Inflammatory Response to Sorbent Hemodialysis

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Inflammation is common and associated with morbidity and mortality in hemodialysis (HD) patients. Exposure to endotoxin contained in the dialysate may trigger inflammation. Dialysate volume is substantially reduced in sorbent HD compared with standard single-pass dialysis. In this prospective study (Clinicaltrials.gov, number: NCT00788905), we compared the inflammatory response to single-pass and sorbent HD. Patients receiving single-pass HD were studied during 1 week of sorbent HD (Allient system; Renal Solutions, Warrendale, PA) and 1 week of single-pass HD. Patients were dialyzed using high-flux polysulfone dialyzers. Midweek pre- and post-HD serum levels of high-sensitivity C-reactive protein, interleukin (IL)-1β, IL-6, IL-10, interferon gamma, tumor necrosis factor alpha (TNF-α), and eotaxin were determined and their intradialytic change corrected for hemoconcentration during single-pass HD and sorbent HD compared by paired t-test. We enrolled 18 patients, nine completed the study. Although TNF-α decreased during both single-pass and sorbent HD ($p < 0.001$), none of the other biomarkers changed significantly during HD. We observed no difference between single-pass and sorbent HD. For the markers investigated in this study, there was no difference in the acute intradialytic inflammatory response to single-pass or sorbent HD. *ASAIO Journal* 2015; 61:463–467.

Key Words: inflammation, sorbent hemodialysis, cytokines, uremic toxins

Purification of fluids by sorbent-based technology has been used for about 4 decades.[1–6] The Allient hemodialysis system (Renal Solutions, Inc., Warrendale, PA, a whole subsidiary of Fresenius Medical Care, North America) was marketed until 2009, uses potable tap water purified through the sorbent column by recirculation through the priming process. The Allient

system is equipped with an ultrafiltration control system that allows the use of high-flux dialyzers.[7] During dialysis, the sorbent column removes circulating uremic toxins, organic molecules, bacteria, and heavy metals. The cartridge binding properties are well known.[8–10] Repeated (about 72 times for a 3 hour treatment) dialysate passage through the sorbent column results in a dialysate fluid with a bacterial count below 2 CFU/ml and endotoxin levels less than 0.3 EU/ml,[8,11] which easily meets the Association for the Advancement of Medical Instrumentation water quality standard and the European Renal Association best practice guidelines standards for ultrapure dialysis fluid (0.1 CFU/ml and endotoxin 0.03 EU/ml).[12]

One of the fundamental differences between sorbent dialysis and conventional hemodialysis (HD) is that patients using the sorbent system are exposed to reduced dialysate volumes of approximately 6 L compared with 150 L per treatment with conventional single-pass HD.

Chronic inflammation is frequently observed in HD patients. It is associated with progression of cardiovascular disease and is a high mortality risk.[13–16] The causes of the inflammatory response are not clearly understood; however, several sources have been suggested, including contaminated dialysate, and endotoxin exposure within acceptable microbiological standards.[17] Markers of inflammation have been associated with poor outcome in the presence of coronary artery disease.[18–20] In this study, we investigated acute intradialytic cytokine responses to single-pass and sorbent HD.

Methods

Patients and Dialysis Treatments

This prospective interventional study (ClinicalTrials.gov NCT00788905) was approved by the Mount Sinai Beth Israel, New York, NY, Institutional Review Board. We enrolled chronic HD patients dialyzing on a thrice weekly schedule, using arterio-venous fistulas or grafts as vascular access. Exclusion criteria were hospitalization and infections requiring antibiotics during 8 weeks preceding enrollment, use of central-venous catheter, an average pre-HD BUN of <30 mg/dl, and mean eKt/V below 1.0 during the 3 months preceding the study, uncontrolled coagulopathies, smokers and dialysis regimen other than thrice weekly HD. The study duration was 2 weeks: 1 week (three treatments) of sorbent dialysis, followed by 1 week of three conventional single-pass HD employing ultrapure dialysate. In both weeks, midweek pre-HD blood samples were drawn from the arterial dialysis needle before the patient was connected. Post-HD blood samples were drawn from the arterial sampling port of the extracorporeal circuit, after the end of the treatment.

Sorbent dialysis was done with the Allient system (then Renal Solutions, Inc., Warrendale, PA).[8] The system consists of a dialysis machine with a pulsatile blood pump, a sorbent cartridge on the dialysate side, and alarm systems comparable to conventional single-pass HD. Because the dialysate

is regenerated in the sorbent cartridge and recirculated, a dialysate volume of 6 L is sufficient.[8,21] The sorbent cartridge consists of four components; in the direction of the dialysate flow, a layer of activated charcoal is followed by a jack bean urease layer, and two layers of zirconium-based ion exchangers. Activated charcoal removes heavy metals and organic compounds such as creatinine, uric acid, p-cresol sulfate, and beta-2 microglobulin (B2M).[22] Urease catalyzes the hydrolysis of urea into carbon dioxide and ammonia, which is then transferred to the zirconium-based cation exchanger (zirconium phosphate) and anion exchanger (zirconium carbonate), where ammonium ion, calcium, magnesium, and potassium are bound and exchange for hydrogen (H) and sodium (Na). There is a reinfusion of calcium, potassium, and magnesium acetate into the dialysate reservoir. The final regenerated dialysate contains these compounds and Na chloride, Na bicarbonate, and Na acetate.

Single-pass HD was performed using 2008 K HD machines (Fresenius Medical Care, Walnut Creek, CA). High-flux polysulfone dialyzers (Optiflux 180NR, *in vitro* KUF 55 ml/h/mm Hg; Fresenius Medical Care, Walnut Creek, CA) were used with both sorbent and single-pass HD. In both type of modalities, blood flow rates (Qb) were maintained at 400 ml/min and dialysate flow rates (Qd) were maintained at 400 ml/min. To ensure that treatments were equally effective, the sorbent dialysis prescription was validated by prior *in vitro* testing.

Laboratory Parameters

Pre- and post-HD blood samples were taken midweek in nonfasting patients. Ethylenediaminetetraacetic acid-plasma aliquots were stored at -70°C until batch analysis of cytokine levels. Urea, creatinine, B2M, albumin, hemoglobin, hematocrit, high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-1β, IL-6, IL-10, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and eotaxin were measured. Eotaxin is a potent eosinophil chemoattractant both *in vitro* and animal models.[18–20]

Cytokines were analyzed in duplicates using the xMAP technology with 6-plex Human Cytokine/Chemokine MILLIPLEX map Kit (Millipore, Billerica, MA) on a Luminex100 System. The minimal detectable concentrations provided by the manufacturer were as follows: eotaxin, 2.2 pg/ml; IL-1β, 0.7 pg/ml; IL-6, 0.7 pg/ml; IL-10, 0.5 pg/ml; IFN-γ, 0.3 pg/ml; and TNF-α, 0.1 pg/ml.

The levels of cytokines and hs-CRP were corrected for the effects of hemoconcentration based on the changes in albumin concentration[23] (Equations 1 and 2).

The hemoconcentration of albumin is given as

$$Alb_h = \frac{Alb_{post}}{Alb_{pre}}, \qquad (1)$$

where Alb_h is the albumin ratio and the indices post- and pre-refer to the concentration of albumin before (Alb_{pre}) and after dialysis (Alb_{post}).

The final correction of each biomarker was given as

$$B_{corr} = \frac{B_{post}}{Alb_h}, \qquad (2)$$

where B_{corr} is the biomarker level corrected for hemoconcentration.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, differences as mean and 95% confidence interval. Differences were compared between HD modalities by paired t-test. The primary outcome of the study was the difference in the intradialytic change of IL-6 between single-pass and sorbent HD. Sample size estimation indicated that eight patients would allow detection of a 10 ± 10 pg/ml difference with a type I error of 0.05 and a type II error of 0.2.[24,25]

Statistical analysis was performed with R (http://www.r-project.org).

Results

Eighteen patients were enrolled (**Figure 1**). Three patients were excluded before the first sorbent HD (one because of vascular access complications, one because of too low a pre-HD blood urea nitrogen, and one because of unavailability due to travel). Fifteen patients initiated sorbent HD. Four patients were unable to successfully complete all three sorbent treatments; one patient dropped out because of vascular access malfunction, which required surgical intervention. Three patients were withdrawn because of persistent blood pump alarms, to the best of our knowledge caused by a too low upper limit of the arterial pump pressure set by the manufacturer. We did not encounter any clinical problems related with the sorbent chemical composition. In two patients, cytokine measurements were not performed because of preanalytic logistic reasons. The remaining nine patients constituted the analytical cohort where all markers of inflammation were measured. Patient characteristics and laboratory parameters of the 15 patients who underwent at least one sorbent HD treatment and the final analytical cohort (N = 9) are summarized in **Table 1**. All subsequent analyses were performed in the analytical cohort.

Clinical and treatment parameters of sorbent and single-pass HD are shown in **Table 2**. Pre-HD mean body weight was 74 ± 8 kg in sorbent HD and 75 ± 8 kg in single-pass
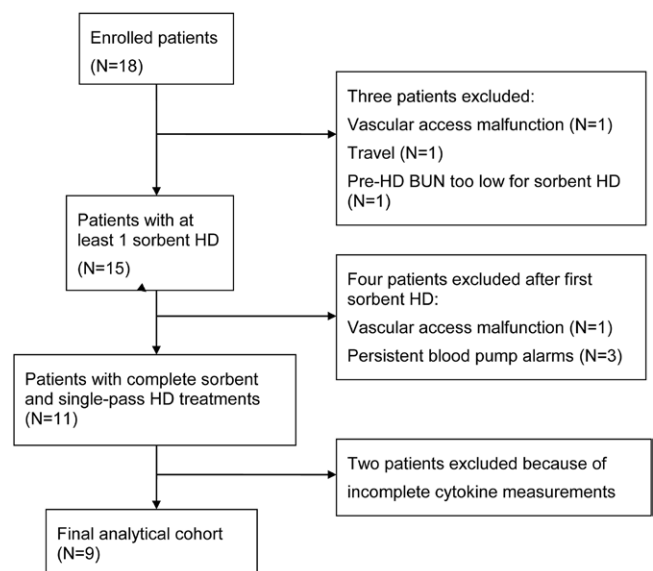

Figure 1. Study flow chart. BUN, blood urea nitrogen; HD, hemodialysis.

Table 1. Demographic and Clinical Characteristics and Baseline Laboratory Parameters

Characteristics	Cohort with At Least One Sorbent HD (N = 15)	Analytical Cohort (N = 9)
Age (years)	52 ± 11	51 ± 12
Males (N, %)	11 (73%)	7 (78%)
Hispanic/Latino ethnicity (N, %)	5 (33%)	3 (33%)
African-American (N, %)	8 (53%)	6 (67%)
Caucasian (N, %)	2 (13%)	0 (0%)
Dialysis vintage (years)	8 ± 7	10 ± 8
Pre-HD body weight (kg)	79 ± 14	74 ± 8
Pre-HD BMI (kg/m²)	27.7 ± 6.5	25.4 ± 3.9
Comorbidities (N, %)		
Diabetes mellitus	3 (20%)	2 (22%)
Hypertension	12 (80%)	8 (89%)
Vascular access (N, %)		
Arterio-venous fistula	12 (80%)	6 (67%)
Arterio-venous graft	3 (20%)	3 (33%)
Pre-HD SBP (mm Hg)	132 ± 20	136 ± 26
Pre-HD DBP (mm Hg)	77 ± 13	80 ± 13
Heart rate (1/min)	77 ± 13	83 ± 10
Albumin (g/dl)	4.3 ± 1.3	3.9 ± 0.3
Serum Na (mEq/L)	140 ± 2.3	141 ± 2.4
Serum K (mEq/L)	4.7 ± 0.7	4.7 ± 0.7
Serum total Ca (mg/dl)	9.0 ± 0.7	9.0 ± 0.8
BUN (mg/dl)	55 ± 19	55 ± 19
Creatinine (mg/dl)	10.3 ± 2.5	10.9 ± 2.5
Hemoglobin (g/dl)	12.3 ± 1.2	12.0 ± 0.9
Hematocrit (%)	36.6 ± 3.8	36.1 ± 3.4

Fifteen patients underwent at least one sorbent HD treatment, nine patients completed the study constituting the final analytical cohort in which all subsequent analyses were performed. All laboratory data refer to pre-HD levels.

Na, sodium; K, potassium; BUN, blood urea nitrogen; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HD, hemodialysis.

pre-HD. Post-HD body weight during both types of dialysis was 72 ± 8 kg. Blood flow rate, dialysate flow rate, and spKt/V did not differ between single-pass and sorbent HD (**Table 2**). There were no differences between the two modalities with regards to levels of albumin, B2M or creatinine (paired t-test).

Cytokine levels are shown in **Table 3**. Intradialytic changes in cytokines and hs-CRP did not differ between the two HD modalities. Levels of hs-CRP and all cytokines except TNF-α remained unchanged during HD when corrected for hemoconcentration. TNF-α, however, decreased significantly during both sorbent and single-pass dialysis ($p < 0.001$). Inflammatory biomarkers were substantially higher in one of the studied patients, possibly related to a failed renal transplant *in situ*. An analysis without this patient yielded materially identical results (data not shown).

Discussion

We found no evidence that the acute immune response to dialysis, as indicated by the intradialytic changes in hs-CRP, IL-6, IL-1β, TNF-α, IFN-γ, and eotaxin, differed between single-pass HD and sorbent HD. The two HD modalities differ with respect to water requirements which are substantially lower with the sorbent system, and the sorbent dialysate includes higher acetate and a variable sodium and bicarbonate concentrations, which is linked to urea removal. Endotoxin and other bacterial contaminants present in the dialysate can cross the dialyzer membrane enter the patient's bloodstream and induce an immune response. Although we did not test the purity of the dialysate in this study, based on previous reports the sorbent-regenerated dialysate is ultra-pure.[8,11] For this reason, the total amount of bacterial contaminants available for transfer into the patient is lower when exposing the patient to around 6 L of dialysate comparing with a 140 L of dialysate in single-pass HD.[26] In HD patients, the levels of CRP, IL-6, and TNF-α are relevant because of their relation with cardiovascular morbidity and mortality.[27–31] A number of studies have specifically investigated intradialytic changes in cytokine levels during HD. Park *et al*.[32] studied 118 patients during a single HD session, measuring the levels of CRP and IL-6 before and after dialysis, however, without correction for hemoconcentration. Study patients were dialyzed with first-use hemophane membranes and ultrapure dialysate, and divided into two groups, responders and non-responders, based on their CRP level response to HD. They

Table 2. Clinical and Treatment Parameters

Parameter (Mid-Week)	Single-Pass HD			Sorbent HD		
	Pre-HD	Post-HD	Post Minus Pre	Pre-HD	Post-HD	Post Minus Pre
SBP (mm Hg)	143 ± 25	134 ± 22	-10 (-21 to 2)	136 ± 26	135 ± 32	- 1 (-14 to 12)
DBP (mm Hg)	78 ± 10	72 ± 7	-6 (-12 to 1)	80 ± 14	77 ± 8	-3 (-9 to 4)
Heart rate (1/min)	86 ± 13	86 ± 11	0.6 (-8 to 10)	83 ± 10	81 ± 13	-2 (-9 to 5)
Weight (kg)	75 ± 8	72 ± 8	-3 (-3 to –2)	74 ± 8	72 ± 8	-2 (-3 to -2)
Albumin (g/dl)	3.9 ± 0.2	4.5 ± 0.4	0.6 (0.3 to 0.9)	4.0 ± 0.3	4.6 ± 0.7	0.6 (0.1 to 0.9)
BUN (mg/dl)	56 ± 12	18 ± 4	-37 (-43 to -31)	54 ± 11	19 ± 4	-35 (-40 to -29)
Creatinine (mg/dl)	12 ± 2	5 ± 0.9	-7 (-8 to -6)	11 ± 2	5 ± 0.9	-6 (-7 to -6)
Beta-2 M (mg/dl)	43 ± 20	26 ± 10	-17 (-24 to -11)	43 ± 8	26 ± 8	-17 (-25 to -9)
Dialysate flow (ml/min)	400		NA	400		NA
Blood flow (ml/min)	319 ± 15		NA	324 ± 18		NA
UFR (ml/h)	886 ± 237		NA	696 ± 355		NA
spKt/V	1.3 ± 0.03		NA	1.21 ± 0.08		NA
URR (%)	67 ± 2		NA	65 ± 3		NA

Pre- and post-HD values are shown as mean ± SD, differences are shown as mean (95% CI).

NA, not applicable; BUN, blood urea nitrogen; spKt/V, single-pool Kt/V; UFR, ultrafiltration rate; URR, urea reduction ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HD, hemodialysis; SD, standard deviation; CI, confidence interval.
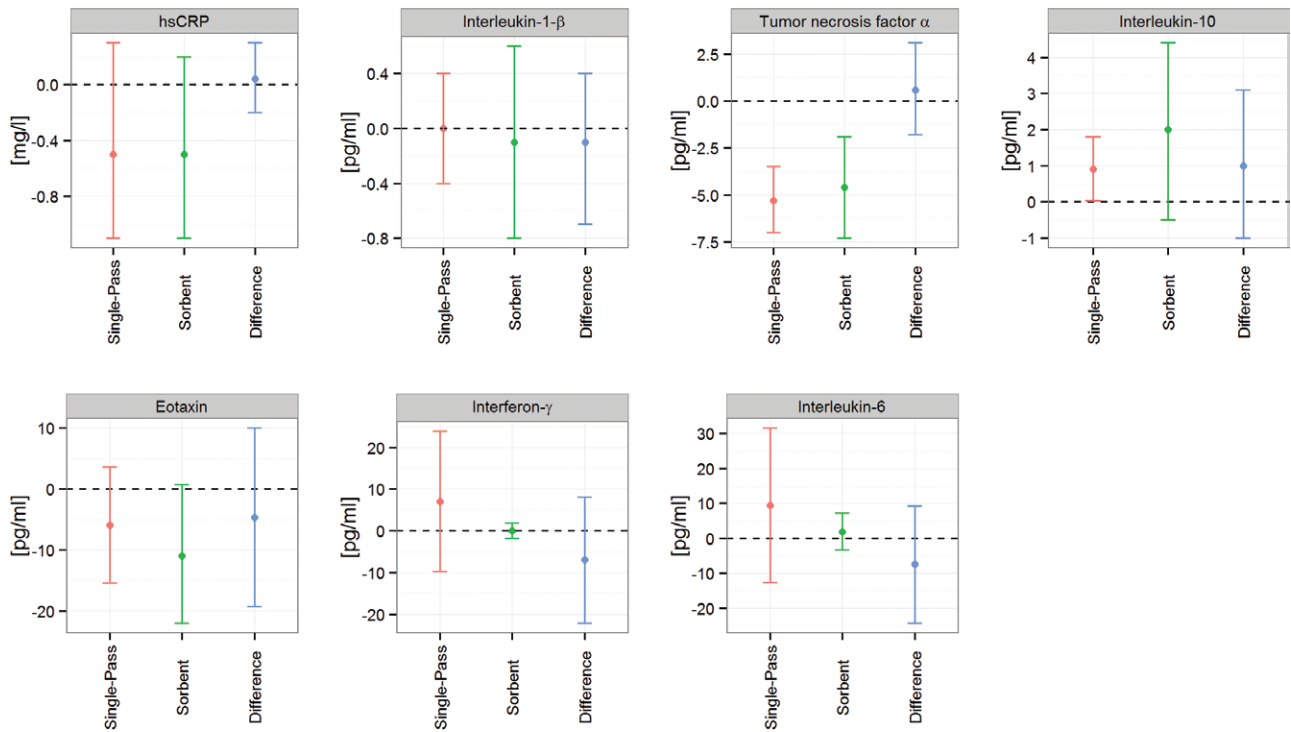
Figure 2. Intradialytic changes of biomarkers of inflammation during single-pass hemodialysis (*red*), sorbent hemodialysis (*green*), and the difference between these changes (*blue*). The data indicate means and 95% confidence intervals. hs-CRP: high-sensitivity C-reactive protein. [full color online]

observed a significant intradialytic rise of CRP in 42 patients (responders) from a median of 6.4 to 8.9 mg/L, and a rise of IL-6 from pre-HD to post-HD in all patients (median increase in responders of 10 pg/ml, in nonresponders 5.4 pg/m). These findings contrast with those reported by Meuwese *et al.*[33] who similarly measured CRP before and after a single HD session, in two independent cohorts of patients. The first cohort of patients (***n = 190) was from the MIMICK study and the second cohort (n = 90) was from the NECOSAD study. The authors found no significant intradialytic CRP change in the two cohort of patients. Unlike Park *et al.*, Meuwese *et al.* corrected the post-HD levels of CRP for hemoconcentration as we did, and although Meuwese protocol's did not specifically addressed intradialytic changes of CRP, it is unclear how quantitatively affected the uncorrected results reported by Park *et al.* were by hemoconcentration.

Bioactive IL-1β was below the detection limit of 0.7 pg/ml, in five patients pre-HD and post-HD in both treatment modalities, an observation corroborated in the literature.[34,35,37]

TNF-α is a potent proinflammatory cytokine with a short half-life regulating both pro- and anti-inflammatory mediators and probably implicated in the early stages of atherogenesis.[36] However, the biological effects of TNF-α during HD are not clear. Tarakcioglu *et al.*[35] reported unchanged TNF-α levels during HD in a cohort of 21 patients using low-flux membranes. This finding was corroborated by other studies.[25,37] On the other hand, Malaponte *et al.*[38] reported significant increases in IL-1β, IL-6, and TNF-α during HD.

Rysz *et al.*[39] measured IL-1β, IL-6, and TNF-α in 18 patients during single-pass HD and found that all cytokines had decreased by 20 min into HD but had increased by 60 min, which was maintained at 240 min and at the end of HD. All

Table 3. Pre- and Post-HD Biomarkers of Inflammation Levels, Intradialytic Biomarker Changes, and Differences in Intradialytic Biomarker Changes Between Single-Pass and Sorbent HD

Variable	Single-Pass HD (N = 9)			Sorbent HD (N = 9)			Difference in Intradialytic Changes (Sorbent Minus Single-Pass) Mean (95% CI)
	Pre-HD Mean ± SD	Post-HD Mean ± SD	Post Minus Pre Mean (95% CI)	Pre-HD Mean ± SD	Post-HD Mean ± SD	Post Minus Pre Mean (95% CI)	
hs-CRP (mg/dl)	9.9 ± 14	9.4 ± 13	-0.5 (-1.1 to 0.3)	9.6 ± 14	9.1 ± 13	-0.5 (-1.1 to 0.2)	0.04 (-0.2 to 0.3)
Eotaxin (pg/ml)	103.6 ± 37	97.7 ± 46	-5.9 (-15.4 to 3.6)	105.7 ± 53	95.1 ± 58	-11 (-22 to 0.7)	-4.7 (-19.3 to 10.0)
IL-10 (pg/ml)	7.4 ± 5	8.2 ± 5	0.9 (0.04 to 1.8)	5.3 ± 1.8	7.3 ± 3	2.0 (-0.5 to 4.4)	1.0 (-1.0 to 3.1)
IL-6 (pg/ml)	10.5 ± 16	19.9 ± 44	9.4 (-12.7 to 31.6)	12.6 ± 27	14.5 ± 34	1.9 (-3.4 to 7.3)	-7.5 (-24.3 to 9.3)
INF-γ (pg/ml)	26.3 ± 66	33.4 ± 88	7.0 (-9.8 to 23.9)	33.0 ± 84	33.0 ± 86	-0.0 (-1.8 to 1.8)	-7.0 (-22.2 to 8.1)
TNF-α (pg/ml)	17.2 ± 4	11.9 ± 3	-5.3 (-7.0 to -3.5)	16.6 ± 6	11.9 ± 4	-4.6 (-7.3 to -1.9)	0.6 (-1.8 to 3.1)
IL-1β (pg/ml)	1.5 ± 2	1.5 ± 2	-0.0 (-0.4 to 0.4)	1.7 ± 3	1.6 ± 2	-0.1 (-0.8 to 0.6)	-0.1 (-0.7 to 0.4)

Post-HD levels were corrected for hemoconcentration.

HD, hemodialysis; hs-CRP: high-sensitivity C-reactive protein; INF, interferon; TNF, tumor necrosis factor; SD, standard deviation.

patients in that study were dialyzed with cuprophane membranes; there was no information regarding a correction of post-HD levels for hemoconcentration. Of note we found a significant intradialytic decrease of TNF-α levels with both HD modalities and unchanged levels of IL-6 and IL-1β.

Our study has limitations, most importantly the small number of patients, high patient withdrawal and cytokines levels available in fewer patients, (only in nine out of 15 patients).

The strengths of our study are the paired, prospective design, and the diversity of assessed biomarkers.

In conclusion, this study did not show a significant difference in the acute immune response between single-pass and sorbent HD. Long-term studies are warranted to assess differences in hard outcomes between these two HD modalities.

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