

EDITORIAL COMMENT

Deciphering the core elements around haemodialysis therapy

Sudhir K. Bowry¹, Alberto Arduan Ortiz² and Frank W. Maddux³

¹Dialysis-at-Crossroads (D@X) Advisory, Bad Nauheim, Germany, ²Nephrology and Hypertension. IIS-Fundación Jiménez Díaz-Universidad Autónoma Madrid, Madrid, Spain and ³Global Medical Office, Waltham, MA, USA

Correspondence to: Sudhir K. Bowry; E-mail: sudhir.bowry@outlook.com

ABSTRACT

The projected future demand for renal replacement therapies for patients with end-stage renal failure requires preparedness at different levels. The deliberations focus predominantly on the disproportionately high financial burden of care for patients on routine dialysis therapy compared with other chronic conditions. However, even today there are concerns regarding the shortage of healthcare workers in the field of nephrology. A substantial increase in trained healthcare professionals is needed for the future delivery and care of patients requiring haemodialysis (HD) that 89% of patients on dialysis receive; a sustainable health workforce is the cornerstone of any healthcare system. The multimorbid nature of chronic kidney disease as well as the complexity—especially the technical aspects—of HD are deterrents for pursuing nephrology as a career. An educational platform that critically examines the essential issues and components of HD therapy was thus considered appropriate to create or renew interest in nephrology. By providing broader and newer perspectives of some of the core principles around which HD evolves, with this set of articles we seek to facilitate a better appreciation of HD. We believe that such a reappraisal of either poorly understood or ill-defined principles, including usage of terminology that is imprecise, will help facilitate a better understanding of the functioning principles of HD.

Keywords: biocompatibility, evidence-based medicine, hemodialysis, membranes, sustainability

Such is the increase in chronic kidney disease (CKD) that by 2040 it is estimated to become the fifth leading cause of death globally; 10% of adults worldwide are now considered to be affected by some form of CKD [1]. Of the 10 most important drivers of increasing burden of diseases and injuries between 1990 and 2019, CKD is among the six causes that largely affects older adults [2].

With no cure for kidney failure patients in the near future, kidney replacement therapy is essential to sustain life [1]. Kidney transplantation is considered the best option, but wider utilization is restricted by the lack of sufficient donors. Thus dialysis remains the only viable alternative. Worldwide,

89% of patients on dialysis receive haemodialysis (HD), >90% of whom live in high- and upper middle-income countries[3]. A substantial number of kidney failure patients are still without access to maintenance dialysis. Only a fraction of the number of people needing dialysis actually receive it; millions are estimated to die prematurely because kidney replacement therapies could not be accessed [4–6]. Among the populations who have access to dialysis, mortality (mainly cardiovascular) remains high and outcomes are suboptimal despite the technological advancements, due to the high number of comorbid conditions associated with CKD as well as many other contributing factors [1, 3, 7]. Life expectancy of kidney

Received: 25.10.2021; Editorial decision: 25.10.2021

© The Author(s) 2021. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

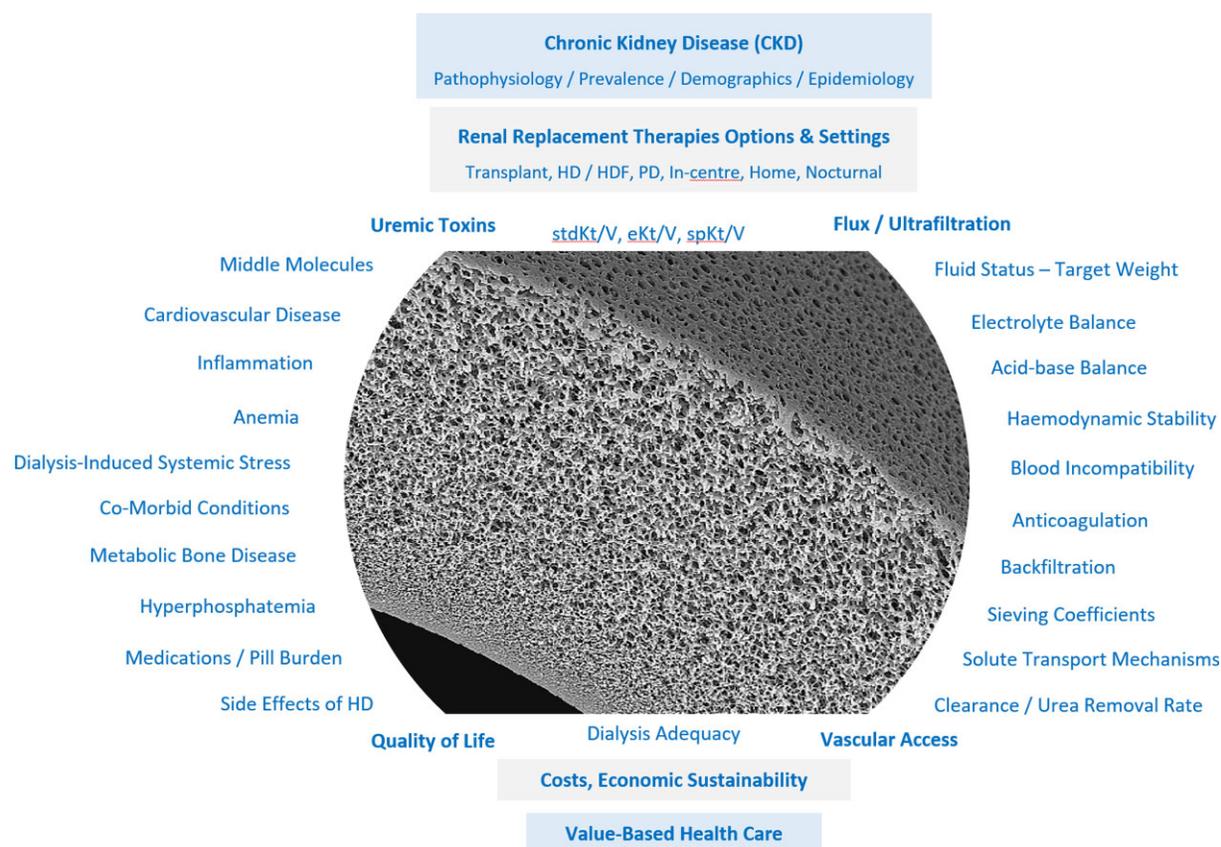


FIGURE 1: To cope with the projected future demand for kidney replacement therapies (especially HD), new nephrologists need to familiarize themselves with numerous medical, scientific and technological disciplines. In addition to the pathophysiology of CKD, clinical care of kidney failure patients requires consideration of multiple comorbid conditions and systemic biochemical pathways that afflict an increasingly aging patient population. The challenges are exacerbated by the need to understand complex scientific concepts and technological principles around which HD is based. With the worldwide difficulties in recruiting doctors and nurses for the care of dialysis patients, a concerted educational programme that is less daunting and aids better understanding of the complexities is required.

failure patients on HD may have improved over the years, but it is still on average only 5–10 years with a poor health-related quality of life [8, 9]. For a 20-year-old on dialysis, life expectancy is ~40 years less than for the general population [10].

Faced with this sobering reality and despite implementation of strategies to prevent or slow the progression of CKD, coping with the expected global demand for HD therapy poses multiple challenges [11–13]. As an example, at the current rate of growth, the number of persons on kidney replacement therapy in Spain will hit 0.23–1.00 million by the end of the century, i.e. 1–4% of the projected population at that time [14]. While the (additional) economic burden is more readily assessable through model-based projections, there are complex issues—scientific, clinical and technical—that need to be better understood and addressed for the future preparedness of delivering dialysis therapies [15–17]. Although HD has evolved today into a safe procedure that is performed tens of millions of times each year, it is still largely constructed around empirical knowledge and concepts [18].

Beginning with the fundamental concept of clearance (‘the hypothetical volume of blood from which a given solute is removed or cleared completely in a specific period of time’), the domain of HD is laden with numerous principles and definitions based on theoretical assumptions and formulae (Figure 1). Many formulations or conventions (e.g. middle molecules) have simply been carried on from the early experimental era in the 1960s–

1980s without due deliberation of their present-day relevance [19, 20]. Some, like whether urea is just a marker (for clearance estimations) or a uraemic toxin or the Kt/V concept as a measure of dialysis adequacy, have been critically re-examined and are differently perceived today conforming to present-day learning [21–24]. Often the differences, interpretation and subtleties of the entities depicted in Figure 1 are only apparent to a minority who have delved into selected topics or to experts with extended experience and reputations in specialist subject matter. For the majority involved in nephrology, especially trainee residents, nurses or biomedical engineers considering specialising in HD, being able to discern between complex, multi faceted principles involving several scientific disciplines is simply too overwhelming. This complexity may also be one reason for the declining interest worldwide in nephrology as a career, raising workforce concerns and debates on the issue, despite the huge demand for skilled nephrology professionals now and into the future [25–27]. One reason is the disconnect between the sheer complexity—scientific and technical—of the HD procedure and the vast expansion of access to safe treatments in many healthcare delivery systems. Other reasons such as long working hours, having to deal predominantly with older patients with multimorbid conditions and comprehending the complex physiochemical principles and concepts (some of which are contentious) involved in HD are also deterrents to the selection of nephrology as a career.

It is with this primary concern—the need to attract and nurture a new generation of healthcare workers to help cope with the future demands for HD therapies—that the editors of *Clinical Kidney Journal* considered dedicating a supplement to address and revisit the defining elements of all HD therapies, with a special focus on dialysis membranes. The health workforce is the cornerstone of any healthcare system; an adequately trained nephrology workforce has been recognized as being critical to a sustainable kidney care system [25, 27, 28]. An educational platform that disseminates and critically examines the essence of key principles around which HD therapy evolves was thus considered appropriate to create or renew interest in the field of nephrology. The hollow fibre membranes of dialysers represent the ‘central processing unit’ of the entire blood purification function of dialysis. This supplement presents deeper insights into the world of membranes and their functions, including inadvertent interactions that occur during the procedure, to emphasize the two-sidedness of dialysis membranes.

Until around the 1960s, the prognosis of patients with kidney failure remained distressing and most uniformly fatal. Prior to that, a century of extraordinary endeavours had failed to provide a satisfactory solution to the dilemma of finding suitable semipermeable membranes that allowed the selective removal of uraemic retention solutes and excess fluid that accumulate in CKD. The advent of hollow fibre membranes affording large surface areas and fitted into more compact devices—dialysers—allowed the practical extracorporeal ‘processing’ of blood of patients and was a major landmark in nephrology. Just a decade or so later, in the mid-1970s, membrane and dialysis technology was sufficiently ripe to pave the way for routine treatment of kidney failure patients. Today, tens of millions of kilometres of hollow fibre dialysis membranes are produced annually using sophisticated technologies to cope with the increasing medical demands of chronic HD.

The four articles in section I of this supplement describe the commonality and peculiarities of natural and man-made membranes in relation to their ability to ‘clear’ blood of its ‘toxic’ content that builds up during uraemia. Insights into the principles involved in the making of hollow fibre membranes on a large scale emphasize not only the difficulties in emulating the functionality of their natural counterpart, but also the technological marvels and constraints involved to meet various clinical prerequisites. The fundamentals, as well as controversies and misconceptions (including nomenclature), surrounding uraemic toxicity and solute removal principles are thereafter discussed. Finally, the HD therapy modality choices and conditions under which the fundamental detoxification function can be achieved most efficiently in clinical settings are detailed against the backdrop of evidence-based and personalized medicine.

Section II of the supplement essentially deals with the ‘other face’ of membranes, transport processes or overall systemic effects of HD therapy as well as the economic constraints that increasingly compromise delivery of dialysis and impact clinical outcomes. Some of these issues are unavoidable consequences of extracorporeal circuits (ECCs) while others, if not adequately minimized or controlled, are detrimental to patient well-being in the short-term or negatively affect outcomes over longer periods. For the clinician, an understanding of the ramifications of adverse events occurring during HD needs to be balanced against the benefits HD therapy strives to achieve. Bioincompatibility, attributed mainly to the repeated contact of blood with artificial surfaces, will always be an issue to contend with in the absence of the protective effects of the endothelium in normal blood vessels. Blood–material interactions with different poly-

mers of the ECCs occur even in the presence of anticoagulation. These reactions, together with induction of pro-inflammatory reactions occurring under certain circumstances by the transport or release (from polymers) of biologically active substances into the blood compartment, collectively contribute to the systemic stress condition that HD is now recognized to be. Clinical aspects of HD therapy that impede the attainment of satisfactory patient outcomes can no longer be dissociated from overall costs of care of HD patients. Coping with increased future demand for dialysis is intricately linked to implementation of more economically sustainable strategies [29, 30].

By providing broader and newer perspectives of the core principles around which HD therapies evolve, we sought with these set of articles to facilitate a better appreciation of HD. We believe that the reappraisal of either poorly understood or ill-defined principles, including usage of terminology that is imprecise, will help facilitate a better understanding of the functioning principles of HD. Above all, we hope the educational value of this treatise renews or creates interest in the field of nephrology.

ACKNOWLEDGEMENT

This article is published as part of a supplement supported by Fresenius Medical Care.

CONFLICT OF INTEREST STATEMENT

S.K.B. received consultancy fees towards the writing of this article. He is a former employee of Fresenius Medical Care, Germany. A.O. has received consultancy or speaker fees or travel support from Advicciene, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Idorsia, Chiesi, Otsuka, Novo Nordisk and Vifor Fresenius Medical Care Renal Pharma and is director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of chronic kidney disease and electrolytes. A.O. is the editor-in-chief for CKJ. F.M. is the global chief medical officer and member of the management board of Fresenius Medical Care.

REFERENCES

1. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. *Lancet* 2021; 398: 786–802
2. Vos T, Lim SS, Abbafati C et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 2020; 396: 1204–1222
3. Himmelfarb J, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. *Nat Rev Nephrol* 2020; 16: 573–585
4. Liyanage T, Ninomiya T, Jha V et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015; 385: 1975–1982
5. Coresh J, Jafar TH. Disparities in worldwide treatment of kidney failure. *Lancet* 2015; 385: 1926–1928
6. Versino E, Piccoli GB. Chronic kidney disease: the complex history of the organization of long-term care and bioethics. why now, more than ever, action is needed. *Int J Environ Res Public Health* 2019; 16: 785
7. Jha V, Garcia-Garcia G, Iseki K et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; 382: 260–272

8. United States Renal Data System. USRDS 2018 Annual Data Report: atlas of end-stage renal disease in the United States. Chapter 5: mortality. https://www.usrds.org/media/1730/v2_c05_mortality_18_usrds.pdf (21 November 2021, date last accessed)
9. Mitema D, Jaar BG. How can we improve the quality of life of dialysis patients? *Semin Dial* 2016; 29: 93–102
10. Kramer A, Boenink R, Stel VS et al. ERA-EDTA Registry Annual Report 2018: a summary. *Clin Kidney J* 2020; 14: 107–123
11. Charles C, Ferris AH. Chronic kidney disease. *Prim Care Clin Off Pract* 2020; 47: 585–595
12. Solomon R. New approach to slowing the progression of chronic kidney disease. *Cardiorenal Med* 2019; 9: 334–335
13. Pugh D, Gallacher PJ, Dhaun N. Management of hypertension in chronic kidney disease. *Drugs* 2019; 79: 365–379
14. Asociación Información Enfermedades Renales Genéticas (AIRG-E), European Kidney Patients' Federation (EKPF), Federación Nacional de Asociaciones para la Lucha Contra las Enfermedades del Riñón (ALCER) et al. RICORS2040: the need for collaborative research in chronic kidney disease. *Clin Kidney J* 2022; <https://doi.org/10.1093/ckj/sfab170>
15. Ma Y, Yu H, Sun H et al. Economic burden of maintenance hemodialysis patients' families in nanchong and its influencing factors. *Ann Palliat Med* 2020; 9: 3877–3884
16. Komenda P, Gavaghan MB, Garfield SS et al. An economic assessment model for in-center, conventional home, and more frequent home hemodialysis. *Kidney Int* 2012; 81: 307–313
17. Foy M, Sperati CJ. What the non-nephrologist needs to know about dialysis. *Semin Dial* 2018; 31: 183–192
18. Murea M, Moossavi S, Garneata L et al. Narrative review of incremental hemodialysis. *Kidney Int Reports* 2020; 5: 135–148.
19. Klinkmann H. Middle molecules and unanswered questions. *Artif Organs* 1981; 4: 1–2.
20. Vanholder R, Van Laecke S, Glorieux G. The middle-molecule hypothesis 30 years after: lost and rediscovered in the universe of uremic toxicity? *J Nephrol* 2008; 21: 146–160
21. Lau WL, Vaziri ND. Urea, a true uremic toxin: the empire strikes back. *Clin Sci* 2017; 131: 3–12
22. Vanholder R, Gryp T, Glorieux G. Urea and chronic kidney disease: the comeback of the century? (in uraemia research). *Nephrol Dial Transplant* 2018; 33: 4–12
23. Vanholder R, Glorieux G, Eloit S. Once upon a time in dialysis: the last days of Kt/V? *Kidney Int* 2015; 88: 460–465
24. Vanholder R, Van Biesen W, Lameire N. A swan song for Kt/v_{urea}. *Semin Dial* 2019; 32: 424–437
25. Sharif MU, Elsayed ME, Stack AG. The global nephrology workforce: emerging threats and potential solutions! *Clin Kidney J* 2016; 9: 11–22
26. Riaz P, Caskey F, McIsaac M et al. Workforce capacity for the care of patients with kidney failure across world countries and regions. *BMJ Glob Health* 2021; 6: e004014
27. Osman MA, Alrukhaimi M, Ashuntantang GE et al. Global nephrology workforce: gaps and opportunities toward a sustainable kidney care system. *Kidney Int Suppl* 2018; 8: 52–63
28. Qarni B, Osman MA, Levin A et al. Kidney care in low- and middle-income countries. *Clin Nephrol* 2020; 93: 21–30
29. Vanholder R, Lameire N, Annemans L et al. Cost of renal replacement: how to help as many as possible while keeping expenses reasonable? *Nephrol Dial Transplant* 2016; 31: 1251–1261
30. Vanholder R, Annemans L, Brown E et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol* 2017; 13: 393–409