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Hemodiafiltration in developing countries

Prit Kusirisin[1,2,3,4] | Nattachai Srisawat[1,2,3,5]

[1]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[2]Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[3]Center of Excellence in Critical Care Nephrology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[4]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

[5]Academy of Science, Royal Society of Thailand, Bangkok, Thailand

Correspondence
Nattachai Srisawat, MD, PhD, Division of Nephrology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.
Email: drnattachai@yahoo.com and nattachai.sr@chula.ac.th

Abstract

Hemodiafiltration (HDF) is a promising kidney replacement therapy modality for patients with end-stage kidney disease. The principle of uremic toxin clearance by combining convection and diffusion can lead to greater benefits compared to conventional hemodialysis. Evidence is building that supports the advantages of HDF with short-term outcomes such as greater intradialytic hemodynamic stability, improved nutritional status, attenuation of anemia, and reduction of inflammatory cytokines which produce improved key long-term impacts including survival and cardiovascular outcomes. Very little is known about the prevalence of HDF treatments in developing countries due to a shortage of national kidney registries. HDF experience is limited in many countries due to the cost of dialysis treatments, availability of online HDF machines, and reimbursement policies. These obstacles have led to nephrologists developing innovations, for example, convective control HDF (CC-HDF), simple mid-dilution, and simple mixed-dilution methods, which may be as effective as commercially available HDF machines. In this article, we will focus on the experience of HDF practice and barriers to adoption in developing countries. Results can guide clinical practice recommendations for implementing HDF in resource-limited settings.

1 | INTRODUCTION

Hemodiafiltration (HDF) is a promising kidney replacement therapy (KRT) modality for patients with end-stage kidney disease (ESKD). HDF can increase the spectrum of uremic toxins cleared by combining convection and diffusion. Evidence supports the benefits of HDF over conventional hemodialysis (HD), with greater intradialytic hemodynamic stability, improved nutritional status, attenuation of anemia, and reduction of inflammatory cytokines.[1,2] Long-term studies have demonstrated that the use of high volume HDF with convective exchanges of at least 23 L/session in post-dilution and 46 L/session in predilution modes could potentially provide 3-year increased survival when compared to standard high-flux HD, predominantly due to a reduction in cardiovascular disease.[3–6] Online HDF (OL-HDF) modality is the most commonly adopted HDF mode in the developed countries particularly Western Europe, Australia, New Zealand, and Japan.[1] Very little is known about the utilization of HDF in developing countries due to shortage of kidney registries. Moreover, the experience of HDF is limited in some developing countries due to the cost of dialysis treatments, lack of OL-HDF machines, and the reimbursement policy. This review will focus on the experience of HDF practice, barriers, and strategies to implement HDF therapy in these developing countries with resource-limited settings.

2 | EPIDEMIOLOGIC DATA AND EXPERIENCE OF HDF IN THE DEVELOPING COUNTRIES

A global survey in 2017 reported that 2,823,000 ESKD patients were treated with HD worldwide (Table 1).[7] Among this total, 286,000 ESKD patients (10%) were receiving HDF mode, including a total of 278,000 patients (97%) using OL-HDF and 7350 patients (3%) using the sterile bags or off-line method.[7] The number of patients treated by HDF and the method varied across Europe, Asia-Pacific, Latin America, North America, and other regions with totals of 122,000 (26%), 148,000 (11%), 3820 (1%), 970 (<1%), and 10,400 patients (4%), respectively.[7] Focusing only on the HDF-treated patients, the

TABLE 1 Epidemiological data of HDF by global region[7]

Number of ESRD patients	Global	Europe	Asia-Pacific	Latin America	North America	Other
HD	2,823,000	463,000	1,336,000	259,000	524,000	241,000
HDF (per HD)	286,000 (10%)	122,000 (26%)	148,000 (11%)	3820 (1%)	970 (<1%)	10,400 (4%)
% HDF per global HDF-treated patients		42.7%	51.8%	1.3%	0.3%	3.6%
Online HDF (per HDF)	278,000 (97%)	120,000 (98%)	144,000 (97%)	3790 (99%)	970 (100%)	10,400 (100%)
Off-line HDF (per HDF)	7350 (3%)	2560 (2%)	4760 (3%)	29 (<1%)	0 (0%)	0 (0%)

Abbreviations: HD, hemodialysis; HDF, hemodiafiltration.

implementation percentage was 42.7%, 51.8%, 1.3%, 0.3%, and 3.6%, respectively.[7] The percentage of patients treated with OL-HDF was 98%, 97%, 99%, 100%, and 100%, respectively. Some countries shared their experience of HDF adoption and conducted several studies compared outcomes with conventional HD (Table 2.)

2.1 | HDF in Asia

2.1.1 | HDF in East Asia

China has the largest number of patients treated with HDF in East Asia with 47,420 patients (31% Asia).[7] An observational study from Shanghai reported an increase in HDF utilization from 7% to 42% from 2007 to 2014.[8] This study also reported increased 8-year survival, especially for patients aged 40 to 60.[8] The majority of treatments were weekly post-dilution OL-HDF 15–25 L/session, due to the limited availability of HDF machines, coupled with reimbursement restrictions from social insurance, and the inability of many patients to self-pay for HDF. In the recent years, the Chinese government has increased health insurance to cover 10 sessions of standard dialysis plus one session of HDF per month at a nominal cost.[9]

2.1.2 | HDF in North Asia

Russia accounts for the second highest HDF utilization in Asia with 10,300 (7% in Asia).[7] The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported an 18.2% prevalence of HDF in Russia between 2012 and 2015.[10] A study of HDF practice in the Russian dialysis network between 2011 and 2016 reported improved 5-year survival rates with post-dilution OL-HDF and convective exchanges of 21–25 L/session.[11] Due to the large geographic area of Russia, the study covered diverse settings in different clinical practices, healthcare policies and the reimbursement structure for dialysis services across different regions.

2.1.3 | HDF in Southeast Asia

The number of patients receiving HDF in Southeast Asian countries is currently unknown. In 2011, a survey from Japanese dialysis companies reported that Thailand had the most experience of HDF with 1400 patients followed by Vietnam with only five to 10 patients.[12] Both countries indicated OL-HDF as an adjunctive therapy for conventional HD for patients who could afford the extra out-of-pocket expenses after insurance reimbursement. The Philippines had 70 OL-HDF consoles, but the number of patients treated by HDF remains unknown as is the case for Malaysia.[12] In 2017, Myanmar had reported up to 70 patients undergoing HDF,[13] whereas Brunei, Laos and Cambodia still have no OL-HDF availability.[13]

Due to the sophistication and high cost of the OL-HDF machine, a nephrology team from King Chulalongkorn Memorial Hospital in Thailand developed an innovative modality which was simple, inexpensive, easily operated, and as effective as commercial OL-HDF machines. This included a convective control double high-flux HDF (CC-HDF), simple mid-dilution, and simple mixed-dilution method.[14–16]

CC-HDF was developed from the original double high-flux HDF which could be set, monitored, and adjusted to the appropriate convection rate in real time by a C-shape clamp (Figure 1). This technique provided better performance than high-flux HD with respect to convection rate, Kt/V urea, β_2-microglobulin (B2M) clearance, and quality of life without clinical and technical complications.[14] In addition, CC-HDF also demonstrated comparable efficacy to OL-HDF for small- and middle-molecule clearances, hematology profile, calcium-phosphorus control, and nutritional status in a 1-year study.[17,18]

Due to the high cost of commercial mid-dilution dialyzer, a simple mid-dilution OL-HDF circuit was applied including two dialyzers connected to blood and dialysate lines while infusing the replacement fluid via an intermediary blood line between the dialyzers (Figure 2). This technique provided a higher clearance of uremic toxins compared to predilution and postdilution modes, along with lower albumin losses than the post-dilution technique.[15]

Due to the high expense of the mixed-dilution OL-HDF dialyzer, the simple mixed-dilution OL-HDF technique was invented consisting of two connecting dialyzers, which function as a single dialyzer unit, and infuses replacement fluid via a predilution and postdilution replacement line using an external peristaltic roller pump to control the postdilution replacement fluid rate (Figure 3). This design provided greater small- and middle-molecule clearances compared to mid-dilution OL-HDF, while phosphate clearances, transmembrane pressure, and albumin loss were comparable.[16]

The 3-year experience of HDF in Thailand has reported benefits for OL-HDF including lower incidence of intradialytic hypotension,

TABLE 2 Study of online hemodiafiltration on survival outcomes in developing countries

Authors	Study design	Country	Number of patients	Follow-up time (years)	Convective dose	Comparison mode	Kt/V	B2M (mg/L)	Survival outcomes
East Asia									
Zhang W, et al.[8]	Retrospective cohort	China	9351	8	Post-dilution: 15–25 L; once a week	HDF (7% to 42%) vs. HD (93% to 58%)	1.24 (IQR 1.03, 1.47) vs. 1.31 (1.10, 1.54)	N/A	- Adjusted HR of death: 0.85 (95%CI 0.71–1.03); by age - Age 40–60: HR 0.65 (0.45–0.94)
North Asia									
Neri L, et al.[11]	Retrospective cohort	Russia	1081	6	Post-dilution: 22.9 ± 3.2 L	OL-HDF (100%)	1.52 ± 0.23	20.0 ± 7.4	- 2-year mortality: 59.5 events/1000 person-years (95%CI 48.7–72.7) - Whole time: 59.1 deaths/1000 person-years (95%CI 50–69.9) - Significant 5-year survival for dose 21–25 L
Southeast Asia									
Tiranathanagul K, et al.[21]	Retrospective cohort	Thailand	66	10	Post-dilution: 26.6 ± 1.1 L Pre-dilution: 44.5 ± 3.0 L; time 4 h	OL-HDF (100%)	2.25 ± 0.40	26.2 ± 6.9	- Mean survival: 8.99 ± 0.64 years - 1-, 3-, 5-, 10-year survival: 95.1%, 83.4%, 77.7%, 61.8% - Comparable long-term survival to KT subgroup ($p = 0.93$)
Middle east Asia									
Ok E, et al.[4]	Prospective RCT (Turkish OL-HDF Study)	Turkey	782	2	Post-dilution: 17.2 ± 1.3 L; thrice weekly, total 12 h/week	OL-HDF (50%) vs. high-flux HD (50%)	1.44 ± 0.27 vs. 1.42 ± 0.25 ($p = 0.29$)	26.5 ± 7.9	- No significant difference (event-free survival 77.6% vs. 74.8%, $p = 0.28$) - Better cardiovascular and overall survival in subgroup of high-efficiency OL-HDF (>17.4 L) ($p = 0.002$ and $p = 0.03$, respectively)
Abdelsalam MS, et al.[25]	Retrospective cohort	Saudi Arabia	60	5	Post-dilution: 22.3 ± 2.5 L	Online HDF (45%) vs. high-flux HD (55%)	1.89 ± 0.27 vs. 1.64 ± 0.31 ($p = 0.002$)	N/A	- No significant difference - Survival in high-flux HD 73% (95%CI 60–84) vs. online HDF 65% (95%CI 54–75)

(Continues)

TABLE 2 (Continued)

Authors	Study design	Country	Number of patients	Follow-up time (years)	Convective dose	Comparison mode	Kt/V	B2M (mg/L)	Survival outcomes
									- Unadjusted HR 0.78 (95%CI 0.10–5.6, $p = 0.81$)
AlSahow A, et al.[23]	Prospective cohort	Saudi Arabia	664	6	Post-dilution 100%	4%	1.34	N/A	- Increasing BFR ≥ 350 ml/min and treatment time ≥4 h thrice weekly will reduce low Kt/V prevalence and may improve survival particularly in women
		Bahrain	59			75%	1.34		
		Oman	147			17%	1.38		
		Kuwait	258			58%	1.19		
		UAE	273			25%	1.53		

Abbreviations: B2M, β_2-microglobulin; BFR, blood flow rate; CI, confidence interval; HD, hemodialysis; HDF, hemodiafiltration; HR, hazard ratio; IQR, interquartile range; KT, kidney transplantation; N/A, not applicable; OL-HDF, online hemodiafiltration; UAE, United Arab Emirates.

effective removal of B2M, and improvements in nutritional status compared to conventional HD.[19] Reusing dialyzers for OL-HDF has been shown to provide efficacy, safety, cost savings, and environmental benefits.[20] In addition, a recent cohort followed for 10-year survival using high-efficiency OL-HDF in both predilution and postdilution modes, with mean a convective dose of 44.5 ± 3 and 26.6 ± 1.1 L, respectively, demonstrated a comparable survival to a subgroup of kidney transplant patients.[21]

2.1.4 | HDF in South Asia

HDF utilization in South Asian countries, that is, India, Pakistan, Bangladesh, Sri Lanka, Bhutan, Nepal, Afghanistan, and the Maldives, remains unknown due to a shortage of registry reports, poor access to healthcare, and the absence of an organized chronic disease management program. Universal reimbursements are rare in this region, and most nations remain dependent on expensive imported KRT technology. Thus, the use of HDF is limited to increasing usage in corporate hospitals or private healthcare settings that cater to wealthy patients and those with access to insurance.[22]

2.1.5 | HDF in middle East Asia

A prospective cohort study which analyzed data from DOPPS for the Gulf Cooperation Council (GCC) countries, including Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates in 2012–2018 demonstrated varying amounts of post-dilution HDF in these countries (75%, 58%, 17%, 0%, 4%, and 25%, respectively).[23]

In 2013, the Turkish OL-HDF study, a prospective randomized-controlled trial, was conducted in Turkey. Although the composite outcome of mortality and cardiovascular events was not different between OL-HDF and high-flux HD, results from a post-hoc analysis showed that high-efficiency post-dilution OL-HDF > 17.4 L was associated with better cardiovascular outcomes and increased survival compared to high-flux HD.[4]

A study from Saudi Arabia demonstrated benefits of high-efficiency post-dilution OL-HDF 19.3 ± 2.1 L in terms of patient satisfaction and quality of life including social, physical, and professional activities compared to high-flux HD.[24] However, the five year survival was not different for patients treated by post-dilution OL-HDF 22.3 ± 2.5 L.[25] Although a recent retrospective study of post-dilution OL-HDF 18–23 L reported a significant benefit in phosphate reduction, increased calcium, Kt/V, higher hemoglobin levels with a reduction in the erythropoiesis-stimulating agent (ESA) doses compared to high-flux HD.[26]

2.2 | HDF in Latin America

One reason for limited HDF adoption in Latin America might be the perceived difficulty by clinics without experience of HDF.[27] There continues to be a scarcity of data on HDF utilization in this region. In

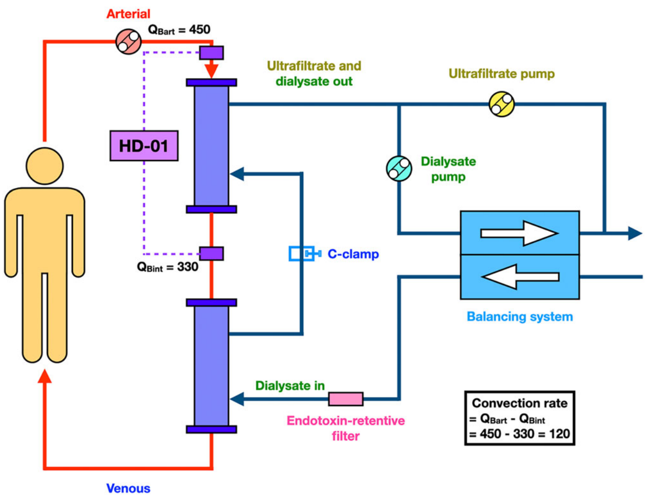

FIGURE 1 Convective control double high-flux hemodiafiltration (CC-HDF)

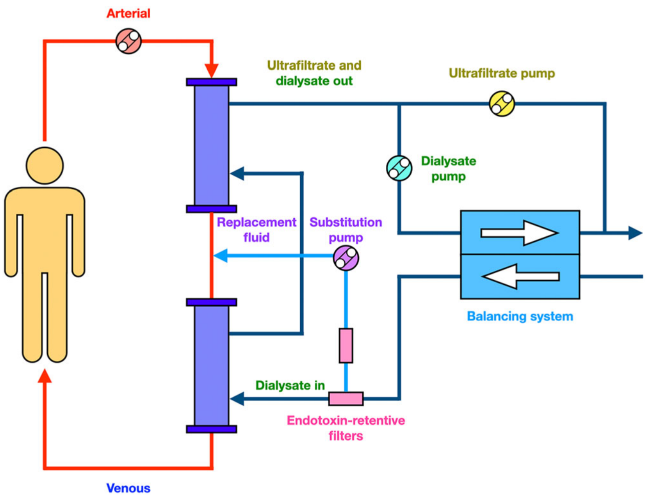

FIGURE 2 Simple mid-dilution online hemodiafiltration

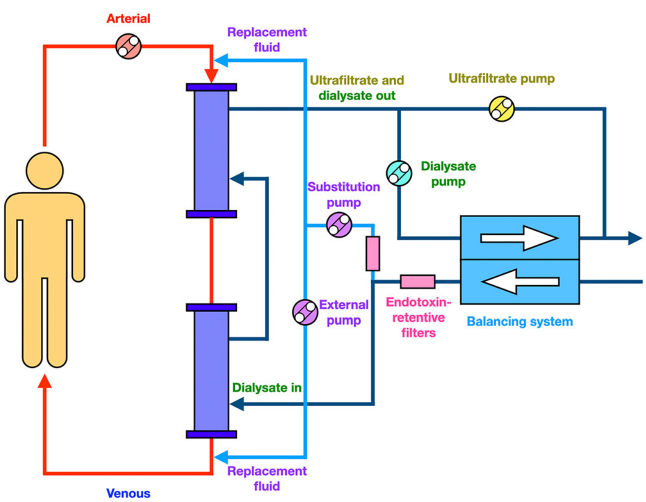

FIGURE 3 Simple mixed-dilution online hemodiafiltration

2015, OL-HDF was recorded to be used in approximately 20% of HD centers in Argentina. While the Latin American Dialysis and Renal Transplantation Registry (LADRTR) has an annual survey on KRT from 20 countries that are members of the Latin American Society of Nephrology and Hypertension (SLANH), the prevalence of HDF is not classified and is included in the total number of HD.[28] In 2019, HD was the most frequently used modality in all countries except Costa Rica.[28]

In Mexico, an experimental study using low-intensity intradialytic exercise during regular HDF thrice a week for at least 6 months showed the potential to decrease the relative blood volume drop and was associated with less hypotension due to intravascular volume loss.[29]

In Brazil, the HDFIT study, a multi-center prospective randomized-controlled trial, investigated the impact of a short exercise training program for patients treated with HDF compared to high-flux HD. Although the main outcome and post-hoc analysis reported no significant effect on physical activity and self-reported sleep duration,[30,31] a convective volume of >22 L/session for 6 months was associated with increased Kt/V and decreased phosphate.

2.3 | HDF in Africa

The absence of kidney registries and limited published data in many African countries leads to unreliable statistics on the prevalence HDF utilization.[32,33] The availability of KRT is limited in this region due to the high cost and shortage of skilled personnel. Most dialysis centers are located in cities, placing a burden on patients who often travel long distances to a center. Funding for KRT is primarily private in much of Africa, with governmental funding for only a small number of patients in some countries (e.g., Cameroon, Guinea, Mali, Mauritius, Mozambique, Rwanda, Sudan, and South Africa).[33] As the majority are self-funded, very few people in African countries are able to afford dialysis payment beyond 6 months and have to stop dialysis when funds are depleted.[33,34]

3 | BARRIERS OF HDF IMPLEMENTATION IN DEVELOPING COUNTRIES

Nonclinical factors have a large impact on delivering HDF in developing countries (Figure 4).

3.1 | Nonclinical factors

3.1.1 | Socioeconomic problems

Socioeconomic factors such as lack of infrastructure to ensure ultra-pure water quality, adequate sanitation, and financial constraints are the main factors limiting the adoption of HDF. The reimbursement

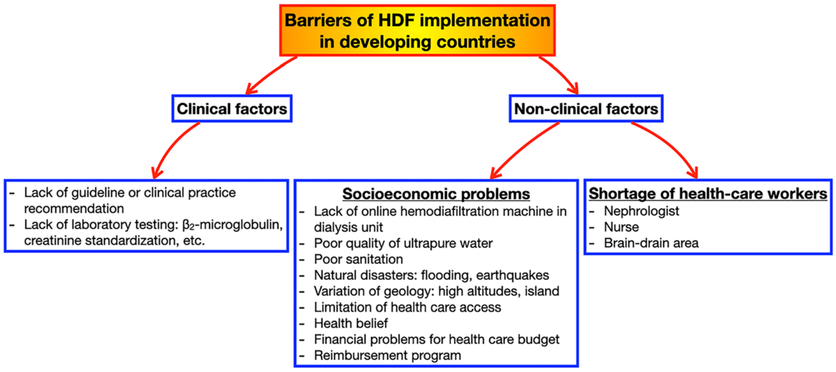

FIGURE 4 Barrier of hemodiafiltration implementation in developing countries

programs of nearly all developing countries do not support the cost of OL-HDF therapy. This results in the need for patient families to make very difficult decisions as to whether to pay extra costs.

3.1.2 | Shortage of healthcare workers

In contrast to the size and population of developing countries, there is a significant difference in the economic remuneration and the gross domestic product in each country. The shortage of skilled healthcare workers including nephrologists and nurses is a major obstacle in almost every region, as most only work in metropolitan areas or large cities. The continued brain-drain of these healthcare providers to richer countries including the United States continues to be a problem in some areas such as Africa.[33]

3.2 | Clinical factors

Even though HDF shows safety and benefits for ESKD patients, there are no absolute indications for adoption. In Thailand, there is a clinical recommendation for using HDF in ESKD patients who have received conventional HD but with unsatisfactory outcomes and who can support out-of-pocket costs under one of the following scenarios: (1) dialysis-related amyloidosis, (2) cardiovascular instability with unsatisfactory treatment of intradialytic hypotension, (3) unexplained anemia with ESA hyporesponsiveness, and (4) malnutrition along with middle and large molecule uremic toxins especially B2M > 27.5 μg/L without an unexplained cause.[35–38] This type of clinical practice guideline may improve HDF utilization in developing countries.

4 | STRATEGIES TO IMPROVE HDF IMPLEMENTATION IN DEVELOPING COUNTRIES

One way of improving ESKD patient care in developing countries would be to increase HDF availability and adoption. The first step should be to report the exact number of OL-HDF machines and the number of patients treated by dialysis units in national registries. This may lead to an increased recognition of HDF usage and may lead to increased machine availability or innovation of novel HDF techniques in resource-limiting settings. In terms of water purification systems, some dialysis units in areas such as India, Brazil and Africa, have inadequate access to suitable potable water supplies.[39] An analysis of water treatment for dialysis should by undertaken by each national nephrology society to maintain and improve standards. In accordance with the shortage of healthcare providers, the implementation of telemedicine might be another tool to improve dialysis care. This is a useful method to help remote dialysis units better communicate with nephrologists and nurses via telephone or web-based online meetings for adjusting dialysis prescriptions or referring patients. It is essential to provide a clinical practice guideline or set of recommendations which are focused on the use of HDF in limited resource settings. Any recommendations should also form the basis for governments to increase reimbursements for improvements in dialysis techniques.

5 | CONCLUSION

HDF is a HD technique that uses additional convection to improve the removal of middle and larger molecule uremic toxins leading to improved patient outcomes, quality of life, and survival compared to conventional HD. Developing countries still have a series of unique obstacles in the context of socioeconomic factors, process of care, and clinical factors that challenge the nephrology team to develop alternative innovative treatments which are simple, inexpensive, practical, and as effective as OL-HDF machines. Strategies to enhance HDF implementation such as clinical practice guidelines or recommendations, adding the modality in more dialysis centers, along with educating and training healthcare workers on this new treatment can help expand HDF implementation worldwide.

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