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Review Article

Attenuating the Systemic Inflammatory Response to Adult Cardiopulmonary Bypass: A Critical Review of the Evidence Base

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Abstract: A wide range of pharmacological, surgical, and mechanical pump approaches have been studied to attenuate the systemic inflammatory response to cardiopulmonary bypass, yet no systematically based review exists to cover the scope of anti-inflammatory interventions deployed. We therefore conducted an evidence-based review to capture "self-identified" anti-inflammatory interventions among adult cardiopulmonary bypass procedures. To be included, trials had to measure at least one inflammatory mediator and one clinical outcome, specified in the "Outcomes 2010" consensus statement. Ninety-eight papers satisfied inclusion criteria and formed the basis of the review. The review identified 33 different interventions and approaches to attenuate the systemic inflammatory response. However, only a minority of papers (35 of 98 [35.7%]) demonstrated any clinical improvement to one or more of the predefined outcome measures (most frequently myocardial protection or length of intensive care unit stay). No single intervention was supported by strong level A evidence (multiple randomized controlled trials [RCTs] or meta-analysis) for clinical benefit. Interventions at level A evidence included off-pump surgery, minimized circuits, biocompatible circuit coatings, leukocyte filtration, complement C5 inhibition, preoperative aspirin, and corticosteroid prophylaxis. Interventions at level B evidence (single RCT) for minimizing inflammation included nitric oxide donors, C1 esterase inhibition, neutrophil elastase inhibition, propofol, propionyl-L-carnitine, and intensive insulin therapy. A secondary analysis revealed that suppression of at least one inflammatory marker was necessary but not sufficient to confer clinical benefit. The most effective interventions were those that targeted multiple inflammatory pathways. These observations are consistent with a "multiple hit" hypothesis, whereby clinically effective suppression of the systemic inflammatory response requires hitting multiple inflammatory targets simultaneously. Further research is warranted to evaluate if combinations of interventions that target multiple inflammatory pathways are capable of synergistically reducing inflammation and improving outcomes after cardiopulmonary bypass. **Keywords:** Inflammation, systemic–CPB, inflammatory response, complications and management–CPB, equipment, inflammatory inhibitors, outcomes. *JECT. 2014;46:197–211*

A systemic inflammatory response is triggered in patients undergoing cardiothoracic surgery with cardiopulmonary bypass (CPB) as a result of the combination of surgical trauma, activation of blood components in the extracorporeal circuit, ischemia/reperfusion injury, and endotoxin release (1–4). There is evidence for activation of all the body's major host defensive pathways, including complement, coagulation, kinins, fibrinolysis, leukocytes, platelets, and inflammatory cytokines (4–13). This broad wave of systemic activation has been linked to adverse clinical outcomes ranging from mild adverse effects (fever or diffuse tissue edema), to moderate adverse effects

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(pathological hemodynamic instability or coagulopathy), to severe complications (acute organ injury requiring mechanical support), and even mortality (14–16).

A variety of approaches have been adopted in an attempt to limit the systemic inflammatory response to CPB. These include modifications to CPB equipment such as filters to remove inflammatory leukocytes or soluble mediators, minimized circuits to reduce surface area, coatings to improve the biocompatibility of extracorporeal surfaces, or the elimination of CPB altogether with off-pump coronary revascularization procedures. A range of pharmaceutical interventions has also been investigated such as steroidal and nonsteroidal anti-inflammatories, complement inhibitors, protease inhibitors, antifibrinolytics, anesthetic regimens, antioxidants, and others. Previous evaluations of the evidence base have been limited to meta-analyses or database reviews for a single intervention such as steroids or biocompatible surface coating, but there has been no systematic evaluation of the literature covering the complete range of anti-inflammatory strategies deployed.

The Society of Thoracic Surgeons (STS) Perfusion Guideline Writing Group is a multicountry, multi-institution initiative tasked with producing evidence-based clinical guidelines on a range of practices affecting outcomes in CPB such as temperature management, renal protection, blood conservation, and anti-inflammatory interventions. An immediate challenge faced by the Inflammation Writing Group was the fact that a previous analysis of the evidence base of pharmacological strategies to attenuate the inflammatory response (17) had reported that only a small minority of papers measured any traditional clinical end points (e.g., death, myocardial infarction, stroke). The problem is compounded by small sample sizes pervading the inflammation literature (median sample size: n = 40) (18), implying that there may not be adequate statistical power to analyze hard clinical end points. A review process covering multiple peer reviews from cardiothoracic, cardiac anesthesia, and perfusion journals as well as guideline writing committees of the STS, The Society of Cardiovascular Anesthesiologists, and The American Society of Extracorporeal Technology eventually concluded that the evidence base would be insufficient to recommend clinical practice guidelines for anti-inflammatory interventions based on traditional clinical end points.

The Inflammation Writing Group has therefore undertaken a critical review of the literature to illustrate the scope of interventions and approaches being deployed in the field to highlight promising areas of research and identify gaps in the literature. In this review, surrogate markers of organ dysfunction and measures of hospital resource use, defined in the "Outcomes 2010" consensus statement, were accepted as outcomes (19), and studies had to "self-identify" as being related to the systemic inflammatory response. Finally, studies had to measure at least one inflammatory marker using a relaxed definition of that term to include markers of complement activation, coagulation, kinins, oxidative stress, endothelial activation, white cell activation, white cell count, or a range of soluble inflammatory mediators. These inclusion criteria yielded a rich evidence base consisting of 98 papers covering a wide range of interventions and approaches to reduce the inflammatory response after adult CPB.

The purpose of this review was to identify gaps in the literature, inform further research, and to critically evaluate the strength of the evidence base for practices capable of attenuating the systematic inflammatory response and their relationship to clinical outcomes.

MATERIALS AND METHODS

Literature Search

The literature search was designed to capture clinical trials reporting on the inflammatory response to adult CPB together with clinical outcomes or surrogate markers for organ injury to five index organs: heart, lung, brain, kidney, and gut. The search terms (Appendix A) recovered >1600 articles in PubMed.

Abstract and Paper Reviews

A title review narrowed the search to 602 abstracts that were submitted for more detailed analysis using the Guideliner™ reviewing software (www.Guideliner.org/default.aspx, accessed September 15, 2014). All abstracts were reviewed in duplicate by independent reviewers, of which 236 were selected for full paper review. To be included, trials had to measure at least one clinical outcome and one inflammatory mediator. The inclusion criteria were as follows: randomized clinical trial (RCT) or meta-analysis, adult CPB, cardiac surgery, perioperative intervention, published 2002–2011, measured at least one inflammatory marker or used an established anti-inflammatory strategy (e.g., steroid or nonsteroidal anti-inflammatory drug), and measured at least one prespecified clinical outcome (defined by "Outcomes 2010" Consensus Statement) (19). The rules for deciding on inclusion/exclusion of papers were based on the Methodology Manual and Policies From the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guideline (http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf); hence, any one reviewer could select an abstract for inclusion in a full paper review, but at least two reviewers had to agree to exclude a paper. The same rules applied at the paper review stage with two reviewers needing to agree whether to exclude a paper. These rules were incorporated into Guideliner™ and the following reviewers performed abstract and paper reviews: R.C.L., J.R.B., D.S.L., and D.F. These same individuals

decided on whether an intervention achieved a clinical benefit. The assessment of clinical benefit was derived from review of each paper with regard to number of subjects studied, quality of the biomarker data, clinical outcomes achieved, and the strength of the statistical associations for reduced inflammation and clinical outcomes. The assignment of Level of Evidence used ACC/AHA guidelines (20). Any discordance between two reviewers was discussed and resolved if necessary by an independent third reviewer (J.H. and L.S.L.).

RESULTS

Synthesis of the Evidence Base

The literature search identified over 1600 papers, of which 602 abstracts were selected based on title review for entry into the Guideliner™ database. The Guideliner™ reviewing software was used in all subsequent steps for synthesizing the evidence base. Of 602 abstracts, 236 were selected for full paper review (Figure 1). After verifying inclusion/exclusion criteria 98 papers made up the final evidence base (listed in the Appendix B). These covered three broad categories of intervention: surgical and perioperative management (19 papers), perfusion-related (35 papers), and pharmacological (44 papers). Thirty-five of the 98 papers demonstrated a clinical benefit and were distributed approximately evenly across the three categories (Table 1). The total number of patients forming the evidence base was 17,676. The complete list of interventions and their associated level of evidence is summarized in Table 2. An analysis of the most relevant interventions according to the strength of evidence follows.

Table 1. Summary of evidence base.

Category of Intervention	Number of Papers	Percentage with Clinical Benefit (%)
Surgical/perioperative management	19	6/19 = 31.6%
Perfusion-related	35	11/35 = 31.4%
Pharmacological	44	18/44 = 40.9%
Total	98	35/98 = 35.7%

Evidence Level A (multiple randomized controlled trials)

Off-Pump Surgery: There were 10 RCTs on off-pump coronary revascularization surgery (Table 2). Four of the 10 papers demonstrated a clinical benefit. The studies were not uniform, however, in that they differed with respect to heparin dosing, and the control CPB groups differed with respect to circuit volume and use of cardioplegia. There was considerable heterogeneity in the reporting of inflammatory biomarkers with each of the 10 studies measuring a different set of markers that reflected inflammation. A best available summary of the evidence suggests that the use of OPCAB may reduce myocardial injury (troponin and CKMB), but this could not be linked in an obligate relationship with inflammatory suppression. Whereas the four studies with improved clinical outcome did show inflammatory suppression, three other studies with suppressed inflammation did not achieve a clinical benefit. The median sample size for the OPCAB studies was 50, reinforcing the thin evidence base even for this relatively well studied intervention.

Minimized Extracorporeal Circulation: There were eight RCTs on approaches to minimize the surface area of the extracorporeal circuit, and three of these eight achieved

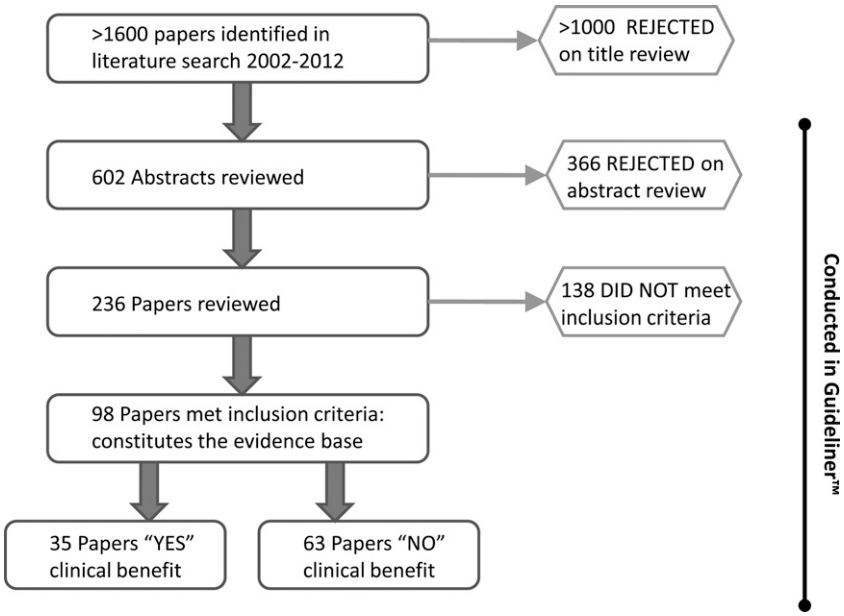

Figure 1. Synthesis of the evidence base. This illustration shows how the final 98 articles comprising the evidence base were derived from the original search strategy and what proportion achieved a clinical benefit. Guideliner™ is a bespoke reviewing software specifically purposed for this review process.

Table 2. Summary of interventions and level of evidence.

Category of Intervention	Intervention	Level of Evidence
Surgical/perioperative management	Off-pump coronary revascularization	Level A
	Preoperative aspirin	Level A
	Preoperative fluvastatin	Level B
	Left ventricular assist	Level B
	Intensive insulin therapy	Level B
	Continuous ventilation	Level B
	No cardioplegic arrest	Level B
Perfusion-related	Minimized extracorporeal circuit	Level A
	Biocompatible circuit coating	Level A
	Leukocyte-depleting filter	Level A
	Ultrafiltration	Level B
	Pericardial blood processing	Level B
	Discard mediastinal blood	Level B
Pharmacological	Steroids	Level A
	Complement inhibitors	Level A
	C1 esterase inhibitors	Level B
	Neutrophil elastase inhibitors	Level B
	Nitric oxide donors	Level B
	Propofol	Level B
	Sevoflurane	Level B
	Aminophylline	Level B
	Propionyl-L-carnitine	Level B
	Hydroxyethyl starch in prime	Level B
	Gelatin colloid	Level B
	Aprotinin	Level B
	Adenosine	Level B
	Ethyl pyruvate	Level B
	Erythropoietin	Level B
	Taurine	Level B
	Glutamine	Level B
	N-acetyl cysteine	Level B
	Dual-dose tranexamic acid	Level B
	Lidocaine	Level B

clinical benefit (Table 3). Again there was heterogeneity in the range of inflammatory biomarkers studied and again there was no clear linkage between suppression of inflammation and clinical outcome; hence, the three studies with improved clinical outcome had suppressed inflammation, yet three other studies with suppressed inflammation did not show clinical improvement. The median sample size for this intervention was 45.

Biocompatible Circuit Coating: There were 14 RCTs examining different biocompatible surface coatings of which six indicated a clinical benefit (Table 3). Heparin was the most widely studied biocompatible coating plus one paper was a direct comparison of two different types of heparin-coated circuits. Poly-2-methoxyethylacrylate and amphophilic silicone–caprolactone oligomer were also studied as surface coatings. The same pattern between inflammatory suppression and clinical outcome was observed with 12 papers reporting inflammatory suppression but only six reporting a clinical benefit. Median sample size was 38.

Leukocyte-Depleting Filters: There were eight RCTs studying leukocyte depletion, seven of which used the same arterial line leuko-depleting filter. Two of these eight studies were assigned a clinical benefit. Although leukocyte numbers were diminished by leukofiltration, inflammatory markers and leukocyte activation status were increased. Median sample size for this intervention was 36.

Corticosteroids: There were 13 RCTs and one Cochrane database review (21) on steroid interventions. The Cochrane meta-analysis was adequately powered (n = 3615) to study hard clinical end points and reported no clinical benefit on mortality or myocardial and pulmonary complications (21). Among the 13 RCTs, three were assigned a clinical benefit (Table 4). Individual steroid regimens showed a clinical benefit in only two of six studies of methylprednisolone, one of six studies of dexamethasone, and not at all in a hydrocortisone trial. The steroid RCTs were relatively small (median n = 30) and lacked uniformity with distinct steroid dosing regimens used in 12 of the 13 studies. The dissociation between inflammation and clinical outcome was quite marked with all but one study showing inflammatory suppression but only three studies able to demonstrate a clinical benefit.

Complement Inhibitors: Five RCTs investigated the use of complement inhibitors, three of which found a clinical benefit. Differences were noted between different complement targets. The C1 esterase inhibitor studies were notable for their study design, using patients undergoing emergency coronary artery bypass grafting (CABG) and for the compelling myocardial protection observed despite a modest sample size (median n = 66). The multicenter PRIMO CABG trial for C5 inhibition missed its primary composite end point of 30-day mortality/myocardial infarction in patients undergoing CABG but was able to demonstrate significant improvement in the highest risk patient group for the combined PRIMO CABG I and II studies (n = 7353 in total).

Aspirin: There was one RCT and one meta-analysis for aspirin given preoperatively (Table 3), and neither study was able to demonstrate a clinical benefit. The meta-analysis for preoperative aspirin use (n = 824) was statistically significantly associated with worsened reoperative rates. Aspirin and clopidogrel given until surgery in combination with aprotinin during surgery did not affect clinical outcome statistically, but there was concern about two deaths in the treatment arm resulting from intestinal embolism in this relatively small trial (n = 50).

Evidence Level B (single randomized controlled trial)

The full list of interventions at evidence level B is included in Tables 3–5, but the most noteworthy interventions are discussed.

Table 3. Summary of surgical and perioperative management interventions.

Intervention (no. of papers)	Type of Study, Surgery	Author (year) [reference][1*]	No.[2†]	Inflammatory Biomarker(s) Suppressed Yes–No: Biomarker[3‡]	Clinical Benefit Yes–No: Outcome Modified	Comment
Off-pump (n = 10)	RCT, CABG	Rastan (2005) [1]	19[4†]	Yes: CRP[5‡]	Yes: lactate, CK-MB	Off-pump verus on-pump beating heart as control group; CK-MB and lactate significantly improved by off-pump
	RCT, CABG	Nesher (2006) [2]	60	Yes: IL-6, IL-8	Yes: CK-MB, cTnI	Significant myocardial protection (CK-MB and TnI) off-pump
	RCT, CABG	Serrano (2009) [3]	40	Yes: IL-8, CRP, WBC, sP-selectin	Yes: CK-MB, cTnI	Significant myocardial protection off-pump (CK-MB and TnI) but no improvement in other clinical end points
	RCT, CABG	Tsai (2010) [4]	12	Yes: IL-6, TNFα, thrombomodulin	Yes: ICU stay	ICU stay and fever significantly improved off-pump
	RCT, CABG	Sahlman (2003) [5]	25	Yes; oxidative stress	No	No improvement in myocardial injury, inotrope use, or ICU stay in off-pump group; no benefit
	RCT, CABG	Wan (2004) [6]	18	Yes: IL-8, TNFα	No	Off-pump versus on-pump beating heart as control group; no improvement in ICU stay or other clinical end points
	RCT, CABG	Velissaris (2004) [7]	26	No	No	No improvement in ICU stay or other clinical end points off-pump
	RCT, CABG	Quaniers (2006) [8]	20	Yes: C5b-9	No	Two off-pump groups, receiving heparin at 1 or 3 mg/kg; no change ICU stay or hard end points in either treatment group
	RCT, CABG	Paulitsch (2009) [9]	50	No	No	No statistically significant changes in ICU stay or other hard clinical end points in off-pump group
	RCT, CABG	Formica (2009) [10]	30	No	No	Comparison of off-pump with miniaturized extracorporeal circuit; no change in myocardial protection or ICU stay
Preoperative aspirin (1)	Meta-analysis valve/CABG	Sun (2008) [11]	412	N/D[6§]	No	Preoperative aspirin is statistically significantly associated with worsened reoperation rates (p <.02), at 325-mg dose
Preoperative aspirin + clopidogrel, perioperative aprotinin (1)	RCT, CABG	Akowuah (2005) [12]	25	Yes: platelet aggregation	No	Aspirin and clopidogrel given preoperative, with perioperative aprotinin; concern regarding two deaths resulting from intestinal embolism
Preoperative fluvastatin (1)	RCT, CABG	Berkan (2009) [13]	23	Yes: soluble P-selectin	Yes: ICU stay, cTnI, inotropes	Fluvastatin (80 mg/day 3 weeks before surgery) significantly improved ICU stay, TnI marker, and need for inotropes
Left ventricular assist (3)	RCT, CABG	Meyns (2002) [14]	105	Yes: NE, C3	No	CABG supported with intracardiac axial pump did not improve any hard clinical endpoints or ICU stay
	RCT, CABG	Stassano (2009) [15]	38	Yes: IL-6, TNFα, CRP, NE	No	LVA (minus oxygenator or heat exchanger) compared to MECC. No myocardial protection or other clinical benefit
	RCT, CABG	Stassano (2010) [16]	21	Yes: IL-6, IL-8, TNFα	No	LVA assisted beating heart surgery vs. conventional CPB. No significant clinical changes
Intensive insulin therapy (1)	RCT, valve	Zheng (2010) [17]	50	Yes: IL-6, IL-10, TNFα	Yes: ICU stay, cTnI	Insulin therapy (Portland Protocol) in patients with no history of diabetes: improved ICU stay and TnI marker
Continuous ventilation (1)	RCT, CABG	Ng (2009) [18]	23	No	No	Continuous ventilation throughout CPB had no effect on bronchoalveolar lavage cell activation status or ICU stay
No cardioplegic arrest (1)	RCT, CABG	Narayan (2011) [19]	41	No	No	CPB without cardioplegic arrest did not alter myocardial injury marker (TnI), neural marker (S100), or ICU stay

[*]Number in square brackets [ ] refers to reference number in the Appendix B: "98 References Comprising the Evidence Base."
[†]N = number of subjects in treatment group.
[‡]Abbreviations used: RCT, randomized controlled trial; CABG, coronary artery bypass grafting; CRP, C-reactive protein; IL, interleukin; WBC, white blood cell count; TNF, tumor necrosis factor; ICU, intensive care unit; NE, neutrophil elastase; C, complement; C5b-9, terminal complement complex; CK-MB, creatine kinase MB fraction; cTn, cardiac-specific troponin; MECC, minimal extracorporeal circulation.
[§]N/D, not done.

Table 4. Summary of perfusion-related interventions.

Intervention (no. of papers)	Type of Study, Surgery	Author (year) [reference][1*]	No.[2†]	Inflammatory Biomarker(S) Suppressed Yes–No: Biomarker[3‡]	Clinical Benefit Yes–No: Outcome Modified	Comment
Heparin coating (9)	RCT, CABG	Heyer (2002) [20][4*]	26 [5†]	Yes: C3a[6‡]	Yes: cognitive function	Significantly improved cognitive dysfunction but no other clinical changes; mild benefit
	RCT, CABG	Svenmarker (2002) [21]	256	Yes: WBC	Yes: neurologic deviation	No difference in mortality, ventilator time or ICU stay, but significantly less neurological deviation; mild benefit
	RCT, CABG	De Vroege (2004) [22]	26	Yes: C3b	Yes: pulmonary shunt	Decreased pulmonary vascular resistance and pulmonary shunt; no other clinical changes
	RCT, mixed valve/CABG	Ueyama (2004) [23]	10	Yes: IL-6, CRP, bradykinin	Yes: A-a O_2 gradient	Two intervention groups: heparin and poly-2-methoxyethyl acrylate (PMEA) coating; both improved the A-a O_2 gradient
	RCT, mixed valve/CABG	Lindholm (2004) [24]	21	Yes: IL-8, NE, C5b-9	No	No statistically significant change in ICU or respirator time or inotrope support; no myocardial protection (Tn T)
	RCT, CABG	Baufreton (2005) [25]	12	Yes: C5b-9	No	No statistically significant improvements in prespecified neurological outcomes
	RCT, mixed valve/CABG	Vanden Eynden (2008) [26]	99	No	No	No myocardial protection (CK-MB); no change in ICU stay, intubation time, or other hard clinical end points
	RCT, CABG	Mirow (2011) [27]	21	Yes: TAT	No	No change in neurological lesions by diffusion-weighted imaging; no change in ICU stay or other clinical outcomes
	RCT, CABG	Baufreton (2011) [28]	12	Yes: C5b-9	No	No statistically significant differences between groups in hard clinical end points
Heparin head-to-head	RCT, mixed valve/CABG	Hoel (2004) [29]	15	N/A[7§]	N/A	No control group in this heparin head-to-head trial; no difference in inflammatory markers or clinical outcomes
Poly-2-methoxyethylacrylate (4)	RCT, mixed valve/CABG	Ueyama (2004) [23]	10	Yes: IL-6, CRP, bradykinin	Yes: A-a O_2 gradient	Two intervention groups: heparin and PMEA coating; both improved the A-a O_2 gradient significantly
	RCT, CABG	Skrabal (2006) [30]	19	Yes: NE	Yes: neurocognitive function	Significant improvement in neurocognitive function (Go/NoGo and Mini-Mental-test); Nn change in ICU stay; mild benefit
	RCT, mixed valve/CABG	Ninomiya (2003) [31]	11	Yes: C3a, NE	No	No improvement in ICU stay or intubation time; no clinical benefit
	RCT, CABG	Thiara (2011) [32]	15	No	No	No benefit of PMEA over phosphorylcholine as control; no difference in ICU stay
Amphophilic silicone-caprolactone oligomer (1)	RCT, CABG	Allen (2005) [33]	20	Yes: IL-10	No	No difference between groups in creatinine, urea, or N-acetyl glucosamine; no change in intubation time or ICU stay
Minimized extracorporeal circuit (8)	RCT, CABG	Kofidis (2008) [34]	50	Yes: IL-8	Yes: ventilator time, cTnI	Improved myocardial protection (Tn I) and ventilator time in minigroup
	RCT, CABG	Gunaydin (2009) [35]	20	Yes: IL-6, C3a, CD11b	Yes: ICU, $O_{2sat.}$ cerebral, CK-MB	Significantly improved ICU stay, myocardial protection (CK-MB), cerebral oxygen saturation, and intubation time
	RCT, CABG	Rimpilainen (2011) [36]	18	Yes: IL-6, IL-8, TNFα, NE, C3a	Yes: ICU stay, cerebral emboli	Significantly decreased ICU time and microemboli by retinal fluorography in minigroup
	RCT, valve	Tanaka (2003) [37]	9	No	No	Closed cardiopulmonary bypass circuit does not improve any prespecified clinical endpoints in this small study

Continued

Table 4. *Continued.*

Intervention (no. of papers)	Type of Study, Surgery	Author (year) [reference][8*]	No.[9†]	Inflammatory Biomarker(S) Suppressed Yes–No: Biomarker[10‡]	Clinical Benefit Yes–No: Outcome Modified	Comment
	RCT, CABG	Abdel-Rahman (2005) [38]	101	Yes: NE, C5b-9	No	No change in ICU duration or other clinical end points in mini-group
	RCT, CABG	Rex (2006) [39]	15	No	No	No improvement in myocardial injury marker (Tn T) in minigroup
	RCT, CABG	Huybregts (2007) [40]	25	Yes: IL-6, thromboxane B2	No	No statistically significant improvements in ICU stay or prespecified clinical end points
	RCT, CABG	Ohata (2008) [41]	34	Yes: IL-8, NE	No	No change in any reported clinical outcomes
Leukocyte-depleting filter (8)	RCT, CABG	Alexiou (2004) [42]	25	Yes: WBC, oxidative burst	Yes: A-a O_2 gradient	Arterial line leuko-depleting filter; improved A-a O_2 gradient; no other clinical changes; mild benefit
	RCT, CABG	Gunaydin (2009) [43]	10	Yes: IL-6, C3a, CD11b	Yes: CK-MB	Dual filter approach (continuous and after x-clamp) provided significant myocardial protection (CK-MB)
	RCT, valve	Zhang (2010) [44]	26	No	No	Arterial line filter improved myocardial protection and respiratory index but increased inflammatory cytokines
	RCT, valve	Hayashi (2003) [45]	10	Yes: NE, oxidative stress	No	Cardioplegia leukocyte-depleting filter placed after oxygenator reservoir did not change clinical outcomes
	RCT, mixed valve/CABG	Chen (2004) [46]	16	Yes: IL-8, sP-sel., sICAM, ox. stress	No	Arterial line filter did not improve prespecified clinical endpoints
	RCT, valve/CABG	Koskenkari (2006) [47]	10	No	No	Arterial line filter did not improve ICU stay or clinical end points; neutrophil activation noted in filter group
	RCT, valve/CABG	Soo (2010) [48]	20	No	No	Arterial line filter did not improve ICU stay or clinical end points; leukocyte activation noted in filter group
	RCT, CABG	Rubino (2011) [49]	41	No	No	Continuous arterial line plus cardioplegia filters did not improve myocardial markers or ICU stay
Ultrafiltration (3)	RCT, CABG	Tallman (2002) [50]	15	No	No	Zero balance ultrafiltration; no change ventilator or ICU time; paradoxical rise in plasma inflammatory markers
	RCT, mixed valve/CABG	Oliver (2004) [51]	62	No	No	Ultrafiltration; no clinical benefit in pulmonary function or other prespecified outcomes
	RCT, CABG	Torina (2010) [52]	20	No	No	Modified ultrafiltration demonstrated no change in A-a O_2 gradient; no benefit
Pericardial blood processing (1)	RCT, CABG	Marcheix (2008) [53]	25	No	No	Blood processing with cell saving device did not significantly improve ICU length of stay or other hard clinical end points
Discard mediastinal blood (1)	RCT, CABG	Westerberg (2004) [54]	17	Yes: IL-8, TNFα	No	Discarding mediastinal and cardiotomy suction blood had no effect on adverse events or myocardial marker (TnT)

[*]Number in square bracket refers to reference number in the Appendix B.
[†]N, number of subjects in treatment group.
[‡]Abbreviations used: RCT, randomized controlled trial; CABG, coronary artery bypass grafting; WBC, white blood cell count; IL, interleukin; CRP, C-reactive protein; TNF, tumor necrosis factor; NE, neutrophil elastase; TAT, thrombin antithrombin; sP-sel., soluble P-selectin; sICAM, soluble ICAM-1; A-a O_2, arterial–alveolar oxygen gradient; CK-MB, creatine kinase MB fraction; cTn, cardiac-specific troponin.
[§]N/A, not appropriate.

Table 5. Summary of pharmacological interventions.

Intervention (no. of papers)	Type of Study, Surgery	Author (year) [reference][1*]	No.[2†]	Inflammatory Biomarker(S) Suppressed Yes–No: Biomarker[3‡]	Clinical Benefit Yes–No: Outcome Modified	Comment
Methylprednisolone (6)	RCT, CABG	Giomarelli (2003) [55][4*]	10[5†]	Yes: IL-6, IL-8, IL-10, TNFα[6‡]	Yes: CK-MB, A-a O_2 gradient	1 g preoperatively, 5 × 125 mg postoperatively; improved myocardial protection creatine kinase MB fraction (CK-MB) and A-a O_2 gradient
	RCT, CABG	Demir (2009) [56]	15	Yes: IL-6, IL-10	Yes: ICU stay, NSE	1 g before CPB; improved intensive care unit (ICU) length of stay and levels of neuron specific enolase (NSE)
	RCT, CABG	Fillinger (2002) [57]	15	Yes: IL-6, IL-10	No	15 mg/kg preoperatively, 4 × .3 mg/kg postoperatively; less nausea but no other changes in clinical outcomes
	RCT, CABG	McBride (2004) [58]	18	Yes: IL-8, IL-10, TNF	No	30 mg/kg before induction; no changes in clinical outcomes
	RCT, CABG	Bourbon (2004) [59]	12	Yes: IL-6, TNF	No	10 mg/kg preoperatively; no clinical changes, no adverse events
	RCT, CABG	Liakopoulos (2007) [60]	40	Yes: IL-6, IL-18, IL-10, TNF, CRP	No	15 mg/kg bolus preoperatively; improved troponin (Tn) T but worsened pulmonary shunt, hyperglycemia, and lactic acidosis
Dexamethasone (6)	RCT, CABG	Von Spiegel (2004) [61]	10	N/D[7§]	Yes: lung water	1 mg/kg after induction; improvement in lung water; mild benefit
	RCT, CABG	Halvorsen (2003) [62]	147	N/D	No	4 mg perioperatively + 4 mg postoperatively; no change in hard clinical end points, inotrope use, or reoperation rates
	RCT, CABG	Loef (2004) [63]	10	N/D	No	1 mg/kg at induction + .5 mg/kg postoperatively; significant glycosuria, controlled through insulin; no clinical benefit
	RCT, mixed valve/CABG	Yared (2007) [64]	37	No	No	.6-mg/kg bolus; no clinical benefit and could not demonstrate inflammatory suppression to a range of markers
	RCT, CABG	Sobiesky (2008) [65]	13	Yes: IL-6	No	100-mg bolus after induction; no change A-a O_2 gradient or ICU stay; no clinical benefit
	RCT, CABG	Amr (2009) [66]	50	Yes: IL-6, IL-8	No	1 mg/kg at induction + .5 mg/kg postoperatively; significant hyperglycemia; no change in hard end points; no benefit
Hydrocortisone (1)	RCT, mixed valve/CABG	Halonen (2007) [67]	120	Yes: CRP	No	100 mg days 1–4 of operation; no change to any prespecified clinical end points
Cochrane review (1)	meta-analysis valve/CABG	Dieleman (2011) [68]	1807	N/D	No	No beneficial effect of corticosteroid use on mortality, cardiac, and pulmonary complications
C1 esterase inhibitor (2)	RCT, emergency CABG	Thielmann (2006) [69]	28	Yes: C3, C4	Yes: cTnI	40-IU/kg bolus + 20 IU/kg infusion showed myocardial protection (Trop. I) with earlier treatment from acute STEMI
	RCT, emergency CABG	Fattouch (2007) [70]	38	Yes: C3a, C4	Yes: ICU stay, cTnI	1000 IU C1 INH provided convincing improvement in ICU length of stay and cardiac function (cTnI and wall motion)
Complement C5 inhibitor (2)	RCT, mixed valve/CABG	Verrier (2004) [71]	1378	Yes: serum complement activity	No	Multicenter trial; missed primary end point 30-day death/MI in CABG, but significant risk reduction in intent to treat analysis
	RCT, mixed valve/CABG	Smith (2011) [72]	2156	Yes: serum complement activity	Yes: mortality	Analysis of combined PRIMO-CABG I and II trials; highest risk patients showed significant benefit at 30-day mortality
Complement receptor 1 inhibitor (1)	RCT, mixed valve/CABG	Lazar (2004) [73]	72	Yes: C3a, C5b-9	No	Striking gender bias; soluble CR1 significantly inhibited death/MI in males but not females; overall no benefit
Neutrophil elastase inhibitor (1)	RCT, valve	Fujii (2010) [74]	6	Yes: IL-6, IL-8, NE	Yes: PaO_2/FiO_2 ratio	Infusion of neutrophil elastase inhibitor significantly improved PaO_2/FiO_2 ratio
Urinary protease inhibitor (2)	RCT, CABG	Bingyang (2007) [75]	15	Yes: IL-6, IL-8, NE, TNFα	Yes: ventilator time, A-a O_2 gradient	Documented antiprotease activity is against neutrophil elastase; improved ventilator time and A-a O_2 gradient
	RCT, valve	Song (2011) [76]	24	No	Yes: ICU stay	Infusion or urintary proteas inhibitor significantly improved ICU stay; no change in inflammatory mediators
Sodium nitroprusside (1)	RCT, CABG	Gol (2002) [77]	10	Yes: IL-6	Yes: ICU stay, inotropes	Na nitroprusside (NO donor) intravenously after x-clamp release; convincing improvement ICU stay and need for inotropes

Continued

Table 5. *Continued.*

Intervention (no. of papers)	Type of Study, Surgery	Author (year) [reference][8*]	No.[9†]	Inflammatory Biomarker(S) Suppressed Yes–No: Biomarker[10‡]	Clinical Benefit Yes–No: Outcome Modified	Comment
Aminophylline (2)	RCT, valve	Luo (2004) [78]	15	Yes: IL-8, IL-10, TNFα	Yes: ICU stay, ventilator time	Perioperative aminophylline infusion significantly improved ventilator time and ICU length of stay
	RCT, valve	Luo (2007) [79]	15	Yes: neutrophil myeloperoxidase	Yes: cTnI	Significant myocardial protection (TnI); fewer neutrophils in coronary sinus with less myeloperoxidase on biopsies
Glutamine (1)	RCT, mixed valve/CABG	Engel (2009) [80]	31	Yes: IL-2, IFN-γ, NE	No	Infusion of glutamine after induction to postoperative day 3 did not affect ventilation time, ICU stay, or organ dysfunction
Taurine (1)	RCT, CABG	Doddakula (2010) [81]	15	Yes: IL-6	No	Infusion of a 2% solution of the antioxidant agent taurine did not affect hard clinical end points or ICU stay
Erythropoietin (1)	RCT, mixed valve/CABG	Poulsen (2009) [82]	22	No	No	2 × 500 IU/kg doses at days –1 and +1; no change in prespecified clinical outcomes
Aprotinin (1)	RCT, CABG	Kipfer (2003) [83]	15	No	No	Bleeding and transfusion benefits; no change in permitted clinical outcomes
Dual-dose tranexamic acid (1)	RCT, CABG	Jimenez (2011) [84]	80	No	No	Double-dose TXA (40 + 40 mg/kg) versus single-dose control; unwanted trend towards increased mortality and seizures
N-acetyl cysteine (1)	RCT, CABG	El-Hamamsy (2007) [85]	50	No	No	Intravenous infusion; concerning trend toward increased death and MI; also trend toward myocardial injury (CK-MB and TnT)
Lidocaine (1)	RCT, mixed valve/CABG	Mathew (2009) [86]	114	No	No	Interaction of lidocaine with diabetes caused significant postoperative cognitive decline
Ethylpyruvate (1)	RCT, mixed valve/CABG	Bennett-Guerrero (2009) [87]	49	No	No	Infusion of ethyl pyruvate did not affect death, MI, ARF, or a raft of clinical markers or hospital resource end points
Propofol (1)	RCT, valve	An (2008) [88]	15	Yes: IL-8, oxidative stress	Yes: ICU stay, ventilation time	Propofol targeted infusion during cross-clamp improved ventilation time, lung compliance and ICU stay
Isoflurane + propofol (1)	RCT, CABG	Huang (2011) [89]	30	Yes:IL-6, TNFα, oxidative stress	Yes: CK-MB, cTnI	Synergistic protective effect of isoflurane with propofol on ICU stay and myocardial protection (CK-MB and TnI)
Sevoflurane (2)	RCT, valve	Kawamura (2006) [90]	13	Yes: IL-6, IL-8	Yes: CK-MB, TnT	Fentanyl + sevoflurane anesthesia versus fentanyl + propofol control; convincing myocardial protection (CK-MB and TnT)
	RCT, valve	Cho (2009) [91]	15	Yes: IL-6, IL-10	No	Sevoflurane anesthesia versus fentanyl + midazolam control; no change in ICU stay or other clinical end points
NO gas (1)	RCT, valve	Gianetti (2004) [92]	14	Yes: soluble P-selectin	Yes: CK-MB, cTnI, BNP	Continuous NO inhalation perioperatively and in ICU; protection of myocardial injury markers (CK-MB, TnI, and BNP)
L-Arginine in cardioplegia (1)	RCT, CABG	Colagrande (2006) [93]	33	Yes: IL-6, TNFα	Yes: ICU stay, CK-MB, cTnI	L-arginine (nitric oxide substrate) added to cardioplegia; convincing improvement in ICU stay, CK-MB, and TnI
Propionyl L-Carnitine (1)	RCT, CABG	Lango (2005) [94]	21	Yes: endothelin, oxidative stress	Yes: lactate	Diabetic cohort; propionyl L-carnitine in cardioplegia significantly improved cardiac index, SVR, PVR, and lactate
Adenosine (1)	RCT, valve	Koksal (2008) [95]	15	Yes: neutrophil count	No	Adenosine as an adjunct to cardioplegia did not improve clinical end points or confer significant myocardial protection
Hydroxyethyl starch in prime (1)	RCT, valve	Choi (2010) [96]	28	Yes: NE	No	Hydroxyethyl starch used as priming solution, versus albumin control, did not affect ICU stay or inotrope use
Gelatin colloid (1)	RCT, CABG	Tamayo (2008) [97]	22	No	No	Priming with gelatin colloid, versus crystalloid control, had no effect on ventilation time, ICU stay, or need for inotropes
N-acetyl cysteine (1)	RCT, CABG	Liu (2009) [98]	15	No	No	In cardioplegia; no change in hard clinical end points but same trend as with intravenous infusion toward myocardial injury (CK-MB)

*Number in square bracket refers to reference number in the Appendix B.
†N = number of subjects in treatment group.
‡Abbreviations used: RCT, randomized controlled trial; CABG, coronary artery bypass grafting; IL, interleukin; TNF, tumor necrosis factor; NE, neutrophil elastase; CRP, C-reactive protein; A-a O_2, arterial–alevolar oxygen gradient; CK-MB, creatine kinase MB fraction; cTn, cardiac-specific troponin; ICU, intensive care unit; STEMI, ST-elevation myocardial infarction.
§N/D, not done.

Nitric Oxide: There were three RCTs examining different methods to deliver nitric oxide (NO) to patients perioperatively: direct inhalation of NO gas, infusion of sodium nitroprusside (NO donor), or L-arginine (NO substrate) added to cardioplegia. Taken together, these small NO trials (median sample size n = 28) all demonstrated clinical benefit.

Neutrophil Elastase Inhibitors: There were three RCTs examining administration of neutrophil elastase inhibitors, two of which used urinary protease inhibitor and one human elastase inhibitor. Taken together, these small neutrophil elastase interventions (median sample size n = 30) were adjudged clinically beneficial.

Propofol: There were two RCTs studying propofol anesthesia. Both studies demonstrated a clinical outcome improvement. One study examined the interaction between isoflurane preconditioning and propofol postconditioning and was able to demonstrate a clinical benefit for this combination.

Aminophylline: There were two RCTs from the same research group on the bronchodilator aminophylline. Both of these small studies (n = 30) demonstrated a clinical benefit.

Sevoflurane: There were two RCTs on sevoflurane anesthesia, only one of which demonstrated an improvement in a clinical outcome.

Intensive Insulin Therapy: There was one RCT on intensive insulin therapy using the Portland Protocol (22) in patients with no history of diabetes. This well-designed study (n = 100) showed a clinical benefit with significantly shortened intensive care unit stay and myocardial protection.

Fluvastatin: There was one RCT on fluvastatin administered for 3 weeks up to the day of surgery; this study demonstrated clinical benefit.

Propionyl-L-Carnitine: There was one RCT on propionyl L-carnitine administration in a diabetic cohort assigned a clinical benefit for this intervention.

Ultrafiltration: There were three RCTs on ultrafiltration using three different ultrafiltration techniques. However, none of the trials recorded a significant depletion of inflammatory biomarkers and none achieved a clinical benefit. There were no indications of negative patient outcomes.

There was little evidence across the many varied interventions for causing harm, but lidocaine infusion exhibited an interaction with diabetes leading to significantly worsened postoperative cognitive dysfunction. Two trials on N-acetyl cysteine manifested a concerning trend for death or myocardial injury in the treatment arm, whether given intravenously or added to cardioplegia. Aspirin given preoperatively was associated with worsened reoperative rates. Finally, double-dose tranexamic acid revealed a trend toward increased mortality and seizures.

Methodological Quality

Variable quality in methodological descriptions was noted across the evidence base, particularly in areas of blood management and the description of perfusion equipment used: 31.6% of papers provided inadequate or nonexistent protocols for blood management and 29.6% of papers were classified as poor for equipment. Surgical protocols were described more adequately with only 12.2% of papers classified as poor in the evidence base.

Association between Inflammatory Suppression and Clinical Benefit

The five most frequently monitored biomarkers for inflammation (interleukin [IL]-6, IL-8, tumor necrosis factor α, neutrophil elastase and complement component C3a) were also the five most often suppressed and most likely to be associated with a clinical benefit. Suppression of biomarkers occurred with similar frequency across the three categories of intervention. It occurred in 68.4% of the studies in surgical/perioperative management, 65.7% of the studies of perfusion-related interventions, and 68.2% of the investigations of pharmacological interventions.

DISCUSSION

The review strategy adopted in this systematic analysis, combining self-identified anti-inflammatory studies with inclusion criteria specified in the Outcomes consensus statement (19), yielded a rich evidence base for anti-inflammatory interventions covering surgical, pharmacological, and perfusion approaches. The overall clinical dividend from this large body of literature yielded only 35.7% of papers capable of demonstrating a clinical benefit. The most widely studied intervention, steroid use, showed no evidence for improvement of clinical outcomes according to our analysis, which supports a recent Cochrane review that concluded corticosteroids exerted no clinical benefit on mortality, cardiac, or pulmonary complications (21). On the positive side, there was little evidence for harm associated with the many varied attempts to inhibit the systemic inflammatory response with only certain isolated interventions earning a precautionary negative recommendation (aspirin, lidocaine in persons with diabetes, N-acetylcysteine, and double-dose tranexamic acid).

Various surface coating and surface reduction strategies showed some promise but no compelling clinical benefit, including biocompatible surface coatings, minimized circuits, and off-pump coronary revascularization. The rationale for heparin coating, however, targeting factor IIa at

the terminus of the coagulation cascade, must remain questionable. It is likely that whatever clinical benefit heparin confers is the result of "part-time" inhibition higher up the cascade at the level of factor IXa (23). We hypothesize that upstream interdictions might provide a better opportunity for anti-inflammatory protection by blocking the avalanche of activated factors at the top of the cascade. On this basis, we highlight interventions using C1 esterase inhibitor (Appendix B: references [69,70]), a pleiotropic agent with upstream targets in coagulation, complement, and fibrinolytic pathways (24). Both C1 esterase inhibitor studies showed a clinical benefit in emergency CABG populations and both demonstrated a gradient effect with improved myocardial protection associated with earlier treatment from the point of acute ST-elevation myocardial infarction. Other promising interventions such as NO therapy (Appendix B: references [77,92,93]) may also have benefited from a pleiotropic mechanism of action, because NO acts to promote vasodilation (25), has antiadhesive effects on leukocytes (26), and anticoagulant properties against platelets (27). We hypothesize that pleiotropic agents like NO or C1 esterase inhibitor are able to achieve a consistent clinical benefit by blocking multiple targets in multiple pathways (13,28,29).

Filtration strategies to remove leukocytes or soluble cytokines were not typically associated with any clinical benefit. This contrasted with arterial line filters for removing microemboli, which earned a class I recommendation in a previous evidence-based review (30). Some studies noted exacerbation of leukocyte activation, presumably as a result of adherence and activation of leukocytes at the filter surface. Our observations are consistent with the findings of other meta-analyses, which concluded that leukocyte-depleting filters or zero-balanced ultrafiltration did not confer significant clinical benefits (31,32).

The authors recognize some limitations to this critical review. First, the review is not intended as a critical care guide to manage patients after they have experienced a severe systemic inflammatory response, but as a guide to clinical practices aimed at limiting the inflammatory response from the outset. We acknowledge that patient distribution in the evidence base was highly skewed with one Cochrane review on steroid use and one multicenter trial on C5 inhibition accounting for over 60% of the total number. We further recognize that a different "mix" of papers was captured by our reviewing strategy compared with other meta-analyses. For example, a previous meta-analysis on biocompatible surface coatings identified 36 papers, whereas only 14 qualified by our inclusion criteria (33). This was attributable to the fact our search was limited to a 10-year window and used more stringent inclusion criteria. Nonetheless, we reached the same conclusion as that meta-analysis: that biocompatible surface coatings without other measures to limit blood activation conferred only limited clinical benefit. In adopting the minimal reporting criteria of the consensus statement, we recognize that clinical benefit may be based on a single clinical variable. Improvement of a single variable may not on its own guarantee improvement in clinical outcome and benefits might best be accrued when treatments are used in combination. Because few such combinations have been evaluated systematically, this becomes an important area for future research. The overall validity of our approach was supported across several interventions with the current review reaching similar conclusions as contemporary meta-analyses in the areas of: corticosteroid use, filtration, and biocompatible surface coating (21,31–33). Regular updates are warranted to capture changing practice and emerging evidence outside the 10-year window of this review (34–36) that may change clinical practice in the future.

The review highlighted several shortcomings in methodological quality. In addition to problems with small sample size and heterogeneity of interventions and biomarkers studied, there were fundamental shortcomings in methodological descriptions. This was particularly apparent for blood management protocols and description of perfusion equipment. Inadequate descriptions of these practices are important, because they can impact inflammatory processes and clinical outcomes (30). We therefore advocate the use of tables in the Methods section to itemize in detail the system components of the bypass circuit and blood management protocols used (37).

The broad scope of the current review yielded novel insight into the relationship between anti-inflammatory action and clinical efficacy. This arose from a secondary analysis showing that 97% of papers with a clinical benefit achieved suppression of at least one inflammatory marker (Tables 3–5). However, over half the papers (57%) that did not find a clinical benefit also did demonstrate suppression of an inflammatory biomarker. This suggests that suppression of one inflammatory biomarker is therefore necessary but not sufficient to translate into a clinical benefit.

CONCLUSIONS

This critical review concludes that no single intervention used on its own demonstrates strong evidence for limiting adverse outcomes as a result of the systemic inflammatory response. A secondary analysis showed that suppression of a single inflammatory biomarker was required but was not sufficient to confer a clinical benefit. The most promising interventions were those that targeted multiple inflammatory pathways. These results are consistent with a "multiple hit" hypothesis, whereby clinically effective suppression of the systemic inflammatory response requires hitting multiple inflammatory targets. Further research is warranted to evaluate combinations of interventions capable of achieving synergy by targeting the many pathways that are activated.

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APPENDIX A. PubMed search structure.

The following search terms recovered >1600 articles in PubMed: ((cardiac surgery OR (((“cardiopulmonary bypass”[TIAB] NOT Medline[SB]) OR “cardiopulmonary bypass”[MeSH Terms] OR (“coronary artery bypass”[TIAB] NOT Medline[SB]) OR “coronary artery

bypass"[MeSH Terms]) OR (valve OR valvular) AND surgery) OR "Heart-lung machine"[MeSH Terms] OR ((hemofiltration OR ultrafiltration) AND (cardiac OR heart)) AND ((Humans[Mesh]) AND (English[lang]))) NOT (cardiac surgery OR ((("cardiopulmonary bypass"[TIAB] NOT Medline[SB]) OR "cardiopulmonary bypass"[MeSH Terms] OR ("coronary artery bypass"[TIAB] NOT Medline[SB]) OR "coronary artery bypass"[MeSH Terms]) OR (valve OR valvular) AND surgery) OR "Heart-lung machine"[MeSH Terms] OR ((hemofiltration OR ultrafiltration) AND (cardiac OR heart)) AND ((Humans[Mesh]) AND (English[lang]) AND ((infant[MeSH] OR child [MeSH] OR adolescent[MeSH])))))) OR ((cardiac surgery OR ((("cardiopulmonary bypass"[TIAB] NOT Medline [SB]) OR "cardiopulmonary bypass"[MeSH Terms] OR ("coronary artery bypass"[TIAB] NOT Medline[SB]) OR "coronary artery bypass"[MeSH Terms]) OR (valve OR valvular) AND surgery) OR "Heart-lung machine"[MeSH Terms] OR ((hemofiltration OR ultrafiltration) AND (cardiac OR heart)) AND ((Humans[Mesh]) AND (English[lang]) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH])))) AND (cardiac surgery OR ((("cardiopulmonary bypass"[TIAB] NOT Medline[SB]) OR "cardiopulmonary bypass"[MeSH Terms] OR ("coronary artery bypass"[TIAB] NOT Medline[SB]) OR "coronary artery bypass"[MeSH Terms]) OR (valve OR valvular) AND surgery) OR "Heart-lung machine"[MeSH Terms] OR ((hemofiltration OR ultrafiltration) AND (cardiac OR heart)) AND ((Humans[Mesh]) AND (English [lang]) AND (adult[MeSH])))) NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR Festschrift[ptyp] OR Historical Article[ptyp] OR Lectures[ptyp] OR Legal Cases[ptyp] OR Legislation[ptyp] OR News[ptyp] OR Newspaper Article[ptyp] OR Patient Education Handout [ptyp]) nerv* OR cogniti* OR cerebr* OR brain OR neurolog* OR neurocognitive OR "cerebral arteries"[mesh] OR "brain chemistry"[mesh] OR "cognition disorders"[mesh] OR "cerebrovascular circulation"[mesh] OR "brain" [mesh] OR "nervous system diseases"[mesh] OR embolism[mesh] OR "Cerebrovascular Disorders"[mesh] inflammatory OR inflammation OR Anti-Inflammatory Agents OR immunology OR SIRS death OR mi OR infarction OR lung OR kidney OR heart OR icu OR dialysis OR patency.

APPENDIX B. References comprising the evidence base.

References in order of appearance in Tables 3, 4, and 5

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