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CLINICAL STUDY

Techniques of extracorporeal cytokine removal: a systematic review of human studies

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Abstract

Background and aims: Hypercytokinemia is believed to be harmful and reducing cytokine levels is considered beneficial. Extracorporeal blood purification (EBP) techniques have been studied for the purpose of cytokine reduction. We aimed to study the efficacy of various EBP techniques for cytokine removal as defined by technical measures. *Method*: We conducted a systematic search for human clinical trials which focused on technical measures of cytokine removal by EBP techniques. We identified 41 articles and analyzed cytokine removal according to clearance (CL), sieving coefficient (SC), ultrafiltrate (UF) concentration and percentage removed. *Results*: We identified the following techniques for cytokine removal: standard hemofiltration, high volume hemofiltration (HVHF), high cut-off (HCO) hemofiltration, plasma filtration techniques, and adsorption techniques, ultrafiltration (UF) techniques relating to cardiopulmonary bypass (CPB), extracorporeal liver support systems and hybrid techniques including combined plasma filtration adsorption. Standard filtration techniques and UF techniques during CPB were generally poor at removing cytokines (median CL for interleukin 6 [IL-6]: 1.09 mL/min, TNF-alpha 0.74 mL/min). High cut-off techniques consistently offered moderate cytokine removal (median CL for IL-6: 26.5 mL/min, interleukin 1 receptor antagonist [IL-1RA]: 40.2 mL/min). Plasma filtration and extracorporeal liver support appear promising but data are few. Only one paper studied combined plasma filtration and adsorption and found low rates of removal. The clinical significance of the cytokine removal achieved with more efficacious techniques is unknown. *Conclusion*: Human clinical trials indicate that high cut-off hemofiltration techniques, and perhaps plasma filtration and extracorporeal liver support techniques are likely more efficient in removing cytokines than standard techniques.

Keywords

Cytokines, dialysis, hemofiltration, interleukins, plasmafiltration

History

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Introduction

Multiorgan dysfunction syndrome (MODS) results in high mortality despite advances in intensive care.[1,2] Variations in etiology, whether induced by microbials or tissue injury, often result in a similar pattern of deterioration.[3] The stimulus for cytokine activation occurs through both pathogen-associated molecular patterns (PAMPS) or damage-associated molecular patterns (DAMPS) initiating common pathways which will ultimately lead to hypercytokinemia.[4]

Although cytokines play a role in limiting damage and helping the process of wound healing, the excessive presence of cytokines in the circulation is believed to be harmful. Thus, reducing its level to a more homeostatic range is believed to improve outcome.[5,6] The use of cytokine antibodies to counteract hypercytokinemia has been found ineffective, and even harmful in critically ill patients.[7,8] Another potential approach is the use of extracorporeal techniques for the purpose of cytokine removal.[9–11] Cytokines are water soluble middle molecules (molecular weight 0.5–60 kDa), which exist in free form in the circulation. These characteristics make them suitable targets for removal by extracorporeal blood purification (EBP) techniques, yet no systematic analysis has been performed to understand which technique and which filtration devices achieve the highest level of efficiency of cytokine removal in critically ill patients.

Methods

We conducted a systematic search using Pubmed database up to November 2012, for relevant articles on human studies on cytokine removal using known modalities of EBP. We then systematically assessed the efficacy of all EBP techniques previously reported in the literature using these data.

Our approach at identifying relevant articles for analysis is outlined in Figure 1.

The following search terms were used: ''cytokine'' AND ''continuous renal replacement therapy''; ''cytokine'' AND ''hemofiltration''; ''cytokine'' AND ''hemodiafiltration''; ''cytokine'' AND ''high volume hemofiltration''; ''cytokine'' AND ''adsorption''; ''cytokine'' AND ''plasmapheresis'';

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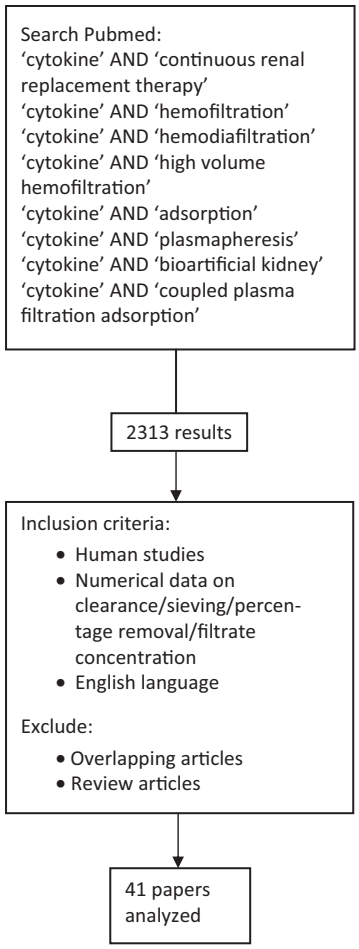

Figure 1. Flow diagram summarizing the manuscript identification and selection process.

''cytokine'' AND ''bioartificial kidney'' and ''cytokine'' AND ''coupled plasma filtration adsorption.'' All the terms used were MESH terms except for ''continuous,'' ''bioartificial kidney,'' ''high volume hemofiltration'' and ''coupled plasma filtration adsorption'' which are keyword searches.

Abstracts of articles retrieved were then screened for two inclusion criteria: human experimental studies and the reporting of a numerical value of at least one of these measures of cytokine removal: clearance, sieving, percentage removal or concentration in the filtrate. Two independent researchers performed the search and then manually screened retrieved articles for those which met both inclusion criteria. Abstracts which did not include enough details as well as publications with no abstracts provided were traced using library resources and each paper screened for inclusion criteria. We excluded review articles and articles published in language other than English.

We used four main ways of expressing cytokine removal: clearance (CL), sieving coefficient (SC), ultrafiltrate (UF) concentration and percentage removed. As this review is concerned with technical aspects of cytokine removal and not patient outcome, we did not focus on survival or other clinical outcomes.

In terms of definitions, we used the term ''standard technique'' to refer to the use of standard high flux hemofilters (nominal cut-off point of 30–40 kDa) at standard doses of filtrate flow (<25 mL/kg/h), while the term ''high cut off techniques'' was used to refer to the use of super high flux hemofilters with a nominal cut-off point of greater than 60 kDa.[11] The term ''high volume hemofiltration'' (HVHF) was used to refer to techniques of hemofiltration using standard hemofilters at doses higher than 50 mL/kg/h. HVHF using standard filters was labeled as Std/HVHF and classified under standard hemofiltration. The term ''plasma filtration'' was used to refer to techniques involving the passing of blood through a large pore plasma filter that resulted in filtration of plasma, where this filtered plasma was discarded and replaced by another source of colloid/plasma. The term liver extracorporeal support was used to refer to the use of devices in liver failure for the purpose of blood purification where blood was dialyzed across an albumin-impermeable membrane (MARS) or where plasma separation was followed by adsorption (Prometheus). The term ''Adsorption techniques'' included all techniques where either whole blood or plasma was exposed to a sorbent. The term ''Combined plasma filtration adsorption'' (CPFA) was used to refer to techniques where there was initial plasma separation followed by the filtrate being exposed to an adsorption device. The term CPFA was also used to refer to a technique in which the proposed mechanism was filtration or diafiltration using a filter that offered a degree of cytokine adsorption. A few techniques relating to cytokine removal during cardiopulmonary bypass were identified; conventional ultrafiltration (CUF) which referred to ultrafiltration performed during the rewarming phase, modified ultrafiltration (MUF) which referred to ultrafiltration after separation from bypass and zero balanced ultrafiltration (ZBUF) which referred to ultrafiltration commenced after 15 min of CPB. Other techniques were labelled as ''UF in bypass'' with a description of how the technique was performed.

Data which were reported only in the form of graphs or figures had their numerical values estimated from the details given in the graphs. When more than one measurement was available, an average value was calculated. Where both UF concentration and plasma concentration are provided for the same time period, SC was taken as the fraction of UF over plasma concentration. CL was then calculated as the product of SC and ultrafiltration rate. The information on CL, SC and percentage removed was analyzed to seek out techniques that offered the highest rate of cytokine removal based on human studies. Where sufficient data were available, these techniques were then analyzed for operating characteristics which appeared to offer the best rate of cytokine removal.

Due to the limited amount of data, we only calculated medians and interquartile ranges for cytokines of which three of more values had been identified. We did not make any statistical comparisons due to the limited number of observations and the variation in operational characteristics.

Results

The data extraction process is summarized in Figure 1.

We identified the following main approaches: standard hemofiltration, high volume hemofiltration (HVHF), high cut-off (HCO) hemofiltration, plasma filtration techniques, adsorption techniques, ultrafiltration (UF) techniques relating to cardiopulmonary bypass (CPB), extracorporeal liver

Table 1. Number of papers and total number of patients studied for each technique.

Technique	No of papers studying technique	Total no of patients exposed to technique
Standard continuous hemofiltration (Std/HF)	13[13,17,18,20,22,23,35,39–41,43,49,51]	201
Standard continuous hemodialysis (Std/HD)	3[18,27,45]	28
Standard continuous hemodiafiltration (Std/HDF)	5[21,24–26,36]	72
Standard high volume hemofiltration (Std/HVHF)	2[19,49]	26
High cut-off continuous hemofiltration (HCO/HF)	3[13,15,16]	48
High cut-off continuous (HCO/HD)	1[15]	12
Plasmafiltration	2[42,47]	22
Combined plasma filtration adsorption (CPFA)	1[32]	10
Ultrafiltration during cardiopulmonary bypass (UF in CPB)	3[28,37,44]	41
Extracorporeal liver support (MARS and Prometheus)	1[12]	8
Adsorption techniques using direct hemoperfusion (Adsorption/DHP)	2[46,52]	14
Conventional ultrafiltration (CUF)	3[29–31]	54
Modified ultrafiltration (MUF)	4[30,33,34,38]	80
Zero-balance ultrafiltration (ZBUF)	1[48]	15
Combined standard hemodiafiltration and adsorption (Std HDF + Adsorption)	1[14]	5
Adsorption via sustained high efficiency daily diafiltration using a mediator adsorbing membrane (Adsorption/SHEDD-fA)	1[50]	25
Combined standard hemodiafilration and plasmafiltration (Std HDF + PF)	1[47]	5

support systems and hybrid techniques, for example combined plasma filtration and adsorption (CPFA). The number of papers studying a particular technique as well as the total number of patients who were studied according to each technique is shown in Table 1. Many articles studied more than one technique and also measured the levels of multiple cytokines. A few papers reported on hybrid therapies such as combined plasma filtration adsorption,[32] adsorption combined with standard hemodiafiltration[14] and plasma filtration combined with standard hemodiafiltration.[47]

Standard techniques include both hemofiltration using standard filters at standard doses[13,17,18,20,22,23,35,39–41,43,49,51] as well as hemofiltration at high volume doses[19,49] according to current definitions; with the latter labeled as HVHF. Standard or high cut-off techniques included continuous hemofiltration,[13,15–18,20,22,23,35,39–41,43,49,51] continuous hemodialysis[15,18,27,45] and continuous hemodiafiltration.[21,24–26,36]

The main cytokines measured in the clinical studies were interleukin-1b (IL-1b), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 receptor antagonist (IL-1Ra) Other cytokines measured were interleukin-2 (IL-2), interleukin-2 receptor (IL-2R), interleukin-6 receptor (IL-6R) and soluble TNF-alpha receptors I and II (sTNFαRI and sTNFαRII). One paper[52] studied many other cytokines and details are included in the footnote of Table 1. Two of the high cut-off studies and a plasma filtration study also included data on albumin loss.[15,16,42]

Tables 2 and 3 show data on clearance (CL) and sieving coefficient (SC) extracted from human studies respectively. The percentage removed data shown in Table 4. The number of patients that contributed data to each measurement is shown for each technique and treatment characteristics. Table 5 shows a list of all devices studied including other relevant details when reported.

The standard techniques achieved low clearance, for all cytokines measured even when combined with high volume hemofiltration. Std/HF techniques also had overall poor SC for various cytokines, mostly in the range of less than 0.1 to 0.2 regardless of operating characteristics. Some exceptions include IL-8, IL-1β and IL-1Ra although the ranges were very wide with some studies finding very poor SC. The percentage removed data shown in Table 4 demonstrated that removal of cytokine was poor for standard techniques even when combined with high volume hemofiltration.

HCO techniques were more consistent in offering moderate to high degree of cytokine clearance, for all cytokines measured. For illustration, the median value of CL for IL-6 using standard HF (Std/HF) was 1.09 mL/min while the corresponding median value of CL for IL-6 for HCO technique (HCO/HF) was 26.5 mL/min (refer Table 3). CL using HCO techniques seemed to improve with increasing UF flows from 1 L/h to 2.5 L/h. HCO with continuous hemofiltration (HCO/HF) was comparable to continuous hemodialysis (HCO/HD) in terms of cytokine removal, however albumin loss was significantly different between these two modes (more than doubled with HF) when UF flows are increased from 1 L/h to 2.5 L/h. HCO techniques consistently showed high SC of close to unity for IL-6 and IL-1Ra. Albumin SC for HCO techniques was reported in one paper and found to be 0.026.[16] Among the cytokines studied, the SC for TNF-alpha using HCO techniques appear to be consistently very low.

There were no studies involving plasma filtration that provided clearance values. Plasma filtration showed a SC of around unity for IL-6 and G-CSF, and moderately high SC for leukemia inhibitory factor (LIF). This is however coupled with a SC of unity for albumin which is expected from the characteristics of the technique.[42] Another study found removal of 40% for IL-18 with plasma filtration, with or without added continuous hemodiafiltration.[47]

For data on adsorption, perhaps due to the nature of the technique, only percentage removed data was reported; with direct hemoperfusion resulting in around 25% removal for IL-1β, IL-6 and IL-1Ra and about 50% removal for IL-8 and TNF-alpha.[46]

Only one paper looked at cytokine clearance with ultrafiltration during cardiopulmonary bypass and zero CL was

Table 2. Clearance (CL) data according to techniques, devices and treatment characteristics.

Technique	Device code	*n*	Qb (mL/min)	Qf (mL/hr)	Qd (mL/hr)	RF	IL1-b	IL2	IL2R	IL6	IL6R	IL8	IL9	IL10	IL1RA	TNFa	sTNFaRI	sTNFaRII	Albumin
Std/HF[13]	4	10		2500		post				0.2					4.43				
Std/HF[17]	7	13	100–150	2000			2.17			1.8						1.47			
Std/HF[18]	8	11	150–200	2000		post				3.3				0		0			
Std/HF[20]	8	13	150	1000						4.92						0			
Std/HF[22]	10	33	150–200	1000		post	7.03	0	0.43	0.56	0	2.19		0	6.62	3.57		0	
Std/HF[39]	12	16		2000						0						0			
Std/HF[51]	41	38	180	2000–2400		pre				1.97		3.33							
Std/HD[18]	8	12	150–200		2000					1.9				0		0			
Std/HD[27]	35	1			2000											0			
Std/HDF[21]	9	9	~100		1000	pre									4	0.15	0.77	0.12	
Std/HDF[24]	12	10	150		1000					1.38		2.74							
Std/HDF[25]	9	20	92	525	1000	pre				2.71						0.069			
Std/HDF[26]	12	18	150		1000		25.1									21.3			
Std/HVHF[19]	34	15		7800						2.01						3.88			
HCO/HF[13]	3	20		2500		post				38.3					39				
HCO/HF[15]	2	6		1000		post				8.43					16.23	0			0.13
HCO/HF[15]	2	6		2500		post				24.6					41.43	0			0.87
HCO/HF[16]	6	16	150	1000		post				14.67						0			
HCO/HD[15]	2	6			1000	post				9					15.43	0			0.16
HCO/HD[15]	2	6			2500	post				21.8					28.33	0			0.35
Adsorption/DHP[52d]	42	9	80–100				24.3			22.4		0.26	14.6	14	6.93				
UF in bypass[28a]	14	20		1000			0			0		0							
MARS[12b]	1	8	200		18000[c]					3		17		16		29	2		
Prometheus[12b]	2	8	200		18000[c]					4		3		46		25	12		

All clearance values are in mL/min.
n = number of patients studied for each technique and treatment characteristics.
[a]Ultrafiltration conducted throughout the whole duration of cardiopulmonary bypass.
[b]Cell-free extracorporeal liver support systems.
[c]300 mL/min.
[d]Other clearances (mL/min) obtained from paper: IL-12 47.3, IL-17A 25.1, FGF basic 31.4, G-CSF 16.1, IFN-γ 15.1, PDGF-bb 26.3, VEGF 50.1, TGF-β 5.32.
Refer Table 4 for device code.
RF, replacement fluid either pre or postdilution; Qb, blood flow; Qf, ultrafiltration rate; Qd, dialysate flow; HCO, high cut-off; HF, hemofiltration; HD, hemodialysis; HDF, hemodiafiltration; Std, standard; HVHF, high volume hemofiltration; DHP, direct hemoperfusion; UF, ultrafiltration; MARS, molecular adsorbents recirculation system.

Table 2.1. Summary of CL values for Std/CVVH and HCO/CVVH.

Technique	Device code	*n*	Qb (mL/min)	Qf (mL/hr)	Qd (ml/hr)	RF	IL1-b	IL2	IL2R	IL6	IL6R	IL8	IL10	IL1ra	TNFa	sTNFaRI	sTNFaRII	Albumin
HCO/HF[13]	3	20		2500		post				38.3				39				
HCO/HF[15]	2	6		1000		post				8.43				16.23	0			0.13
HCO/HF[15]	2	6		2500		post				24.6				41.43	0			0.87
HCO/HF[16]	6	16	150	1000		post				14.67					0			
Median	26.49										40.22							
IQR	(13.1–28.0)										(27.6–40.2)							
Std/HF[13]	4	10		2500		post				0.2				4.43				
Std/HF[17]	7	13	100–150	2000			2.17			1.8					1.47			
Std/HF[18]	8	11	150–200	2000		post				3.3			0		0			
Std/HF[20]	8	13	150	1000						4.92					0			
Std/HF[22]	10	33	150–200	1000		post	7.03	0	0.43	0.56	0	2.19	0	6.62	3.57		0	
Std/HF[39]	12	16		2000						0					0			
Std/HF[51]	41	38	180	2000–2400		pre				1.97		3.33						
Median	1.09										0.735							
IQR	(0.38–2.64)										(0–1.47)							

achieved for all cytokines studied.[28] Ultrafiltration techniques during CPB has reported unusual and implausible figures of SC exceeding 1 for TNF-alpha.[28,30,48] This may indicate extracorporeal-circuit-induced formation of TNF-alpha or an error with measurements. However, the overall removal of all other cytokines as measured by SC was poor (less than 0.1) with this technique. Only one study on this technique reported percentage removed and found 28% removal of IL-6 and 59% removal of IL-8.[31]

Only clearance values were reported for the extracorporeal liver support systems. The molecular adsorption recycling system (MARS) and Prometheus were the only techniques overall which showed high CL for TNF-alpha ranging from 25 to 29 mL/min.[12] The Prometheus system also achieved high CL for IL-10 (46 mL/min) and moderately high CL for sTNFαRII (12 mL/min), while MARS achieved moderate CL with both IL-8 (17 mL/min) and IL-10 (16 mL/min).

Similarly not all measurements were reported for the hybrid techniques. Only one paper evaluated coupled plasma filtration adsorption (CPFA) and found excellent percentage removal for IL-10 and TNF-a (close to 100%).[32] There were a number of other hybrid techniques described.[14,47,50] Other hybrid techniques generally found low levels of cytokine removal. Standard hemodiafiltration using a filter capable of adsorption found low SC with the technique.[14] Standard HDF combined with plasma filtration found only 38.8% removal of IL-18 and zero removal of IL-6. SHEDD-fA (sustained high efficiency daily diafiltration using a mediator adsorbing membrane) which utilizes a combination of hemodiafiltration and adsorption found low levels of removal of IL-6 (21%) with single pass measurements, and this is only when levels of IL-6 in the blood were more than 50 pg/mL with zero removal with lower blood levels of IL-6.[50]

Discussion

Key findings

We performed a systematic analysis of human clinical studies involving different techniques of EBP to determine their efficacy in the removal of cytokines. We found the high cut-off techniques consistently achieved moderate to high cytokine clearance as demonstrated by CL and SC values. In contrast, standard techniques or ultrafiltration techniques appeared to be inefficient or unreliable in removing cytokines even when coupled with high volume hemofiltration. Plasma filtration achieved high removal of cytokines, as expected, but this clearance was predictably coupled with high albumin loss. CPFA and adsorption techniques showed promising results based on percentage removed data, although only one paper for each technique of could be identified. Hemodiafiltration using filters capable of adsorbing mediators did not offer a high degree of removal through single pass and is largely under-studied. Finally, extracorporeal liver support systems may also remove cytokines.

Relation to previous literature

To our knowledge, there are no other reviews of all human studies in the literature which have assessed objective, technical measurements of cytokine removal such as CL,

Table 3. Sieving coefficient (SC) data for different techniques and devices with specific treatment characteristics.

Technique	Device code	*n*	Qb (mL/min)	Qf (mL/h)	Qd (mL/h)	RF	IL1-b	IL2	IL2R	IL6	IL6R	IL8	IL10	IL1ra	TNFa	sTNFa R1	sTNFa RII	Alb	GCSF	LIF
Std/HF[13]	4	10		2500		post				0.007				0.1						
Std/HF[17]	7	13	100–150	2000			0.073			0.067					0.053					
Std/HF[22]	10	33	150–200	1000		post	0.42	0	0.05	0.04	0	0.12	0	0.41	0.22		0			
Std/HF[23]	11	16	150	2000		post	0.02			0	0.62				0					
Std/HF[40]	25	13	250–300	2000–4000		pre	0.33								0.16					
Std/HF[41]	26	7	200	2500		post						0.62								
Std/HF[43]	28	15	100–200	25.4–44.3 mL/min		post	0.22			0.18			0	0.28	0.16	0.006	0.003			
Std/HF[35]	20	5		2000			0.18			0		0.25			0					
Std/HF[39]	12	16		2000						0					0					
Std/HF[51]	41	38	180	2000–2400		pre				0.05		0.09								
Std/HD[45]	20	16		2000		post	0.09			0		0.68			0					
Std/HDF[36]	21	15	100–150	10.4–4.3 mL/min	10–30 mL/min	post						0.19			0.18					
Std/HDF[21]	9	9	~100		1000	pre								0.45	0.02	0.09	0.01			
Std/HDF[25]	9	20	92	525	1000	pre				0.27					0.017					
HCO/HF[13]	3	20		2500		post				0.9				0.92						
HCO/HF[15]	2	6		1000		post				0.92				1	0					
HCO/HF[15]	2	6		2500		post				>0.92				1	0					
HCO/HF[16]	6	16	150	1000		post				0.82					0			0.026		
HCO/HD[15]	2	6			1000	post				0.92				1	0					
HCO/HD[15]	2	6			2500	post				>0.92				1	0					
PF[42]	27	14		*a*						0.93								0.99	1.29	0.66
UF in bypass[28b]	14	20		1000			0			0		0			2.3					
UF in bypass[37c]	22	11								<0.001		0.004								
UF in bypass[44d]	39	16								1.246										
CUF[30]	16	11		62 mL/min						0.035			poor		1.01					
CUF[30]	17	10		42 mL/min						0.037			poor		2.72					
CUF[29]	15	10	100–120				0.67			0.04		0.22			0.9				0.04	
MUF[30]	16	11		82 mL/min						0.005			0.1		2.22					
MUF[30]	17	9		93 mL/min						0.003			poor		2.01					
MUF[34]	12	20								0.03		0.12								
MUF[38]	23	20	10–15 ml/kg/min												0.23					
MUF[33]	38	20	300–400 (during MUF)	*						0.25		0.06	0							
ZBUF[48]	32	15		#			0.39			0.019					194					
Std/HDF + adsorption[14]	5	10	90–130	2000	NA	pre	0.05			0.03		0.07			0					

n = number of patients studied for each technique and treatment characteristics.
a = 100 mL/kg for first 4–6 h and then 150 mL/kg over 28–30 h.
b, ultrafiltration conducted throughout the whole duration of cardiopulmonary bypass.
c, from aortic cross clamp until end of CPB.
d, from aortic cross clamp until within 5 minutes of clamp removal.
*1200 to 1800 mL total during MUF.
#Fluid removal of 1 L every 10 min until 3 L/m2 BSA removed.
Refer Table 4 for device code
RF, replacement fluid either pre or postdilution; Qb, blood flow; Qf, ultrafiltration rate; Qd, dialysate flow; HCO, high cut-off; HF, hemofiltration; HD, hemodialysis; HDF, hemodiafiltration; Std, standard; PF, plasmafiltration; UF, ultrafiltration; CUF, conventional ultrafiltration; MUF, modified ultrafiltration; ZBUF, zero balance ultrafiltration.

Table 4. Percentage removal data for different cytokines.

Technique	Device code	*n*	Qb (mL/min)	Qf (ml/H)	Qd (mL/min)	RF	IL1-b	IL2	IL6	IL8	IL10	IL1ra	IL18	TNFa
CUF[31]	18	23	100	100–300 ml/kg					28	59				
Std/HF[49]	25	11	200	1000		pre		0		0	3.15			0
Std/HVHF[49]	33	11	300	6000		1/3pre 2/3post		0		0	3.45			0
Adsorption/DHP[46]	29	5	100				24.7		24.65	54		28.5		52.25
PF[47]	31	8	80	***b***					0				42.9	
CPFA[32]	19 + 36 + 37	10	155	***a***							99.8			99.6
Std HDF + PF[47]	30(+31)	5	100 (CHDF) + 80 (PE)	***b***					0				38.8	
Adsorption/ SHEDD-fA[50]	40	25	150	1500		post			21					

n = number of patients studied for each technique and treatment characteristics.
a = 30–40 mL/min (Qp); (32–38 mL/min UF + dialysate outflow).
b = 3.6–4.0 L plasma exchanged per session.
Refer Table 4 for device code.
RF, replacement fluid either pre or postdilution; Qb, blood flow; Qf, ultrafiltration rate; Qd, dialysate flow cut-off; HF, hemofiltration; HD, hemodialysis; HDF, hemodiafiltration; HVHF, high volume hemofiltration; Std, standard; PF, plasmafiltration; CUF, conventional ultrafiltration; CPFA, combined plasmafiltration adsorption; DHP, direct hemoperfusion; PD, peritoneal dialysis; MUF, modified ultrafiltration; ZBUF, zero balance ultrafiltration; SHEDD-fA, sustained high efficiency daily diafiltration using a mediator adsorbing membrane.

SC and percentage removed for comparison. We had earlier published two systematic reviews on the same topic focusing on ex-vivo cytokine removal and cytokine removal in animal studies respectively.[53,54] The findings of the human studies reported here are broadly consistent with the findings of these two previous systematic reviews.

Significance of study findings

Despite an appreciable number of publications studying EBP techniques or devices in ex-vivo, animal experiments and human studies, details of the ideal operative characteristics to ensure the highest efficacy of cytokine removal have not been clearly outlined. Our reviews suggest that high cut-off techniques may be most consistent in offering moderate to high cytokine removal regardless of operating characteristics. Other techniques which also offer significant cytokine clearance includes extracorporeal liver support, plasma filtration and adsorption techniques but their complexity is greater and the number of studies less. Some of these complex techniques require expertise, special equipment, are expensive and cannot be employed around the clock. High cut-off techniques on the other hand use standard hemodialysis or hemofiltration equipment and standard flows of ultrafiltrate (all of which are widely available worldwide) with the only difference being the use of a filter with larger pores. The operating characteristics and the expertise required to initiate this treatment, although remains essential, are largely similar to that employed during standard continuous renal replacement therapies providing advantages for the use of high cut-off technique in terms of feasibility. More importantly, high cut-off techniques also appear to be one of the safest at a clinical level. High volume hemofiltration for example can result in hypophosphatemia, and loss of circuit in CPFA which occurs due to clotting, especially if recurrent, can result in significant blood loss. Albumin loss caused by the high cut-off techniques on the other hand, can be replaced by infusing albumin solutions.

Strengths and limitations

The strength of this review is that it is the first to comprehensively assess all techniques of EBP for their ability to remove cytokines in humans. This information is crucial for the further evolution of blood purification technology as a potential tool to modulate inflammation in sepsis. The limitations of this review include exclusion of articles in languages other than English and the inability to perform statistical comparisons due to the paucity of studies. Some techniques such as adsorption are under-represented as measures relating to clearance and sieving are not relevant to these techniques. The studies included have marked variability in other aspects of treatment and clinical circumstances as well as limited numbers of patients studied. Thus the external validity of our findings is limited. Finally, the clinical significance of cytokine removal like that of electrolyte changes[55,56] remains unknown.

Conclusions

In conclusion, our systematic review on EBP techniques found that HCO techniques, plasma filtration and

Table 5. Device codes.

Reference	Device name	Device code	Filter type	Filter size (m^2)	Molecular cut-off point	Features
12	MARS	1	albumin impermeable membrane + charcoal + anion exchange resin + dialyzer		60 kDa	*
12	Prometheus	2	albumin filter (polysulfone) + neutral resin adsorber + anion exchange adsorber + dialyzer (polysulfone)		250 kDa	#
13,15	P2SH	3	polyamide	1.1	60 kDa in vivo	
13,16	Polyflux 11 s	4	polyamide	1.1	30 kDa	
14	Multiflow 60 + polymyxin B	5	AN69 (polyacrylonitrile) with Polymyxin B immobilized fibre	0.6		
16	PSH1	6	Polyamide	0.6	60 kDa	
17	Prisma	7	AN69	0.9	35–40 kDa	
18,20	Multiflow 60	8	AN69	0.6	40 kDa	
21,25	AN69HF	9	AN69			
22	AV600	10	polysulfone	1.35	30 kDa	
23	FH66	11	polyamide			
24,26,34	AN69S	12	polyacrylonitrile			
28	650 SF 1.3	14	polyacrylonitrile		30 kDa	
29	Diafilter 20	15	polysulfone			
30	Jostra BC20	16	polyamide	0.2		
30	Jostra BC60	17	polysulfone	0.65		
31	DHF02	18	polyethersulfane	0.25		
32	MPS 07	19	polyethersulfone	0.7		
35	FH66D	20	polyamide			
36	AN69	21	polyacrylonitrile	1.6		
37	PF40	22	polysulfone		40 kDa	
38	Bently Hemoconcentrator	23	polysulfone	0.3		
40	AN69	25	AN69	1.2		
41	BL627	26	polysulfone			
42	PF1000	27	polypropylene	0.14		
43	Multiflow 100	28	AN69	0.9	35–40 kDa	
46	Lixelle	29	β2-microglobulin adsorption column (cellulose beads + hexadecyl groups)		30 kDa	
47	Panflow APF06S	30	polyacrylonitrile			
47	Plasmaflow OP08W	31	plasma filter			
48	HPH1400	32	polysulfone	1.3	65 kDa	
49	Filtral 16	33	AN69	1.6		
19	Flat plate filter (15 parallel membranes)	34	polyacrylonitrile	0.43	30–40 kDa	
27	Hemoflow F60	35	polysulfone			
32	BLS 627	36	polysulfone	1.2		
32	Amberchrom	37	reverse phase styrenic polymer resin	surface 600 to 800 m^2/g		
33	Diafilter D30-NR	38	polysulfone			
44	Hemocor HPH1000	39	polysulfone			
50	Filtrizer BG-PO	40	polymethylmethacrylate			
51	NI-PRO UF-205	41	cellulose triacetate	1.9		
52	Toraymyxin 20R	42	polymyxin B			

Note: *20% human serum albumin as dialysate which then passes thru columns of charcoal and anion exchange resins. Water soluble substances cleared by low flux dialyzer in a secondary circuit.

#Following separation plasma passes through two columns containing different adsorbents. Water soluble substances cleared by high-flux dialyzer directly inserted into the blood circuit.

extracorporeal liver support system are able to significantly remove cytokines. Adsorption and CPFA techniques show promise although the data on these techniques are limited. Because of the technical simplicity of HCO techniques, they may represent the most appropriate technique for randomized controlled trials of cytokine removal by EBP.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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