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SPECIAL REPORT

Hemoadsorption combined with hemodialysis (HAHD): a consensus statement from an international expert panel

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ABSTRACT

Clinical outcomes in patients on maintenance dialysis are still unsatisfactory. Despite delivery of adequate dialysis, residual symptoms and signs of uremic intoxication are often present, such as pruritus and xeroderma, restless leg syndrome, sleep disorders, cognitive impairment, anxiety and depression, cramps, fatigue, and muscular weakness, mineral and bone disorders, cardiovascular complications, chronic inflammation, and accelerated atherosclerosis. These have been correlated with retention of inflammatory chemical mediators, protein-bound uremic toxins, and middle to large molecular weight toxins that are insufficiently cleared by current dialysis techniques. A new extracorporeal technique combining hemoadsorption with hemodialysis (HAHD) has been utilized with promising results but enormous variability of procedures, resulting in limited evidence. Previous experience in incorporating innovative approaches has demonstrated that, after several years of pioneering work, a common pathway is necessary to generate sufficient evidence, spanning from case reports, expert debates, retrospective and observational studies, registries, and underpowered trials to multicenter international randomized clinical trials and meta-analyses. Thus, the widespread adoption of HAHD requires the application of implementation science techniques supported by healthcare policies. The scope of this conference is to conduct an objective appraisal of current knowledge and to propose a standardized application modality, enabling the design of comparable clinical trials and the acquisition of homogeneous datasets suitable for evaluation and discussion.

Keywords: adsorption, hemoadsorption, hemodiafiltration, hemodialysis, uremic toxins

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INTRODUCTION

Hemoadsorption (HA) has been used for >70 years in extracorporeal blood purification therapies (EBPT) [1]. Recent efficient and safe sorbent devices for both acute and chronic therapies [2, 3], have spurred new interest in this technology. The combination of hemoadsorption (preferred term in recent nomenclature [4]) with classic dialysis modalities [low- and high-flux hemodialysis (HD), expanded hemodialysis (HDx), and hemodiafiltration (HDF)], seems to overcome the limitations of these techniques. This paper discusses the association between HA and classic dialysis modalities used in patients with chronic kidney disease stage 5D (i.e. kidney failure). The application in acute settings, or stand-alone HA are beyond the scope of this work. In this regard, the removal of antibodies, endotoxins, and in poisoning are discussed elsewhere [2].

Although significant technological progress has been made in the field of dialysis, patients continue to face a substantial burden of illness. Prevalent symptoms include fatigue, pain, and poor sleep quality, which affect patients' quality of life and well-being. Furthermore, comorbid conditions such as cardiovascular disease present earlier with higher severity, and overall survival rates remain unsatisfactory. The accumulation of compounds included under the overarching definition of "uremic toxins" is believed to contribute to these poor outcomes. Traditional EBPT relies on diffusion and convection for mass transport and blood clearance of compounds accumulated in patients with kidney failure. However, an incomplete clearance of uremic toxins, which are not adequately cleared by conventional dialysis modalities, is associated with a high residual disease risk [5, 6]. HA allows an incremental removal of uremic toxins associated with unresolved symptoms [7]. Nonetheless, there is limited scientific evidence for HA's causative role in symptom resolution and improvement in clinical outcomes.

The cartridges used for HA (Fig. 1) contain hemocompatible polymers (mainly from polystyrene divinylbenzene) in the form of beads (Fig. 2). Although HA with HD (HAHD) has been utilized in various settings and countries, differences in the treated populations and variability in prescription, modality of application, and delivery often make results hardly comparable [8–13]. This lack of uniformity occurred in the past with other innovative EBPT, such as HDF, preventing a standardized approach and a systematic collection of consistent data for many years. To collect comparable data to provide solid evidence for HAHD, consensus should be reached on the most suitable modality, prescription, and application for each specific indication. A consensus conference was organized with the scope of making an objective appraisal of the current knowledge concerning HAHD and proposing a standardized approach to facilitate homogeneous data collection in future studies. The conference aimed at defining and characterizing HAHD, establishing relevant nomenclature, standardization, and adequate endpoints for clinical trials.

A final scope was benchmarking best practices to allow safe and uncomplicated adoption of the therapy, applying strategies from frameworks developed by implementation scientists [14–17]. The paper applied the ACCORD (ACcurate COnsensus Reporting Document) checklist for the report of consensus methods. Importantly, not all the items were fulfilled as disclosed in Supplemental Table S1 [18].

METHODS

Panelists and endorsing bodies

The HAHD Consensus Statement derives from the conference promoted by the International Renal Research Institute of Vicenza in Rome in January 2025. In October 2024, an email invitation was sent to 23 international experts to participate in the survey. The faculty consisted of one bioengineer and 23 clinicians [one chair (CR)] with notable expertise in EBPT who regularly provide HAHD. Panelists were appointed by the international scientific societies endorsing the event based on their contributions to the field in the last 5 years and experience in managing consensus processes. Experts represented 15 countries from different continents and socio-economic regions. The complexity of understanding technical terminology related to the HAHD domains and the scientific appraisal of evidence precluded patients or the public from being included on the panel. Thus, no patients, caregivers, patient representatives, or non-patient stakeholders attended. Participants were not reimbursed for their time.

Design

This was a consensus conference informed by Delphi principles. The approach has been utilized as previously described [19]. However, it did not involve a Delphi methodologist, and the study protocol was not registered. The process was designed to be transparent and sensitive to dissenting opinions. Results reflected discussions and compromises between opposing points of view. The ultimate goal was to develop a set of questions and statements useful to achieve adequate recommendations for the implementation of HAHD.

In the pre-conference phase, full-text versions of relevant publications were provided to all members. Rounds using online questionnaires were not conducted, and panelists were aware of the identities of the other members. Participants further gathered relevant studies through the National Institutes of Health PubMed platform, Medline, Scopus, and Web of Science databases, in resemblance to a narrative review approach. No date restrictions were applied. Searches were generally limited to articles published in English; however, articles in other languages were also considered when identified and presented by group members. The last search was conducted on 5 January 2025.

Objective and dispassionate distillation of the literature provided a description of the current state of HAHD practice. This led to a list of key questions to be answered with consensus statements.

Faculty members were divided into three groups: (i) rationale, indications, and patient selection for HAHD; (ii) prescription and modality of application of HAHD in clinical practice; and (iii) technical and clinical evaluation and treatment monitoring.

The conference phase consisted of four plenary sessions with formal presentations and three breakout group sessions with the following schedule: (i) question definition and refinement; (ii) statements drafting with figures and tables; and (iii) final statements, figures, and tables. All members had an equal voice during breakout and plenary sessions. Consensus was defined as a two-thirds majority for the definition of questions, statements, figures, and tables. Whenever this threshold was not met, the item was suppressed. The detailed percentage of agreement was not recorded; therefore, the decisions were dichotomous.

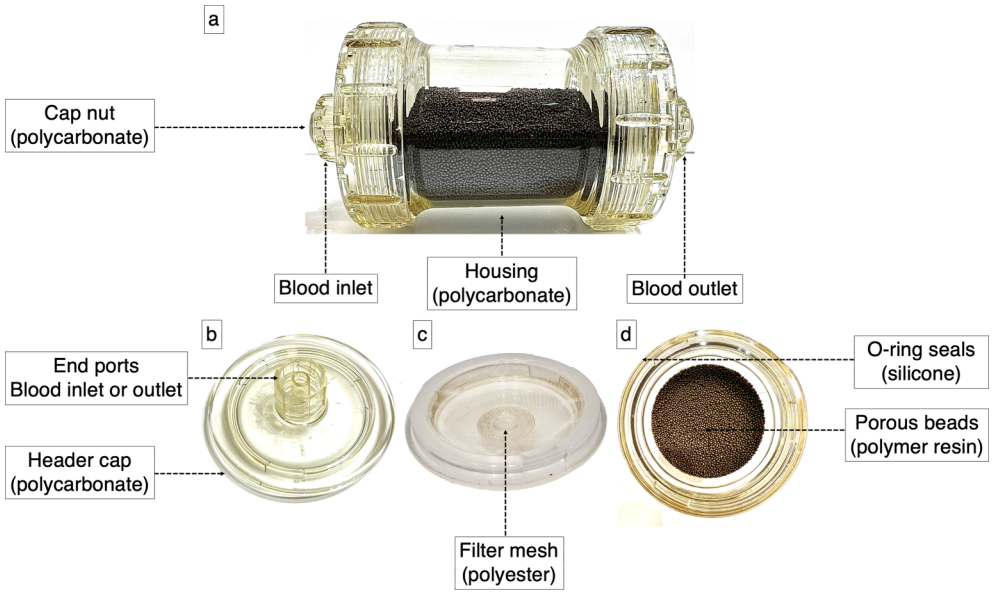

Figure 1: Cartridge components for HAHD. (a) Longitudinal view demonstrating the beads that usually occupy 40% to 60% of the cylindrical recipient's volume. (b) Blood inlet and outlet end ports. (c) Axial view of the filter mesh that prevents embolization of the beads. (d). Axial view after the removal of the header cap, exposing the beads.

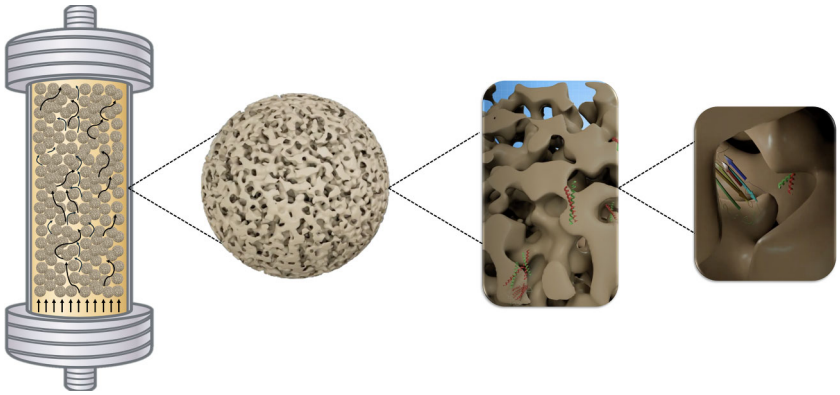

Figure 2: Schematic illustration of a cartridge for HAHD containing spherical porous resin in the form of beads. The curved arrows represent flow patterns. In the magnification, the trabecular feature of the beads is demonstrated. Importantly, most of the adsorption occurs inside the beads, not on their surface. Adapted from reference 2 with permission .

The statements are presented in the paper as "key consensus points" and were drafted after the agreement on the questions. Majority and dissenting opinions were used to resolve any disputes. Minority viewpoints were appraised and eventually incorporated into revised questions, statements, figures, and tables. We tracked all modifications to slide decks for each round and documented the excluded items.

In the absence of sufficient evidence, rationale for application, clinical indications, prescription, and monitoring were based on expert opinion. The literature revealed a lack of high-quality evidence for HAHD, and our aim was to provide alternative solutions where there may be barriers to evidence-based practices; therefore, the GRADE methodology was not used [20]. A thorough research agenda was proposed. Thus, recommendations should be considered for work-in-progress with great potential for improvement and evolution as new evidence develops.

The post-conference phase comprised the elaboration of the paper. A writing committee formed by the chair (CR) and the three group leaders (MO, TR, VC) collected and edited the individual sections from each workgroup, crafting the final version of the draft. The document was circulated to all members for comment, revision, and approval. External reviewers were not consulted. All members were co-authors and equally contributed to the content of the paper. All authors take responsibility for the final content of the paper. Conflict of interest declarations for the panelists are provided in a subsequent section of this paper.

RESULTS

Indications and patient selection

Question: What is the pathophysiological rationale for using HAHD to manage uremia-related symptoms and complications?

Key consensus points

1. There is a recognized correlation between retention of specific uremic toxins and the pathophysiology of symptoms and complications.

2. The main concept is that via adsorptive clearance, HAHD could further remove uremic toxins, scarcely eliminated by diffusion and convection.

Rationale

Uremic toxins are involved in HD complications due to functional alterations of different organs (Supplementary Table S2). Vascular involvement may begin with subclinical endothelial dysfunction, which can evolve into premature vascular aging, ultimately leading to major adverse cardiovascular events [21]. Conventional HD with high-flux filters primarily relies on diffusive transport, thereby limiting clearance of medium-middle (i.e. molecular weight >15–25 kDa) and large-middle (i.e. >25–58 kDa) molecules [22, 23], as diffusion is inversely related to the molecule's hydrodynamic radius [5]. By using filters with a higher retention onset, such as medium cutoff membranes for HDx, an increment in convective clearance is obtained. Finally, HDF with high convection rates further enhances the removal of these solutes [24]. Still, the removal of large-middle molecules is unsatisfactory [25–27], and these increments are insufficient to reduce pre-dialysis blood levels. HAHD could enhance the removal of middle molecules. β_2-microglobulin is widely adopted as a surrogate for the removal of middle molecules in clinical trials [28, 29]. Several studies have shown the effectiveness and superiority of HAHD in β_2-microglobulin removal [30], compared to HD [12, 31]. In a prospective trial including 20 patients, each patient underwent a total of six sessions: three sessions using low-flux HD, high-flux HD, and HDF, which were followed by three sessions of the same modalities combined with HA. The device for HA was the HA130 cartridge (Jafron Biomedical, Zhuhai City, China) containing polystyrene divinylbenzene resin in the form of beads (Fig. 1). The additional application of HA significantly enhanced β_2-microglobulin removal [13]. In the comparison between low-flux HD and low-flux HAHD, the mean and standard deviation of reduction ratios were 4.6 ± 7.3% and 13.7 ± 4.4%, respectively ($P < .001$). By contrast, between high-flux HD and high-flux HAHD, 72.7 ± 6.0% and 78.8 ± 4.8% ($P > .05$). Finally, between HDF and hemoadsorption with post-filter replacement hemodiafiltration (HAHDF), 83.9 ± 6.4% and 86.0 ± 4.9% ($P = .008$). Despite statistically significant differences, such as in the comparison of HDF and HAHDF, it is fair to debate whether a 2.5% increase in β_2-microglobulin reduction ratio could have a clinically meaningful impact.

Pathophysiological rationale is further supported by a recent publication proposing that enhanced removal of pro-inflammatory mediators may contribute to mitigate the inflammatory pathway leading to increased β_2-microglobulin production [32].

Protein-bound uremic toxins (PBUT) also require enhanced removal by EBPT. These are small molecules (<0.5 kDa) that are bound to larger carrier proteins. During dialysis, the unbound fraction behaves like small molecules, whereas the bound fraction behaves like their carrier protein, which for most PBUT is albumin. This makes PBUT difficult to remove by HD [33]. HAHD may increase PBUT clearance due to direct contact of blood with the sorbent material [30]. *In vitro* and *ex vivo* experiments demonstrated the feasibility [34], although efficacy depends on the type of sorbent used, such as hexadecyl-immobilized cellulose [i.e. Lixelle cartridge (Kaneka Corporation, Osaka, Japan)] [35], or with other polystyrene divinylbenzene cartridge, [36]. Importantly, commercially available cartridges with activated charcoal are not intended for application routinely in patients with kidney failure. Recent biotechnological advancements have improved both sorbent biocompatibility and efficiency, paving the way for new clinical applications of HAHD for PBUT removal [7, 37]. Ramírez-Guerrero *et al*. compared the removal of advanced glycation end products (AGEs), a PBUT, with HAHD using the HA130 cartridge and high-flux HD in an open-label, randomized, pilot clinical trial including 20 maintenance dialysis patients. High-flux HAHD significantly improved the removal of the AGE N-carboxymethyllysine compared to high-flux HD alone. The median and interquartile range of the reduction ratios were 39.3 (33.8%–49.4%) and 64.7 (52.6%–74.9%), ($P = .045$) [38]. Confounding might exist because each study arm included only 10 individuals, and baseline patient characteristics and medical history are likely unevenly distributed. Maduell *et al*., however, did not achieve the same results in terms of reduction ratios for indoxyl sulfate and p-cresyl sulfate [13]. Both studies utilized the same cartridge but evaluated different PBUT.

Of note, these studies did not examine the long-term reduction in pretreatment concentrations of these compounds, but rather the pre- versus post-session concentration difference. The impact of an intervention on pretreatment concentration, a surrogate for cumulative exposure (i.e. area under the curve), portends a higher biological value.

While these preliminary trials suggest improved removal of certain toxins, they were limited by small sample sizes and short follow-up and did not assess clinical endpoints. Their results should be viewed as hypothesis-generating and support the conduct of clinical trials evaluating hard outcomes, for example, survival and cardiovascular events as primary outcomes.

Question: What are the indications for HAHD?

Key consensus point

The indications to start HAHD should consider the presence of specific symptoms and signs, molecular biomarkers, patient-reported outcomes assessed by questionnaires and scales, and performance tests. The combination of all these variables translates into a precision-medicine-based approach rooted in the interpretation of patients' endophenotyping.

Rationale

Table 1 lists examples of variables that can be used in a decision-making algorithm for HAHD in common indications, including chronic kidney disease-associated pruritus, restless leg syndrome, post-dialysis recovery time, chronic fatigue, sarcopenia, and frailty syndrome [39, 40]. Supplementary Table S3 lists questionnaires used to assess patient-reported outcomes. Notably, the uremic population is highly heterogeneous. An attempt to select patients who will likely benefit from an intervention aims to subdivide them based on their phenotype, subphenotype, and ultimately, endotype. The endotype is a subset of patients within the same subphenotype who might respond better to HAHD application, as shown in Fig. 3. In Japan, the selection of patients eligible for HAHD using the Lixelle cartridge has been framed within a precision-medicine approach [41]. The phenotype is represented by patients on maintenance dialysis. The subphenotype is described by those who develop carpal tunnel syndrome. The endotype is represented by a group with histologic evidence of β_2-microglobulin amyloid deposition or bone imaging findings demonstrating a causative effect. This last group presents a strong rationale for benefiting from HAHD. This approach requires validation [42], and future trials should test whether patient selection based on endotypes actually increases the likelihood of benefit from receiving HAHD. Figure 4 presents a pro-

Table 1: Variables for patient selection and evaluation for hemoadsorption coupled with hemodialysis (HAHD).

Condition	Biomarker	Symptoms and signs	Patient- or caregiver-reported	Performance
Chronic kidney disease-associated pruritus	–	Itching, xerosis, crusts, or erosions	Worse Itching Intensity Numerical Scale; 5-D itch scale; KDQOL-36	–
Restless leg syndrome	Ferritin, hepcidin, polysomnography	Urge to move that appears during rest and disappears during movement	Restless leg syndrome rating scale; Pittsburgh sleep quality index; KDQOL-36	–
Post-dialysis recovery time	–	Malaise, weakness	Minutes or hours until full recovery; KDQOL-36	Step-count
Chronic fatigue	C-reactive protein	Fatigue, muscle and joint pain, brain fog, loss of memory	Brief fatigue inventory; SF-36; KDQOL-36	–
Frailty syndrome/Sarcopenia	Lean tissue mass assessed by bioimpedance or DXA; rectus femoris thickness or cross-sectional area assessed by ultrasound, MRI, or CT scan	Weakness, exhaustion, slow walking speed, falls	Clinical Frailty Scale, falls	Grip strength; chair stand test; timed up and go test, gait speed test; 400-m walk; short physical performance battery

Footnote: CT, computed tomography; DXA, dual-energy X-ray absorptiometry; SF-36, short form 36; MRI, magnetic resonance imaging.

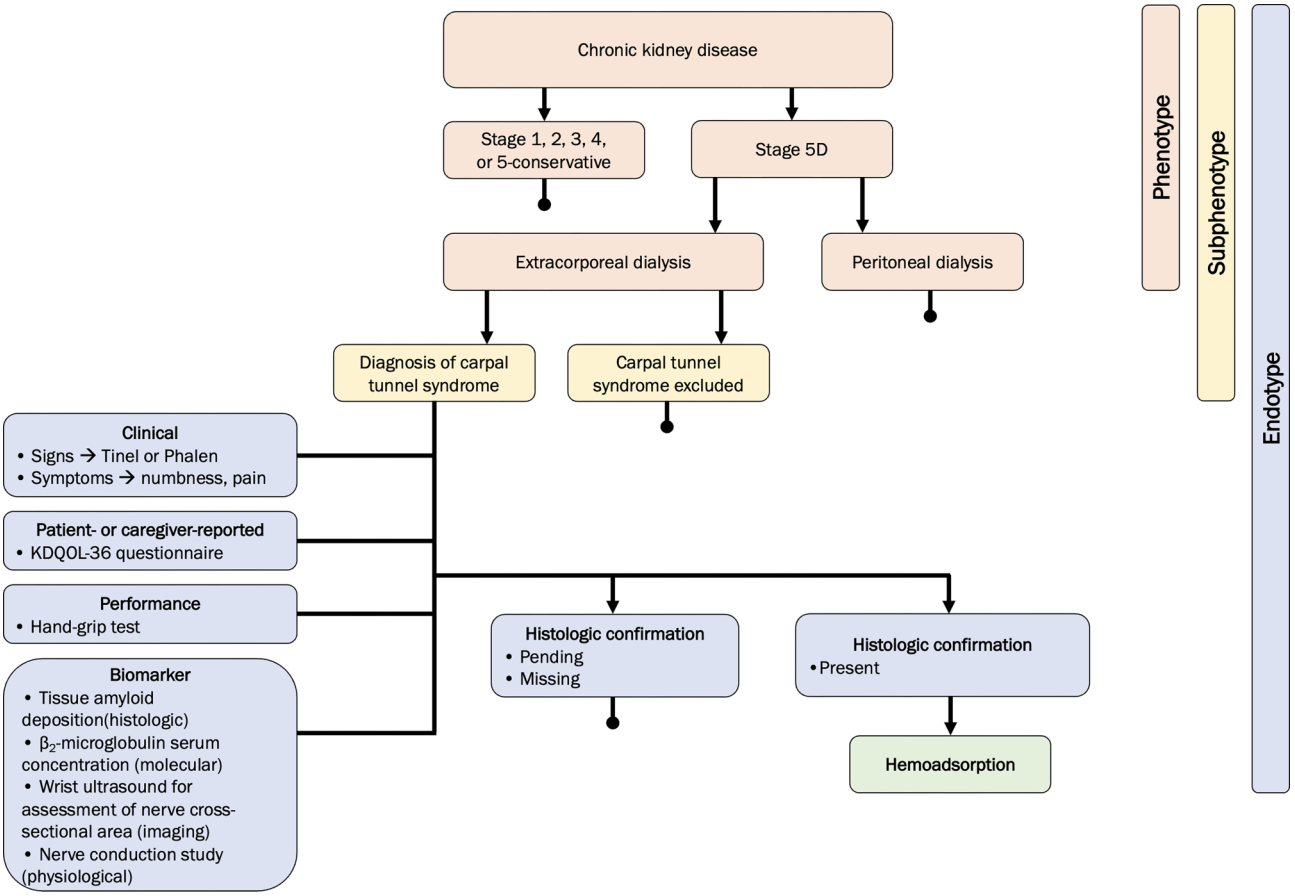

Figure 3: Precision-medicine approach for the indication of HAHD. A decision-making flowchart, using the carpal tunnel syndrome as an example. Here, the phenotype is represented by a subset of patients with chronic kidney disease requiring dialysis, but excluding those on peritoneal dialysis because these patients do not have dedicated venous access. The subphenotype is represented by the patients who develop carpal tunnel syndrome, which may or may not be caused by the accumulation of the middle molecule β_2-microglobulin (12 kDa), a uremic toxin. For patients diagnosed with carpal tunnel syndrome, the further characterization of a specific endotype depends on clinical variables, patient- or caregiver-reported outcomes, performance tests, and assessment of biomarkers (e.g. molecular, imaging, histological, and physiological). Finally, if no contraindications are present, HAHD would be proposed. Obviously, patients on peritoneal dialysis experiencing refractory symptoms should consider changing their dialysis modality, and when on extracorporeal dialysis regimens, they should be evaluated for HAHD.

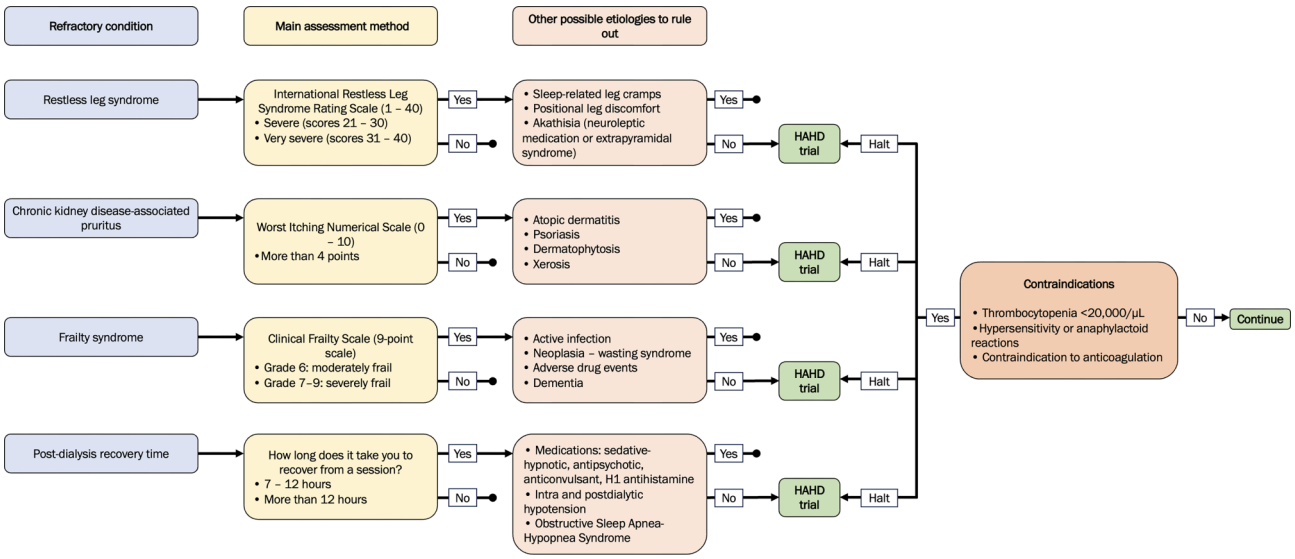

Figure 4: Proposed decision tree for patient selection for HAHD. The recognition of refractory conditions triggers the application of a questionnaire or a scale, followed, if possible, by the exclusion of other plausible etiologies of the clinical presentation. A trial of HAHD is considered if no contraindications are present. Sessions are monitored and HAHD might be suspended if the patient develops contraindications.

posed decision tree to identify candidate patients for HAHD. At the present state of knowledge, we propose reserving HAHD for patients living with kidney failure who exhibit difficult-to-manage problems attributed to uremic toxin accumulation, after standard therapies have been exhausted. There is not enough evidence to recommend its routine use in asymptomatic patients or those without the alluded conditions.

Recommendations for research

1. Standardization of assays to measure the blood or plasma concentration of uremic toxins, deemed as targets for removal by adsorption, aiming to define their *in vitro* and *in vivo* adsorption kinetics with different sorbents.
2. Exploration of patient-reported outcomes and performance tests to better evaluate patient endophenotyping.

Question: What are the contraindications for HAHD?

Key consensus point

We consider applying HAHD in the absence of technical and clinical contraindications, in accordance with the manufacturer's instructions and local regulatory frameworks, to minimize risks and ensure efficacy.

Rationale

In the past, adverse events related to HA such as thrombocytopenia and leukopenia were mostly due to poor biocompatibility of sorbents [43–45]. Deposition of fibrinogen on the bead's surface may promote platelet adhesion and formation of platelet aggregates and thrombi. Overexpression of the complement receptor 3 on neutrophils may occur, triggering the formation of platelet-neutrophil complexes [46]. When the platelet count is $\leq$20 000/mm^3 and the absolute neutrophil count is $\leq$1 000/mm^3, which are arbitrary cutoffs, the use of HA may be postponed to the next dialysis session. These phenomena are rare with the current sorbent resins and have been described in the field of critical care [47], not in maintenance dialysis.

Hypersensitivity or anaphylactoid reactions may occur. Before establishing an absolute contraindication to HAHD, the association of these reactions to medications infused during dialysis—including heparin, intravenous iron, erythropoiesis-stimulating agents, or active vitamin D analogs—should be ruled out [48]. If none of these medications are deemed triggers of the allergic response, hypersensitivity reactions to circuit components—such as needles, filters, lines, and wound dressings—should be excluded before contraindicating subsequent HAHD treatments.

Modality of application of HAHD in clinical practice

Question: What extracorporeal dialysis modalities are compatible with HA?

Key consensus point

All extracorporeal dialysis modalities can be combined with HA, including low-flux HD (HAHD), high-flux HD (HAHFD), expanded HD (HAHDx), and HDF (HAHDF).

Rationale

HA can be effectively integrated with all major extracorporeal dialysis modalities (Fig. 5). Most published literature reports the integration of hemoadsorption with low-flux and high-flux HD [10, 12, 49]. A registry from Shanghai included 9351 patients who started maintenance HD from 2007 to 2014 [50]. Of those, 7207 carried out either low- or high-flux HD. Furthermore, 2144 underwent a mixed regimen where online HDF was mainly prescribed once weekly, and in the remaining two sessions of the week, patients received HD. In the group of patients not receiving HDF, only 0.5% also received HA, whereas 6% of the patients receiving HDF were also on HA [50].

A recent meta-analysis included data from 12 studies, in which seven were randomized controlled trials, and five cohort studies, involved a total of 1287 patients. Of those, 583 were treated with HAHD and the technique was well tolerated and was associated with improved survival in up to 2 years when compared with low- or high-flux HD. This trend was also maintained when pooling data exclusively from the randomized controlled trials included in the meta-analysis [49]. These results should be interpreted parsimoniously and do not support premature conclusions that HAHD improves survival in kidney fail-

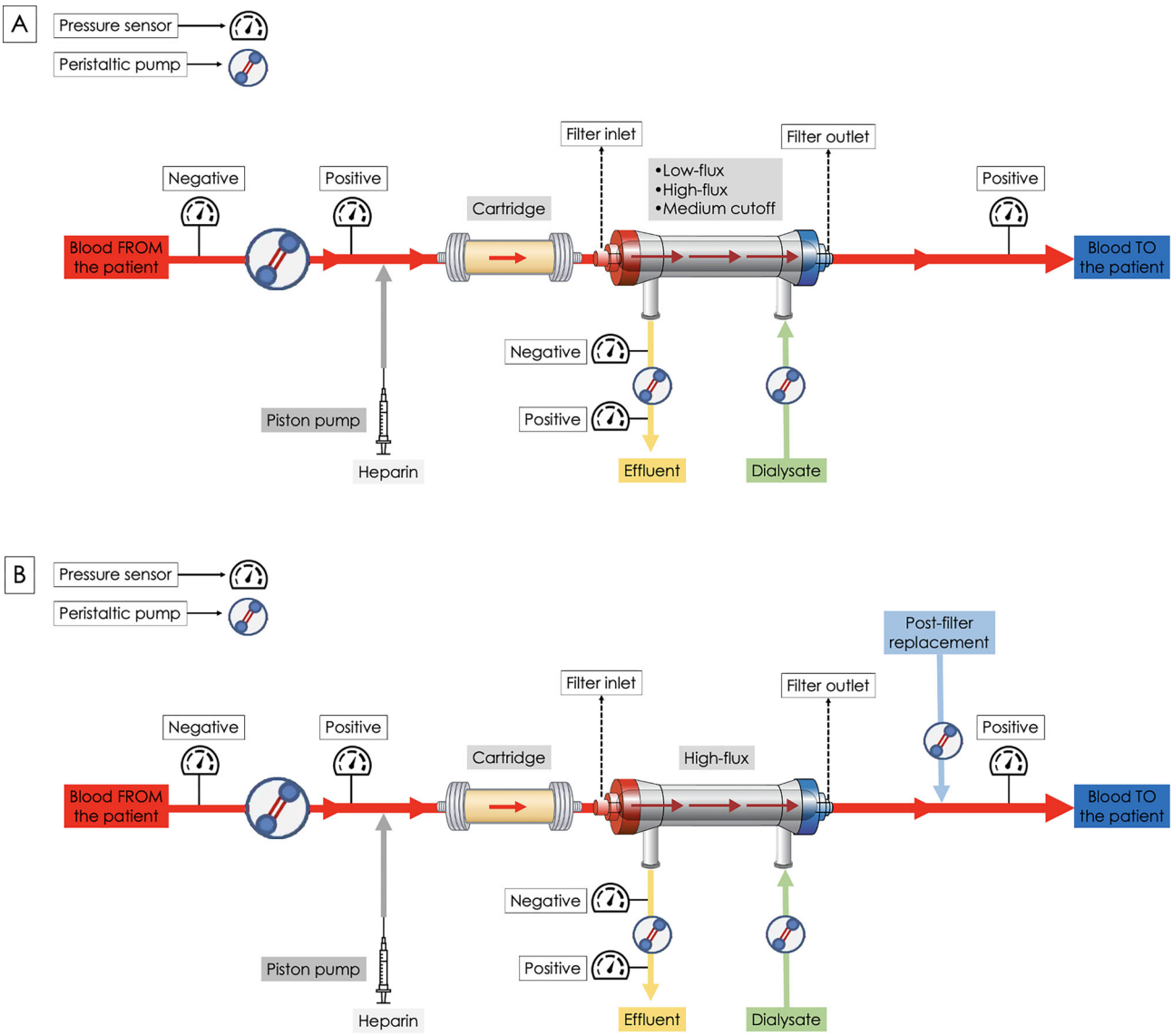

Figure 5: Schematic representation of the possible modalities for HAHD. In both examples, the cartridge is placed before the filter. Upstream of the first peristaltic pump, the pressure in the extracorporeal circuit is negative. After this pump, the circuit's pressure becomes positive and heparin is given. (a) Hemoadsorption combined with low-flux or high-flux filters (HAHD) or medium cutoff filters for expanded hemodialysis (HAHDx). (b) Hemoadsorption with post-filter replacement hemodiafiltration (HAHDF).

ure patients. In addition, significant heterogeneity among these studies concerning treatment delivery precludes extrapolations. To date, no randomized clinical trial has been powered to investigate survival as the primary outcome, comparing HAHD to other dialysis techniques.

Remarkably, the combination of HA applying the HA130 device with modalities with enhanced convective clearance, such as online HDF or HDx, was explored in observational and intervention trials, where no technical or safety issues were reported [7, 13, 51, 52]. In contrast to other applications for hemoadsorption, such as intoxications [53], where HA can be applied as a stand-alone treatment, for maintenance dialysis patients, HA is always combined in series with HD, HDx, or HDF.

Finally, regulatory and reimbursement issues may hinder the implementation of HAHD in different jurisdictions. For instance, HA130 is approved in the European Union, Latin America, the West, Central, and East Asia. In addition, this cartridge is available in some African and Oceanian countries. In the USA, the HA130 is not approved, and the Lixelle is under the Humanitarian Device Exemption pathway for the treatment of dialysis-related amyloidosis. Financially, in middle-income countries such as Brazil, the use of HAHD might triple the cost of an HD session. In contrast, in Italy, HAHD might incur a 20%–50% increase in the expenditure; however, even in the same country, this is influenced by regional deals and if the HA is associated with HD or HDF.

Question: What is the minimum set of characteristics of HAHD prescription?

Key consensus points

1. HAHD implementation holds the premise that the best achievable extracorporeal dialysis prescription and technique have been applied.
2. The prescription of technical parameters remains the same as the original technique with the addition of HA.
3. Based on previous studies on pathophysiology and clinical experience, the commonly prescribed treatment frequency of HAHD consists of one session per week. This frequency

can be modified according to the patient's requirements and response.
4. In conditions and countries where HAHD is considered a "special technique" as HDF or HDx, the frequency of application should be thrice weekly.

Rationale

The main variables in prescribing extracorporeal dialysis include vascular access, blood flow, filter, anticoagulation, dialysate flow, replacement flow for HDF, and electrolytic adjustments [6, 54, 55]. For blood flows above 300 ml/min, 15 or 14-gauge needles are suggested [55]. For patients with tunneled catheters, 14.5 to 16 Fr size, are required [56]. High-flux and medium cutoff filters, filter surface area $\geq$2.0 m^2 and high convective flows provide higher clearance of uremic toxins and improved clinical outcomes [57–61]. Specifically for HAHDF, blood flows above 350 ml/min are required to achieve a convection volume of 23 l per session, adjusted to body surface area in a 4-hour session [24].

Apart from the specific cartridge preparation, anticoagulation protocols remain the same [62]. Unfractionated heparin and low molecular weight heparin are the most prescribed anticoagulants, and in general, no dose escalation is necessary. For patients already using daily direct factor Xa inhibitors (e.g. apixaban, rivaroxaban) for other clinical indications (e.g. atrial fibrillation) who were receiving a reduced heparin dose or no anticoagulation during dialysis, an additional dose might be necessary since direct factor Xa inhibitors are effectively cleared by adsorption onto styrene-divinylbenzene resins [63].

Prescribed dialysate flow (400 to 600 ml/min) [64, 65] should remain the same in HAHD. Bicarbonate, calcium, glucose, magnesium, potassium, and sodium are not influenced by hemoadsorption. Consequently, no dialysate flow or electrolyte adjustments are required [66]. The circuit pressures and transmembrane pressure are not significantly affected by the presence of the sorbent cartridge [67].

HAHD has been prescribed as a single weekly session [7, 10–12, 68],. However, patients with refractory pruritus or restless leg syndrome may receive up to three sessions per week. For refractory clinical conditions, experts recommend HAHD initially thrice weekly for 2 weeks, then de-escalated to twice weekly for the next 2 weeks, and finally maintained once weekly [69]. Some centers even allow one session every 2 weeks, although this approach might provide insufficient clearance of uremic toxins, and the potential benefits might be blunted or take longer to be demonstrated [70].

Where possible, a thrice-weekly regime is considered for a full correction of signs and symptoms. The duration of sessions at most Chinese centers is 2 hours. Therefore, in the first 2 hours of the session, the patient receives HAHD, then blood is returned, the circuit is primed with saline, and the HD or HDF session is resumed for the remaining 2 hours. In other regions of the world, this approach might be cumbersome and logistically challenging because it increases nurses' workload. Nowadays, the proposition is to apply HA throughout the entire HD or HDF session. In this manner, all the disposables are discarded simultaneously at the end of the session. Zhang and colleagues compared these approaches and demonstrated that the clotting risk and other adverse events were not higher with 4-hour HAHD sessions than with 2-hour sessions [32]. In most centers in the West, the duration of the HA sessions coincides with the complete duration of the dialysis procedure, and we understand this is the ideal approach [13, 38, 51, 52, 71].

Question: What is the recommended priming procedure for HAHD?

Key consensus point

The preparation and priming of the cartridge before its placement in the circuit should be done according to the manufacturer's instructions, as different types of cartridges are available. The priming of the extracorporeal circuit remains the same.

Rationale

The priming of the cartridge and the extracorporeal circuit serves multiple essential purposes. Firstly, the priming fluid washes out residues of substances utilized in the manufacturing and sterilization processes that could provoke hypersensitivity reactions [72]. Most cartridges are pre-filled with a saline solution that must be rinsed. Secondly, during the priming phase, the air contained in the cartridge must be removed by adequate maneuvers to prevent air embolism [48] and reduce the risk of clotting. Some manufacturers recommend heparinizing the cartridge before placing it into the extracorporeal circuit. This step in the preparation involves injecting 25 000 IU of unfractionated heparin into the cartridge, manually homogenizing it, and waiting up to 30 minutes before rinsing the heparinized solution from the cartridge [73]. In HD machines, after the cartridge is inserted into the circuit, up to 2 to 3 l of saline solution in bags are used for rinsing. In HDF machines where no saline bags are required for priming, the ultrapure fluid produced by the machine serves as priming fluid for the extracorporeal circuit, including the cartridge. The rinse volume is set at 2 to 3 l, lasting usually <10 minutes. Regarding the tubbing and dialysis filter, the priming procedures should remain unchanged in accordance with each center's standard practices.

Recommendations for research

Studies should be planned to evaluate the safety and efficacy of varying blood flow, anticoagulation, positioning of the cartridge (i.e. pre- or post-filter), duration, frequency, and combinations with different extracorporeal dialysis modalities.

Treatment evaluation and monitoring

Question: What are the parameters for monitoring HAHD therapy?

Key consensus point

We recommend usual monitoring techniques for HAHD as in standard HD. Potential safety concerns include the risks of adverse reactions, coagulation disorders, thrombocytopenia, leukopenia, and inadvertent adsorption of medications and molecular biomarkers.

Rationale

In HAHD the HA cartridge is placed in series before the HD filter [74]. Treatment monitoring should be the same as in standard HD [75, 76]. Circuit pressures during HAHD are informative and can guide interventions, such as blood flow adjustment or early termination of therapy when circuit clotting is imminent.

Safety should be monitored, considering the common risks of standard HD as well as those unique to HA [73]. Like in other EBPT, there is a risk of allergic reactions and air embolism. HA-specific concerns include mild, transient thrombocytopenia and leukopenia [77, 78]. In an open-label, prospective, randomized, multicenter clinical study, 438 patients from 20 Chinese provinces were allocated into four groups and followed for 12 months. All patients underwent standard dialysis treatment:

4-hour sessions, thrice weekly, blood flow of 250 ml/min, and dialysate flow of 500 ml/min. The groups received either low-flux HD, high-flux HD, low-flux HAHD, or high-flux HAHD. The HA cartridge was the HA130 and the patients allocated to the HA arms received one session of HAHD per week. Peculiarly, HAHD sessions consisted of 2 hours of HAHD, followed by 2 hours of only HD, after the removal of the cartridge from the extracorporeal circuit. Intradialytic hypotension and circuit clotting were the most frequent adverse events, but the incidence was the same in all four groups [12]. Considering the long-term safety profile of HAHD, an observational trial explored 75 patients receiving HAHD sessions once weekly for 6 months, with their records, where weekly HAHD sessions were shortened [32]. In the prospective phase, the HAHD sessions lasted 4 hours, and throughout the treatment, the cartridge was interposed (i.e. connected) into the HD circuit. This prescription is considered the conventional approach in Europe and Latin America. In the retrospective phase, during the first 2 hours, HAHD, the cartridge was interposed into the HD circuit; thereafter, blood was returned to the patient, the cartridge was disconnected from the circuit, and the patient received the remaining 2 hours only on HD. The latter is considered standard practice in China. In the prospective period, patients received a mean and standard deviation of 30.22 ± 9.9 sessions, and a total of 2176 sessions were carried out. In the retrospective period, the mean and standard deviation of sessions were 29.14 ± 9.87, totaling 2098 treatments. No differences in hematological parameters and albumin concentrations were observed during the two phases. Premature circuit clotting occurred in 1.62% of treatments during the 2-hour HAHD phase, compared with 1.79% during the 4-hour phase ($P = .665$). In both phases, adverse events such as chills, fever, dyspnea, and anaphylactoid reactions were not observed, implying an acceptable safety profile of HAHD.

Question: What are the criteria to determine the efficacy of HAHD?

Key consensus points

1. The evaluation of efficacy depends on the primary aim of HAHD therapy and the therapeutic response. Criteria include patient- and caregiver-reported outcomes, functional status, objective clinical outcomes (e.g. cardiovascular events, hospitalization, and death), and biomarker assessment.
2. When assessing patient-reported outcomes in trials, the minimal clinically important difference (MCID) should be predefined for each outcome and used to calculate the study sample size to determine the efficacy of HAHD.

Rationale

The MCID defines the smallest benefit of value to patients; consequently, it is a patient-centered concept. The adequate analysis of changes in numerical scales (e.g. pruritus scales) or semi-quantitative questionnaires [e.g. kidney disease quality of life 36 (KDQOL-36)] must consider not only statistical significance, but its meaningfulness to patients [79]. Since statistical significance is positively correlated with sample size, in large samples, statistical significance of a variable between the intervention and control groups may be detected, but may be clinically meaningless [80, 81]. Therefore, in trials exploring the efficacy of HAHD in conditions such as pruritus or post-dialysis recovery time (Table 1), the MCID should be predefined during the study design and used to determine the number of patients to enroll. We consider using MCID as a superior hierarchical endpoint in trials in comparison to surrogates such as reduction in the concentration of uremic toxins.

HAHD efficacy has been assessed primarily by evaluating changes in patients' symptoms attributed to uremia [82] and degree of uremic toxin removal [8–10, 12, 38, 68, 83–93] (Table 2 and Supplementary Table S4). Commonly assessed molecular biomarkers include removal ratios of middle molecules (e.g. β_2-microglobulin, parathormone) and PBUT (e.g. indoxyl sulfate, p-cresyl sulfate) [13, 83]. Some studies have also evaluated changes in inflammatory biomarkers, such as IL-6, TNF-α, and C-reactive protein, to assess the impact of HAHD on systemic inflammation and associated clinical outcomes [68, 94].

The previously mentioned Chinese randomized clinical trial that enrolled 438 patients with kidney failure examined both surrogate and clinical endpoints [12]. These patients were followed for 12 months and randomized into four groups: (i) HAHD with low-flux filter; (ii) HAHD with high-flux filter; (iii) low-flux HD; and (iv) high-flux HD. The HAHD sessions were carried out once weekly. Pre-dialysis concentrations of β_2-microglobulin decrease significantly in both HAHD groups, as well as in the high-flux HD group, which may indicate better HD adequacy, irrespective of hemoadsorption. Nonetheless, these improvements were more pronounced in the HAHD groups, suggesting greater HA efficacy. Regarding pruritus, the authors applied the Duo pruritus Score system and found a statistically significant percentage reduction in the HA groups [95].

Notably, we advocate using pruritus metrics previously used in trials with pharmacological interventions, as this enables comparisons of the impact of blood purification strategies, anchored in prior results from medication trials. In the landmark trial exploring the efficacy of difelikefalin for chronic kidney disease-associated pruritus [96], the primary outcome used the Worst Itching Intensity Numerical Rating Scale; the 5-D itch scale and the Skindex-10 scale were secondary outcomes. Ideally, future HAHD trials should also adopt these outcomes. Furthermore, incorporating performance and physiological tests to evaluate HAHD efficacy, such as the hand-grip test for sarcopenia [40] and nerve conduction studies in the workup for carpal tunnel syndrome, increases the study's robustness [97]. Hence, a standardized approach that integrates patient- and caregiver-reported outcomes, functional status evaluated with performance tests, objective clinical assessments, and biomarkers is needed (Table 1). This framework aims to improve the consistency and reliability of HAHD outcome assessments.

Recommendations for research

1. Development of national and international registries to gather longitudinal data on HAHD efficacy, effectiveness, and safety for short- and long-term outcomes.
2. Design of pragmatic, multicenter clinical trials focusing on the impact of HAHD not only for the treatment but also for the prevention of dialysis-related conditions and symptoms.

Question: What are the additional aspects to consider in HAHD compared to HD alone?

Key consensus points

1. Since non-selective removal of molecules, including medications, may potentially lead to subtherapeutic drug concentrations, where feasible, we encourage administering medications after the session.

Table 2: Clinical trials comparing HAHD versus HD or HDF.

First author, design, country, and year of publication, (reference number)	HD arm (control)	HAHD arm (intervention)	Primary outcome	Follow-up	Results
Li, RCT, China, 2017 (9)	• $n = 30$ • age: 55.4 ± 15.4 years • filter: low-flux • blood flow: 250–300 ml/min • dialysate flow: 500 ml/min	• n (HA with H130) = 30; (HA with HA330) = 30 • age HA130: 52.3 ± 12.1 years; HA330: 54.2 ± 13.4 years • filter: low-flux • blood flow 250–300 ml/min • dialysate flow: 500 ml/min • HAHD prescription: once every 2 weeks, for 2 hours, blood flow 200 ml/min • HA resin: polystyrene divinylbenzene	Visual analog scale for chronic kidney disease-associated pruritus	8 weeks	Statistically significant reductions in both HAHD with HA130 or HAHD with HA330 groups
Yamamoto, observational, Japan, 2018 (35)	• $n = 15$ • age: 65.5 (62.3–68.0) years • filter: high-flux • blood flow: 180–250 ml/min • dialysate flow: 500 ml/min	The same group of patients after 2 weeks of HAHD with Lixelle S-35 • HAHD prescription: thrice weekly, for 4 hours, blood flow 180–250 ml/min • HA resin: hexadecyl-immobilized cellulose	Pre- versus post-cartridge concentration of free fraction or total PBUT	2 weeks	• Statistically significant reductions in the free fraction of indoxyl sulfate, indoleacetic acid, phenyl sulfate, and p-cresyl sulfate. Not statistically significant reductions in the total concentration of all these compounds
Tiranathanagul, crossover, Thailand, 2022 (11)	• $n = 10$ • age: 60.9 ± 9.7 years • filter: high-flux • modality: HDF • blood flow: 400 ml/min • dialysate flow: 800 ml/min • post-filter replacement flow: 108 ml/min or 26.0 ± 1.8 l/session	• $n = 10$ • age: 60.9 ± 9.7 years • filter: medium cutoff • blood flow: 400 ml/min • dialysate flow: 800 ml/min • HAHD prescription: once weekly, for 2 hours, blood flow 200 ml/min • HA resin: polystyrene divinylbenzene	Removal of the protein-bound uremic toxin indoxyl sulfate by percentage reduction ratio	16 weeks	• Indoxyl sulfate reduction ratios of HAHD and HDF (52.0 ± 11.7 vs 56.3 ± 7.5%, $P = .14$) • Baseline indoxyl sulfate reduction after 8 weeks of HAHD (40.0 ± 20.7 vs 34.9 ± 12.4 mg/l, $P = .3$) • Baseline indoxyl sulfate reduction after 8 weeks of HDF (42.5 ± 21.8 vs 43.9 ± 19.9 mg/l, $P = .7$)

Table 2: Continued

First author, design, country, and year of publication, (reference number)	HD arm (control)	HAHD arm (intervention)	Primary outcome	Follow-up	Results
Zhao, RCT, China, 2022 (12)	• *n* (low-flux HD) = 39; (high-flux HD) = 92 • age low-flux HD: 54 ± 14 • age high-flux HD: 50 ± 13 • filter: low-flux or high-flux • blood flow: 250 ml/min • dialysate flow: 500 ml/min	• *n* (HAHD low-flux) = 86; (HAHD high-flux) = 102 • age HAHD low-flux: 49 ± 13 • age HAHD high-flux: 49 ± 12 • filter: low-flux or high-flux • cartridge: HA130 • blood flow 250 ml/min • dialysate flow: 500 ml/min • HAHD prescription: once weekly, for 2 hours, blood flow 200 ml/min • HA resin: polystyrene divinylbenzene	Reduction in pre-session concentration of β_2-microglobulin	56 weeks	• Higher reduction with HAHD low-flux vs low-flux HD ($P < .001$) • Higher reduction with HAHD high-flux vs high-flux HD ($P < .001$)

RCT, randomized controlled trial.

2. The inadvertent adsorption of molecular biomarkers may affect appropriate interpretation.

Rationale

An essential consequence of HA therapy is the non-selective removal of compounds, including medications such as factor Xa inhibitors, antimicrobials, and anticonvulsants, potentially resulting in subtherapeutic concentrations and treatment failure [98, 99]. Unintended removal of drugs is possible; clinicians should be vigilant about medications with high adsorption potential (see Table 3) and adjust dosing or monitoring accordingly. Most studies investigating the effects of HA on drug removal were conducted in acute settings, using adsorption cartridges that differ from those used for HAHD [100, 101], albeit often with a similar adsorptive resin (i.e. styrene-divinylbenzene) [63, 102–104]. There are limited direct data on the impact of HA on drug removal in maintenance dialysis patients. Thus, we encourage administering medications in the last 60 to 30 minutes of the session to prevent underdosing.

Some situations require empirical dose adjustment. For instance, the removal of anticonvulsant medications such as valproate could precipitate seizures. Hence, an envisioned approach to prevent underdosing is to administer a dose just before session initiation, aiming for a peak concentration near the end of the session. This peak is expected to be blunted by the adsorptive clearance, and an additional dose in the last hour of the session might minimize subtherapeutic concentrations. In addition, measuring drug concentration before the session, 2 hours after its start, and at the end of the session could provide relevant information. These results would prompt adjustments in drug dosing and timing of administration. Of course, these adjustments would not take place in the sampling session because results would not be readily available, but rather in the planning for the following HAHD treatments. This theoretical approach has not been explored so far.

Furthermore, key diagnostic molecular biomarkers, such as NT-proBNP (8.4 kDa), procalcitonin (13 kDa), bilirubin (0.6 kDa), and myoglobin (17 kDa), may be removed, which needs to be considered when interpreting results [105–107]. Solutes with molecular weight above 50 kDa are not removed by either polystyrene divinylbenzene (HA130) or hexadecyl-immobilized cellulose (Lixelle) cartridges. Therefore, removal of inflammatory biomarkers such as C-reactive protein (115 kDa) or ferritin (450 kDa) is negligible.

Hormones, including parathormone (9 kDa), prolactin (23 kDa), and triiodothyronine (0.8 kDa) might be removed. Notably, parathormone and prolactin have half-lives of 3 and 30 minutes, respectively [108, 109]. Therefore, pre-session concentrations might quickly return to baseline since their generation is expected to be sustained. By contrast, the half-life of triiodothyronine can exceed 24 hours [110], and its removal by HAHD might imply meaningful clinical effects.

Question: What are the criteria for adjusting HAHD prescription?

Key consensus point

The adjustment of the prescription is informed by initial indication, patient evaluation, technical aspects, safety concerns, and the therapeutic response.

Table 3: Medications with plasma protein binding ≥80% likely removed via adsorption with styrene-divinylbenzene resin and poorly removed by HD, expanded HD, or HDF.

Medication	Class	Unintended consequences of removal
Apixaban and rivaroxaban	Factor Xa inhibitor	Thrombotic events (stroke in atrial fibrillation, worsening or relapse of deep vein thrombosis or pulmonary embolism)
Ticagrelor	Antiplatelet ($P2Y_{12}$ inhibitor)	Myocardial infarction (e.g. intrastent thrombosis), ischemic stroke
Amlodipine	antihypertensive (calcium channel blocker)	Hypertensive crisis
Teicoplanin	Antimicrobial	Bacterial treatment failure
Carbamazepine and valproate	Anticonvulsant	Seizures
Quetiapine	Antipsychotic	Nausea, agitation, insomnia, tachycardia
Paroxetine and sertraline	Antidepressant (selective serotonin reuptake inhibitor)	Antidepressant withdrawal syndrome

Rationale

The panel acknowledges that standardized criteria for adjusting HAHD are lacking, and that prescription changes therefore remain empirical and individualized. Initial prescription depends on the scope of HAHD, either rescue or preventive treatment for complications. Adjustments are considered when symptoms persist or improve, when patient-reported outcome changes, or when biomarkers such as β_2-microglobulin, C-reactive protein, and IL-6 show rising trends or fail to improve. Safety concerns, including adverse reactions, cytopenia, or unintended drug removal requiring modifications in drug dosing, may also necessitate changes in therapy. Cartridge exchange within a session is not performed except in cases of premature clotting or technical failure.

Adjustments to the HAHD regimen involve the frequency of treatment. HAHD is usually performed once weekly, but escalation to two or three sessions per week may be warranted for unmanageable situations, followed by stepwise de-escalation back to once weekly as symptoms improve. In stable responders, the frequency may be reduced to every 2 weeks, with the caveat that this may attenuate therapeutic benefit in some patients. Most centers, aside from China, apply HAHD as a rescue therapy for refractory conditions. However, there is a rationale for using this therapy as a preventive rather than solely a curative strategy. Persistent technical problems, such as repeated pressure alarms, elevated transmembrane pressure, or recurrent clotting, should prompt reassessment of anticoagulation before altering the treatment frequency.

CONCLUSION AND FUTURE DIRECTIONS

As with previous techniques, the absence of robust, evidence-based data should not necessarily preclude the use of HAHD. The cartridges currently commercialized demonstrate excellent biocompatibility and safety. HAHD has been used in compassionate settings and experimental protocols; it may be considered on a case-by-case basis, where conventional therapies have failed, though its routine implementation awaits further evidence.

A multitude of therapies applied across different areas of medicine are supported by data from observational studies, registries, and expert consensus, underpinned by a solid rationale. After a couple of decades of technological stagnation, noticeable progress was made in EBPT for patients on maintenance dialysis. Examples include HDF, HDx, and HAHD. Specifically for the latter, there is still a lack of definitive evidence to endorse its routine implementation; consequently, HAHD application should be tailored to each patient's unique needs. Simultaneously, future research should focus on well-designed and adequately powered randomized controlled trials, selecting plausible outcomes. At present, establishing guidelines for HAHD is not feasible. Nonetheless, a uniformity in prescription can be suggested, and a research agenda can be proposed through consensus. The quality of life and life expectancy of patients are far from ideal, and there is room for improvement. HAHD may have a role in restoring the patient's health and well-being, toward full rehabilitation.

SUPPLEMENTARY DATA

Supplementary data is available at *Nephrology Dialysis Transplantation* online.

CONFLICT OF INTEREST STATEMENT

Relevant to this manuscript, the following COIs apply to advisory board participation, consultation, or honoraria: Claudio Ronco: Ashahi, BBraun, Jafron, Nipro. Francisco Maduell: Jafron Gonzalo Ramírez-Guerrero: Jafron Thiago Reis: BBraun, Jafron, Medcorp. The other authors declare no conflict of interest. .

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

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