-6 modulates hepatic and muscle protein synthesis during hemodialysis. *Kidney Int* 2008; **73**: 1054-1061 [PMID: 18288103 DOI: 10.1038/ki.2008.21]

113 **van Hall G**. Cytokines: muscle protein and amino acid metabolism. *Curr Opin Clin Nutr Metab Care* 2012; **15**: 85-91 [PMID: 22123617 DOI: 10.1097/MCO.0b013e32834e6ea2]

114 **van Hall G**, Steensberg A, Fischer C, Keller C, Møller K, Moseley P, Pedersen BK. Interleukin-6 markedly decreases skeletal muscle protein turnover and increases nonmuscle amino acid utilization in healthy individuals. *J Clin Endocrinol Metab* 2008; **93**: 2851-2858 [PMID: 18430776 DOI: 10.1210/jc.2007-2223]

115 **Raj DS**, Adeniyi O, Dominic EA, Boivin MA, McClelland S, Tzamaloukas AH, Morgan N, Gonzales L, Wolfe R, Ferrando A. Amino acid repletion does not decrease muscle protein catabolism during hemodialysis. *Am J Physiol Endocrinol Metab* 2007; **292**: E1534-E1542 [PMID: 17264222 DOI: 10.1152/ajpendo.00599.2006]

116 **Gutierrez A**, Bergström J, Alvestrand A. Hemodialysis-associated protein catabolism with and without glucose in the dialysis fluid. *Kidney Int* 1994; **46**: 814-822 [PMID: 7996803 DOI: 10.1038/ki.1994.337]

117 **Gutierrez A**. Protein catabolism in maintenance haemodialysis: the influence of the dialysis membrane. *Nephrol Dial Transplant* 1996; **11** Suppl 2: 108-111 [PMID: 8804008 DOI: 10.1093/ndt/11.supp2.108]

118 **Gutierrez A**, Alvestrand A, Wahren J, Bergström J. Effect of in vivo contact between blood and dialysis membranes on protein catabolism in humans. *Kidney Int* 1990; **38**: 487-494 [PMID: 2232492 DOI: 10.1038/ki.1990.230]

119 **Susantitaphong P**, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. *Nephrol Dial Transplant* 2013; **28**: 438-446 [PMID: 23291370 DOI: 10.1093/ndt/gfs514]

120 **Ikizler TA**, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, TerWee P, Teta D, Wang AY, Wanner C; International Society of Renal Nutrition and Metabolism. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013; **84**: 1096-1107 [PMID: 23698226 DOI: 10.1038/ki.2013.147]

121 **Stegmayr B**. Dialysis Procedures Alter Metabolic Conditions. *Nutrients* 2017; **9** [PMID: 28554992 DOI: 10.3390/nu9060548]

122 **Farrell PC**, Hone PW. Dialysis-induced catabolism. *Am J Clin Nutr* 1980; **33**: 1417-1422 [PMID: 7395770 DOI: 10.1093/ajcn/33.7.1417]

123 **Ikizler TA**, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RM. Increased energy expenditure in hemodialysis patients. *J Am Soc Nephrol* 1996; **7**: 2646-2653 [PMID: 8989743 DOI: 10.1681/ASN.V7122646]

124 **Borah MF**, Schoenfeld PY, Gotch FA, Sargent JA, Wolfsen M, Humphreys MH. Nitrogen balance during intermittent dialysis therapy of uremia. *Kidney Int* 1978; **14**: 491-500 [PMID: 750694 DOI: 10.1038/ki.1978.154]

125 **Maroni BJ**, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 1985; **27**: 58-65 [PMID: 3981873 DOI: 10.1038/ki.1985.10]

126 **Slomowitz LA**, Monteon FJ, Grosvenor M, Laidlaw SA, Kopple JD. Effect of energy intake on nutritional status in maintenance hemodialysis patients. *Kidney Int* 1989; **35**: 704-711 [PMID: 2709673 DOI: 10.1038/ki.1989.42]

127 **Johnson S**, Crane PB, Neil J, Christiano C. Coping with Intradialytic Events and Stress Associated with Hemodialysis. *Nephrol Nurs J* 2019; **46**: 13-21 [PMID: 30835092]

128 **Kuipers J**, Oosterhuis JK, Paans W, Krijnen WP, Gaillard CAJM, Westerhuis R, Franssen CFM. Association between quality of life and various aspects of intradialytic hypotension including patient-reported intradialytic symptom score. *BMC Nephrol* 2019; **20**: 164 [PMID: 31088398 DOI: 10.1186/s12882-019-1366-2]

129 **van der Willik EM**, Meuleman Y, Prantl K, van Rijn G, Bos WJW, van Ittersum FJ, Bart HAJ, Hemmelder MH, Dekker FW. Patient-reported outcome measures: selection of a valid questionnaire for routine symptom assessment in patients with advanced chronic kidney disease - a four-phase mixed methods study. *BMC Nephrol* 2019; **20**: 344 [PMID: 31477039 DOI: 10.1186/s12882-019-1521-9]

130 **van Loon IN**, Bots ML, Boereboom FTJ, Grooteman MPC, Blankestijn PJ, van den Dorpel MA, Nubé MJ, Ter Wee PM, Verhaar MC, Hamaker ME. Quality of life as indicator of poor outcome in hemodialysis: relation with mortality in different age groups. *BMC Nephrol* 2017; **18**: 217 [PMID: 28679361 DOI: 10.1186/s12882-017-0621-7]

131 **Nair D**, Finkelstein FO. Toward Developing a Patient-Reported Outcome Measure for Fatigue in Hemodialysis. *Am J Kidney Dis* 2019; **74**: 151-154 [PMID: 31155324 DOI: 10.1053/j.ajkd.2019.03.425]

132 **Flythe JE**, Hilliard T, Castillo G, Ikeler K, Orazi J, Abdel-Rahman E, Pai AB, Rivara MB, St Peter WL, Weisbord SD, Wilkie C, Mehrotra R. Symptom Prioritization among Adults Receiving In-Center Hemodialysis: A Mixed Methods Study. *Clin J Am Soc Nephrol* 2018; **13**: 735-745 [PMID: 29559445 DOI: 10.2215/CJN.10850917]

133 **Finkelstein FO**, Finkelstein SH. Time to Rethink Our Approach to Patient-Reported Outcome Measures for ESRD. *Clin J Am Soc Nephrol* 2017; **12**: 1885-1888 [PMID: 28847907 DOI: 10.2215/CJN.04850517]

134 **Finkelstein FO**, Schiller B, Daoui R, Gehr TW, Kraus MA, Lea J, Lee Y, Miller BW, Sinsakul M, Jaber BL. At-home short daily hemodialysis improves the long-term health-related quality of life. *Kidney Int* 2012; **82**: 561-569 [PMID: 22622497 DOI: 10.1038/ki.2012.168]

135 **Kliger AS**, Finkelstein FO. Can we improve the quality of life for dialysis patients? *Am J Kidney Dis* 2009; **54**: 993-995 [PMID: 19932876 DOI: 10.1053/j.ajkd.2009.09.005]

136 **Jaar BG**, Chang A, Plantinga L. Can we improve quality of life of patients on dialysis? *Clin J Am Soc Nephrol* 2013; **8**: 1-4 [PMID: 23296376 DOI: 10.2215/CJN.11861112]

137 **Jaber BL**, Lee Y, Collins AJ, Hull AR, Kraus MA, McCarthy J, Miller BW, Spry L, Finkelstein FO; FREEDOM Study Group. Effect of daily hemodialysis on depressive symptoms and postdialysis recovery time: interim report from the FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study. *Am J Kidney Dis* 2010; **56**: 531-539 [PMID: 20673601 DOI: 10.1053/j.ajkd.2010.04.019]

138 **Mapes DL**, Bragg-Gresham JL, Bommer J, Fukuhara S, McKevitt P, Wikström B, Lopes AA. Health-related quality of life in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2004; **44**: 54-60 [PMID: 15486875 DOI: 10.1053/j.ajkd.2004.08.012]

139 **Mapes DL**, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK. Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 2003; **64**: 339-349 [PMID: 12787427 DOI: 10.1046/j.1523-1755.2003.00072.x]

140 **Odudu A**, Eldehni MT, McCann GP, McIntyre CW. Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients. *Clin J Am Soc Nephrol* 2015; **10**: 1408-1417 [PMID: 25964310 DOI: 10.2215/CJN.00200115]

141 **McIntyre CW**, Goldsmith DJ. Ischemic brain injury in hemodialysis patients: which is more dangerous, hypertension or intradialytic hypotension? *Kidney Int* 2015; **87**: 1109-1115 [PMID: 25853331 DOI: 10.1038/ki.2015.62]

142 **Grant CJ**, Huang SS, McIntyre CW. Hepato-splanchnic circulatory stress: An important effect of hemodialysis. *Semin Dial* 2019; **32**: 237-242 [PMID: 30937954 DOI: 10.1111/sdi.12782]

143 **Karaboyas A**, Zee J, Brunelli SM, Usvyat LA, Weiner DE, Maddux FW, Nissenson AR, Jadoul M, Locatelli F, Winkelmayer WC, Port FK, Robinson BM, Tentori F. Dialysate Potassium, Serum Potassium, Mortality, and Arrhythmia Events in Hemodialysis: Results From the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2017; **69**: 266-277 [PMID: 27866964 DOI: 10.1053/j.ajkd.2016.09.015]

144 **Pun PH**, Middleton JP. Dialysate Potassium, Dialysate Magnesium, and Hemodialysis Risk. *J Am Soc Nephrol* 2017; **28**: 3441-3451 [PMID: 28993507 DOI: 10.1681/ASN.2017060640]

145 **Rhee CM**, Chou JA, Kalantar-Zadeh K. Dialysis Prescription and Sudden Death. *Semin Nephrol* 2018; **38**: 570-581 [PMID: 30413252 DOI: 10.1016/j.semnephrol.2018.08.003]

146 **Charytan DM**, Foley R, McCullough PA, Rogers JD, Zimetbaum P, Herzog CA, Tumlin JA; MiD Investigators and Committees. Arrhythmia and Sudden Death in Hemodialysis Patients: Protocol and Baseline Characteristics of the Monitoring in Dialysis Study. *Clin J Am Soc Nephrol* 2016; **11**: 721-734 [PMID: 26763255 DOI: 10.2215/CJN.09350915]

147 **Roy-Chaudhury P**, Tumlin JA, Koplan BA, Costea AI, Kher V, Williamson D, Pokhariyal S, Charytan DM; MiD investigators and committees. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int* 2018; **93**: 941-951 [PMID: 29395340 DOI: 10.1016/j.kint.2017.11.019]

148 **Gorcsan J 3rd**, Haugaa KH. Ventricular Arrhythmias and Reduced Echocardiographic Inferior Wall Strain: Is Regional Function an Important Risk Marker? *Circ Cardiovasc Imaging* 2017; **10** [PMID: 28003223 DOI: 10.1161/CIRCIMAGING.116.005900]

149 **Kalra PA**, Green D, Poulikakos D. Arrhythmia in hemodialysis patients and its relation to sudden death. *Kidney Int* 2018; **93**: 781-783 [PMID: 29571451 DOI: 10.1016/j.kint.2017.12.005]

150 **Nguyen MN**, Kiriazis H, Gao XM, Du XJ. Cardiac Fibrosis and Arrhythmogenesis. *Compr Physiol* 2017; **7**: 1009-1049 [PMID: 28640451 DOI: 10.1002/cphy.c160046]

151 **Nguyen TP**, Qu Z, Weiss JN. Cardiac fibrosis and arrhythmogenesis: the road to repair is paved with perils. *J Mol Cell Cardiol* 2014; **70**: 83-91 [PMID: 24184999 DOI: 10.1016/j.yjmcc.2013.10.018]

152 **Kooman JP**, Katzarski K, van der Sande FM, Leunissen KM, Kotanko P. Hemodialysis: A model for extreme physiology in a vulnerable patient population. *Semin Dial* 2018; **31**: 500-506 [PMID: 29675862 DOI: 10.1111/sdi.12704]

153 **Dekker MJE**, Kooman JP. Fluid status assessment in hemodialysis patients and the association with outcome: review of recent literature. *Curr Opin Nephrol Hypertens* 2018; **27**: 188-193 [PMID: 29621026 DOI: 10.1097/MNH.0000000000000409]

154 **Dekker MJE**, van der Sande FM, van den Berghe F, Leunissen KML, Kooman JP. Fluid Overload and Inflammation Axis. *Blood Purif* 2018; **45**: 159-165 [PMID: 29478061 DOI: 10.1159/000485153]

155 **Zoccali C**, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, Wabel P, Stuard S. Chronic Fluid Overload and Mortality in ESRD. *J Am Soc Nephrol* 2017; **28**: 2491-2497 [PMID: 28473637 DOI: 10.1681/ASN.2016121341]

156 **London GM**. Ultrafiltration intensification for achievement of dry weight and hypertension control is not always the therapeutic gold standard. *J Nephrol* 2011; **24**: 395-397 [PMID: 21725927 DOI: 10.5301/jn.5000006]

157 **van der Sande FM**, van de Wal-Visscher ER, Stuard S, Moissl U, Kooman JP. Using Bioimpedance Spectroscopy to Assess Volume Status in Dialysis Patients. *Blood Purif* 2020; **49**: 178-184 [PMID: 31851988 DOI: 10.1159/000504079]

158 **Pinter J**, Chazot C, Stuard S, Moissl U, Canaud B. Sodium, volume and pressure control in haemodialysis patients for improved cardiovascular outcomes. *Nephrol Dial Transplant* 2020; **35**: ii23-ii30 [PMID: 32162668 DOI: 10.1093/ndt/gfaa017]

159 **Tentori F**, Zhang J, Li Y, Karaboyas A, Kerr P, Saran R, Bommer J, Port F, Akiba T, Pisoni R, Robinson B. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2012; **27**: 4180-4188 [PMID: 22431708 DOI: 10.1093/ndt/gfs021]

160 **Fotheringham J**, Sajjad A, Stel VS, McCullough K, Karaboyas A, Wilkie M, Bieber B, Robinson BM, Massy ZA, Jager KJ. The association between longer haemodialysis treatment times and hospitalization and mortality after the two-day break in individuals receiving three times a week haemodialysis. *Nephrol Dial Transplant* 2019; **34**: 1577-1584 [PMID: 30820580 DOI: 10.1093/ndt/gfz007]

161 **van der Sande FM**, Dekker MJ, Leunissen KML, Kooman JP. Novel Insights into the Pathogenesis and Prevention of Intradialytic Hypotension. *Blood Purif* 2018; **45**: 230-235 [PMID: 29478062 DOI: 10.1159/000485160]

162 **Locatelli F**, Buoncristiani U, Canaud B, Köhler H, Petitclerc T, Zucchelli P. Haemodialysis with on-line monitoring equipment: tools or toys? *Nephrol Dial Transplant* 2005; **20**: 22-33 [PMID: 15632348 DOI: 10.1093/ndt/gfh555]

163 **Sinha AD**, Light RP, Agarwal R. Relative plasma volume monitoring during hemodialysis AIDS the assessment of dry weight. *Hypertension* 2010; **55**: 305-311 [PMID: 20038754 DOI: 10.1161/HYPERTENSIONAHA.109.143974]

164 **Leung KCW**, Quinn RR, Ravani P, Duff H, MacRae JM. Randomized Crossover Trial of Blood Volume Monitoring-Guided Ultrafiltration Biofeedback to Reduce Intradialytic Hypotensive Episodes with Hemodialysis. *Clin J Am Soc Nephrol* 2017; **12**: 1831-1840 [PMID: 29018100 DOI: 10.2215/CJN.01030117]

165 **Zhang H**, Chan L, Meyring-Wösten A, Campos I, Preciado P, Kooman JP, van der Sande FM, Fuertinger D, Thijssen S, Kotanko P. Association between intradialytic central venous oxygen saturation and ultrafiltration volume in chronic hemodialysis patients. *Nephrol Dial Transplant* 2018; **33**: 1636-1642 [PMID: 28927232 DOI: 10.1093/ndt/gfx271]

166 **Harrison LE**, Selby NM, McIntyre CW. Central venous oxygen saturation: a potential new marker for circulatory stress in haemodialysis patients? *Nephron Clin Pract* 2014; **128**: 57-60 [PMID: 25342499 DOI: 10.1159/000362557]

167 **Polinder-Bos HA**, Elting JWJ, Aries MJ, García DV, Willemsen AT, van Laar PJ, Kuipers J, Krijnen WP, Slart RH, Luurtsema G, Westerhuis R, Gansevoort RT, Gaillard CA, Franssen CF. Changes in cerebral oxygenation and cerebral blood flow during hemodialysis - A simultaneous near-infrared spectroscopy and positron emission tomography study. *J Cereb Blood Flow Metab* 2020; **40**: 328-340 [PMID: 30540219 DOI: 10.1177/0271678X18818652]

168 **Santoro A**, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood volume regulation during hemodialysis. *Am J Kidney Dis* 1998; **32**: 739-748 [PMID: 9820442 DOI: 10.1016/s0272-6386(98)70128-3]

169 **Beaubien-Souligny W**, Denault A, Robillard P, Desjardins G. The Role of Point-of-Care Ultrasound Monitoring in Cardiac Surgical Patients With Acute Kidney Injury. *J Cardiothorac Vasc Anesth* 2019; **33**: 2781-2796 [PMID: 30573306 DOI: 10.1053/j.jvca.2018.11.002]

170 **Trinh E**, Weber C. The Dialysis Sodium Gradient: A Modifiable Risk Factor for Fluid Overload. *Nephron Extra* 2017; **7**: 10-17 [PMID: 28413417 DOI: 10.1159/000453674]

171 **Selby NM**, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. *Clin J Am Soc Nephrol* 2006; **1**: 1216-1225 [PMID: 17699351 DOI: 10.2215/CJN.02010606]

172 **Schneditz D**. Temperature and thermal balance in hemodialysis. *Semin Dial* 2001; **14**: 357-364 [PMID: 11679105 DOI: 10.1046/j.1525-139X.2001.00088.x]

173 **Maggiore Q**, Pizzarelli F, Santoro A, Panzetta G, Bonforte G, Hannedouche T, Alvarez de Lara MA, Tsouras I, Loureiro A, Ponce P, Sulkovà S, Van Roost G, Brink H, Kwan JT; Study Group of Thermal Balance and Vascular Stability. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis* 2002; **40**: 280-290 [PMID: 12148100 DOI: 10.1053/ajkd.2002.34506]

174 **Brunelli SM**, Spiegel DM, Du Mond C, Oestreicher N, Winkelmayer WC, Kovesdy CP. Serum-to-dialysate potassium gradient and its association with short-term outcomes in hemodialysis patients. *Nephrol Dial Transplant* 2018; **33**: 1207-1214 [PMID: 28992343 DOI: 10.1093/ndt/gfx241]

175 **Hecking M**, Karaboyas A, Saran R, Sen A, Inaba M, Rayner H, Hörl WH, Pisoni RL, Robinson BM, Sunder-Plassmann G, Port FK. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. *Clin J Am Soc Nephrol* 2012; **7**: 92-100 [PMID: 22052942 DOI: 10.2215/CJN.05440611]

176 **Basile C**, Rossi L, Lomonte C. Dialysate bicarbonate concentration: Too much of a good thing? *Semin Dial* 2018; **31**: 576-582 [PMID: 29885083 DOI: 10.1111/sdi.12716]

177 **Nitta K,** Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, Nakai S, Goto S, Wada A, Hamano T, Hoshino J, Joki N, Abe M, Yamamoto K, Hidetomo Nakamoto on behalf of Japanese Society for Dialysis Therapy Renal Data Registry Committee. Annual dialysis data report 2017, JSDT Renal Data Registry. *Ren Replace Ther* 2019; **5**: 53 [DOI: 10.1186/s41100-019-0248-1]

178 **Depner TA**. Uremic toxicity: urea and beyond. *Semin Dial* 2001; **14**: 246-251 [PMID: 11489197 DOI: 10.1046/j.1525-139X.2001.00072.x]

179 **Meyer TW**, Hostetter TH. Approaches to uremia. *J Am Soc Nephrol* 2014; **25**: 2151-2158 [PMID: 24812163 DOI: 10.1681/ASN.2013121264]

180 **Maduell F**, Arias M, Durán CE, Vera M, Fontseré N, Azqueta M, Rico N, Pérez N, Sentis A, Elena M, Rodriguez N, Arcal C, Bergadá E, Cases A, Bedini JL, Campistol JM. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. *Nephrol Dial Transplant* 2012; **27**: 1619-1631 [PMID: 21931125 DOI: 10.1093/ndt/gfr491]

181 **Maduell F**, Ojeda R, Arias-Guillen M, Rossi F, Fontseré N, Vera M, Rico N, Gonzalez LN, Piñeiro G, Jiménez-Hernández M, Rodas L, Bedini JL. Eight-Year Experience with Nocturnal, Every-Other-Day, Online Haemodiafiltration. *Nephron* 2016; **133**: 98-110 [PMID: 27265268 DOI: 10.1159/000446970]

182 **Ağbaş A**, Canpolat N, Çalışkan S, Yılmaz A, Ekmekçi H, Mayes M, Aitkenhead H, Schaefer F, Sever L, Shroff R. Hemodiafiltration is associated with reduced inflammation, oxidative stress and improved endothelial risk profile compared to high-flux hemodialysis in children. *PLoS One* 2018; **13**: e0198320 [PMID: 29912924 DOI: 10.1371/journal.pone.0198320]

183 **Shroff R**, Smith C, Ranchin B, Bayazit AK, Stefanidis CJ, Askiti V, Azukaitis K, Canpolat N, Ağbaş A, Aitkenhead H, Anarat A, Aoun B, Aofolaju D, Bakkaloglu SA, Bhowruth D, Borzych-Dużałka D, Bulut IK, Büscher R, Deanfield J, Dempster C, Duzova A, Habbig S, Hayes W, Hegde S, Krid S, Licht C, Litwin M, Mayes M, Mir S, Nemec R, Obrycki L, Paglialonga F, Picca S, Samaille C, Shenoy M, Sinha MD, Spasojevic B, Stronach L, Vidal E, Vondrák K, Yilmaz A, Zaloszyc A, Fischbach M, Schmitt CP, Schaefer F. Effects of Hemodiafiltration versus Conventional Hemodialysis in Children with ESKD: The HDF, Heart and Height Study. *J Am Soc Nephrol* 2019; **30**: 678-691 [PMID: 30846560 DOI: 10.1681/ASN.2018100990]

184 **Fischbach M**, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. *Nephrol Dial Transplant* 2010; **25**: 867-873 [PMID: 19889872 DOI: 10.1093/ndt/gfp565]

185 **Li T**, Wilcox CS, Lipkowitz MS, Gordon-Cappitelli J, Dragoi S. Rationale and Strategies for Preserving Residual Kidney Function in Dialysis Patients. *Am J Nephrol* 2019; **50**: 411-421 [PMID: 31630148 DOI: 10.1159/000503805]

186 **Wang AY**. Preserving Residual Kidney Function in Hemodialysis Patients-Back in the Spotlight. *J Am Soc Nephrol* 2016; **27**: 3504-3507 [PMID: 27493256 DOI: 10.1681/ASN.2016060693]

187 **Obi Y**, Rhee CM, Mathew AT, Shah G, Streja E, Brunelli SM, Kovesdy CP, Mehrotra R, Kalantar-Zadeh K. Residual Kidney Function Decline and Mortality in Incident Hemodialysis Patients. *J Am Soc Nephrol* 2016; **27**: 3758-3768 [PMID: 27169576 DOI: 10.1681/ASN.2015101142]

188 **Krediet RT**. Preservation of Residual Kidney Function and Urine Volume in Patients on Dialysis. *Clin J Am Soc Nephrol* 2017; **12**: 377-379 [PMID: 28228463 DOI: 10.2215/CJN.00330117]

189 **Snauwaert E**, Holvoet E, Van Biesen W, Raes A, Glorieux G, Vande Walle J, Roels S, Vanholder R, Askiti V, Azukaitis K, Bayazit A, Canpolat N, Fischbach M, Godefroid N, Krid S, Litwin M, Obrycki L, Paglialonga F, Ranchin B, Samaille C, Schaefer F, Schmitt CP, Spasojevic B, Stefanidis CJ, Van Dyck M, Van Hoeck K, Collard L, Eloot S, Shroff R. Uremic Toxin Concentrations are Related to Residual Kidney Function in the Pediatric Hemodialysis Population. *Toxins (Basel)* 2019; **11** [PMID: 31022857 DOI: 10.3390/toxins11040235]

190 **Marants R**, Qirjazi E, Grant CJ, Lee TY, McIntyre CW. Renal Perfusion during Hemodialysis: Intradialytic Blood Flow Decline and Effects of Dialysate Cooling. *J Am Soc Nephrol* 2019; **30**: 1086-1095 [PMID: 31053638 DOI: 10.1681/ASN.2018121194]

191 **Graboski AL**, Redinbo MR. Gut-Derived Protein-Bound Uremic Toxins. *Toxins (Basel)* 2020; **12** [PMID: 32932981 DOI: 10.3390/toxins12090590]

192 **Yamamoto S**, Kazama JJ, Omori K, Matsuo K, Takahashi Y, Kawamura K, Matsuto T, Watanabe H, Maruyama T, Narita I. Continuous Reduction of Protein-Bound Uraemic Toxins with Improved Oxidative Stress by Using the Oral Charcoal Adsorbent AST-120 in Haemodialysis Patients. *Sci Rep* 2015; **5**: 14381 [PMID: 26395517 DOI: 10.1038/srep14381]

193 **Mafra D**, Borges NA, Lindholm B, Shiels PG, Evenepoel P, Stenvinkel P. Food as medicine: targeting the uraemic phenotype in chronic kidney disease. *Nat Rev Nephrol* 2021; **17**: 153-171 [PMID: 32963366 DOI: 10.1038/s41581-020-00345-8]

194 **Schulman G**, Berl T, Beck GJ, Remuzzi G, Ritz E, Arita K, Kato A, Shimizu M. Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD. *J Am Soc Nephrol* 2015; **26**: 1732-1746 [PMID: 25349205 DOI: 10.1681/ASN.2014010042]

195 **Kjellstrand CM**, Buoncristiani U, Ting G, Traeger J, Piccoli GB, Sibai-Galland R, Young BA, Blagg CR. Short daily haemodialysis: survival in 415 patients treated for 1006 patient-years. *Nephrol Dial Transplant* 2008; **23**: 3283-3289 [PMID: 18458034 DOI: 10.1093/ndt/gfn210]

196 **Laville M**, Fouque D. Nutritional aspects in hemodialysis. *Kidney Int Suppl* 2000; **76**: S133-S139 [PMID: 10936810 DOI: 10.1046/j.1523-1755.2000.07617.x]

197 **Peters SA**, Bots ML, Canaud B, Davenport A, Grooteman MP, Kircelli F, Locatelli F, Maduell F, Morena M, Nubé MJ, Ok E, Torres F, Woodward M, Blankestijn PJ; HDF Pooling Project Investigators. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016; **31**: 978-984 [PMID: 26492924 DOI: 10.1093/ndt/gfv349]

198 **Davenport A**, Peters SA, Bots ML, Canaud B, Grooteman MP, Asci G, Locatelli F, Maduell F, Morena M, Nubé MJ, Ok E, Torres F, Woodward M, Blankestijn PJ; HDF Pooling Project Investigators. Higher convection volume exchange with online hemodiafiltration is associated with survival advantage for dialysis patients: the effect of adjustment for body size. *Kidney Int* 2016; **89**: 193-199 [PMID: 26352299 DOI: 10.1038/ki.2015.264]

199 **Wong J**, Vilar E, Davenport A, Farrington K. Incremental haemodialysis. *Nephrol Dial Transplant* 2015; **30**: 1639-1648 [PMID: 26038351 DOI: 10.1093/ndt/gfv231]

200 **Garofalo C**, Borrelli S, De Stefano T, Provenzano M, Andreucci M, Cabiddu G, La Milia V, Vizzardi V, Sandrini M, Cancarini G, Cupisti A, Bellizzi V, Russo R, Chiodini P, Minutolo R, Conte G, De Nicola L. Incremental dialysis in ESRD: systematic review and meta-analysis. *J Nephrol* 2019; **32**: 823-836 [PMID: 30604150 DOI: 10.1007/s40620-018-00577-9]

201 **Susantitaphong P**, Koulouridis I, Balk EM, Madias NE, Jaber BL. Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis. *Am J Kidney Dis* 2012; **59**: 689-699 [PMID: 22370022 DOI: 10.1053/j.ajkd.2011.12.020]

202 **Culleton BF**, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA* 2007; **298**: 1291-1299 [PMID: 17878421 DOI: 10.1001/jama.298.11.1291]

203 **Koh TJK**. Nocturnal hemodialysis: improved quality of life and patient outcomes. *Int J Nephrol Renovasc Dis* 2019; **12**: 59-68 [PMID: 31040710 DOI: 10.2147/IJNRD.S165919]

204 **FHN Trial Group**, Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Kliger AS. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010; **363**: 2287-2300 [PMID: 21091062 DOI: 10.1056/NEJMoa1001593]

205 **Wilk AS**, Lea JP. How Extended Hemodialysis Treatment Time Can Affect Patient Quality of Life. *Clin J Am Soc Nephrol* 2019; **14**: 1687-1689 [PMID: 31672796 DOI: 10.2215/CJN.12241019]

206 **Trinh E**, Chan CT. The Rise, Fall, and Resurgence of Home Hemodialysis. *Semin Dial* 2017; **30**: 174-180 [PMID: 28066912 DOI: 10.1111/sdi.12572]

207 **Doenyas-Barak K**, de Abreu MHFG, Borges LE, Tavares Filho HA, Yunlin F, Yurong Z, Levin NW, Kaufman AM, Efrati S, Pereg D, Litovchik I, Fuchs S, Minha S. Non-invasive hemodynamic profiling of patients undergoing hemodialysis - a multicenter observational cohort study. *BMC Nephrol* 2019; **20**: 347 [PMID: 31481031 DOI: 10.1186/s12882-019-1542-4]

208 **Feng Y**, Zou Y, Zheng Y, Levin NW, Wang L. The value of non-invasive measurement of cardiac output and total peripheral resistance to categorize significant changes of intradialytic blood pressure: a prospective study. *BMC Nephrol* 2018; **19**: 310 [PMID: 30400887 DOI: 10.1186/s12882-018-1087-y]

209 **Kolb J**, Kitzler TM, Tauber T, Morris N, Skrabal F, Kotanko P. Proto-dialytic cardiac function relates to intra-dialytic morbid events. *Nephrol Dial Transplant* 2011; **26**: 1645-1651 [PMID: 20923927 DOI: 10.1093/ndt/gfq599]

210 **Ekinci C**, Karabork M, Siriopol D, Dincer N, Covic A, Kanbay M. Effects of Volume Overload and Current Techniques for the Assessment of Fluid Status in Patients with Renal Disease. *Blood Purif* 2018; **46**: 34-47 [PMID: 29649794 DOI: 10.1159/000487702]

211 **Torino C**, Gargani L, Sicari R, Letachowicz K, Ekart R, Fliser D, Covic A, Siamopoulos K, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Martinez-Castelao A, Coudert-Krier MJ, Rossignol P, Gueler F, Hannedouche T, Panichi V, Wiecek A, Pontoriero G, Sarafidis P, Klinger M, Hojs R, Seiler-Mussler S, Lizzi F, Siriopol D, Balafa O, Shavit L, Tripepi R, Mallamaci F, Tripepi G, Picano E, London GM, Zoccali C. The Agreement between Auscultation and Lung Ultrasound in Hemodialysis Patients: The LUST Study. *Clin J Am Soc Nephrol* 2016; **11**: 2005-2011 [PMID: 27660305 DOI: 10.2215/CJN.03890416]

212 **Loutradis C**, Papadopoulos CE, Sachpekidis V, Ekart R, Krunic B, Karpetas A, Bikos A, Tsouchnikas I, Mitsopoulos E, Papagianni A, Zoccali C, Sarafidis P. Lung Ultrasound-Guided Dry Weight Assessment and Echocardiographic Measures in Hypertensive Hemodialysis Patients: A Randomized Controlled Study. *Am J Kidney Dis* 2020; **75**: 11-20 [PMID: 31732234 DOI: 10.1053/j.ajkd.2019.07.025]

213 **Torino C**, Tripepi R, Loutradis C, Sarafidis P, Tripepi G, Mallamaci F, Zoccali C. Can the assessment of ultrasound lung water in haemodialysis patients be simplified? *Nephrol Dial Transplant* 2021; **36**: 2321-2326 [PMID: 33373998 DOI: 10.1093/ndt/gfaa285]

214 **Stewart J**, Stewart P, Walker T, Horner DV, Lucas B, White K, Muggleton A, Morris M, Selby NM, Taal MW. A Feasibility Study of Non-Invasive Continuous Estimation of Brachial Pressure Derived From Arterial and Venous Lines During Dialysis. *IEEE J Transl Eng Health Med* 2021; **9**: 2700209 [PMID: 33200053 DOI: 10.1109/JTEHM.2020.3035988]

215 **Stewart J,** Stewart P, Walker T, Viramontes-Hörner D, Lucas B, White K, Taal MW, Selby NM, Morris M. An iterative run-to-run learning model to derive continuous brachial pressure estimates from arterial and venous lines during dialysis treatment. *Biomed Signal Proces* 2021; **65**: 102346 [DOI: 10.1016/j.bspc.2020.102346]

216 **Foley RN**, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**: S112-S119 [PMID: 9820470 DOI: 10.1053/ajkd.1998.v32.pm9820470]

217 **Kooman JP**, Wieringa FP, Han M, Chaudhuri S, van der Sande FM, Usvyat LA, Kotanko P. Wearable health devices and personal area networks: can they improve outcomes in haemodialysis patients? *Nephrol Dial Transplant* 2020; **35**: ii43-ii50 [PMID: 32162666 DOI: 10.1093/ndt/gfaa015]

218 **Villarroel M**, Jorge J, Meredith D, Sutherland S, Pugh C, Tarassenko L. Non-contact vital-sign monitoring of patients undergoing haemodialysis treatment. *Sci Rep* 2020; **10**: 18529 [PMID: 33116150 DOI: 10.1038/s41598-020-75152-z]

219 **Floege J**, Gillespie IA, Kronenberg F, Anker SD, Gioni I, Richards S, Pisoni RL, Robinson BM, Marcelli D, Froissart M, Eckardt KU. Development and validation of a predictive mortality risk score from a European hemodialysis cohort. *Kidney Int* 2015; **87**: 996-1008 [PMID: 25651366 DOI: 10.1038/ki.2014.419]

220 **Couchoud CG**, Beuscart JB, Aldigier JC, Brunet PJ, Moranne OP; REIN registry. Development of a risk stratification algorithm to improve patient-centered care and decision making for incident elderly patients with end-stage renal disease. *Kidney Int* 2015; **88**: 1178-1186 [PMID: 26331408 DOI: 10.1038/ki.2015.245]

221 **Kuhlmann U**, Maierhofer A, Canaud B, Hoyer J, Gross M. Zero Diffusive Sodium Balance in Hemodialysis Provided by an Algorithm-Based Electrolyte Balancing Controller: A Proof of Principle Clinical Study. *Artif Organs* 2019; **43**: 150-158 [PMID: 30260035 DOI: 10.1111/aor.13328]

222 **Canaud B**, Kooman J, Selby NM, Taal M, Francis S, Kopperschmidt P, Maierhofer A, Kotanko P, Titze J. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. *Kidney Int* 2019; **95**: 296-309 [PMID: 30665570 DOI: 10.1016/j.kint.2018.09.024]

223 **Bucalo ML**, Barbieri C, Roca S, Ion Titapiccolo J, Ros Romero MS, Ramos R, Albaladejo M, Manzano D, Mari F, Molina M. The anaemia control model: Does it help nephrologists in therapeutic decision-making in the management of anaemia? *Nefrologia (Engl Ed)* 2018; **38**: 491-502 [PMID: 29875061 DOI: 10.1016/j.nefro.2018.03.004]

224 **Barbieri C**, Cattinelli I, Neri L, Mari F, Ramos R, Brancaccio D, Canaud B, Stuard S. Development of an Artificial Intelligence Model to Guide the Management of Blood Pressure, Fluid Volume, and Dialysis Dose in End-Stage Kidney Disease Patients: Proof of Concept and First Clinical Assessment. *Kidney Dis (Basel)* 2019; **5**: 28-33 [PMID: 30815462 DOI: 10.1159/000493479]

225 **Canaud B**, Collins A, Maddux F. The renal replacement therapy landscape in 2030: reducing the global cardiovascular burden in dialysis patients. *Nephrol Dial Transplant* 2020; **35**: ii51-ii57 [PMID: 32162663 DOI: 10.1093/ndt/gfaa005]

**Footnotes**

**Conflict-of-interest statement:** Canaud B is acting as scientist consultant for FMC. No conflict of interest exists for other authors.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Corresponding Author's Membership in Professional Societies:** Francophone Society of Nephrology, Dialysis and Transplant; ERA - EDTA; ISN; American Society of Nephrology.

**Peer-review started:** March 26, 2021

**First decision:** October 17, 2021

**Article in press:**

**Specialty type:** Urology and nephrology

**Country/Territory of origin:** Germany

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Patoulias D, Greece **S-Editor:** Wang JJ **L-Editor:** Wang TQ **P-Editor:**

**Figure Legends**



**Figure 1 Intermittent extracorporeal renal replacement therapy is the source of permanent stress in hemodialysis patients.** HD: Hemodialysis; CVC: Central venous catheter.



**Figure 2 Dialysis Related Pathology linked to patient outcomes.** GI:Glycaemic index; PROM: Patient reported outcomes measures; PREM: Patient reported experience measures; HRQOL: Health-related quality of life.



**Figure 3 Action plan to design and implement a more cardioprotective renal replacement treatment in order to improve patient outcomes.** HD: Hemodialysis; PBUT: Protein bound uremic toxins; LMW: Low-molecular-weight; HMW: High-molecular-weight; HDF: On-line hemodiafiltration.