Intensive Care Med
https://doi.org/10.1007/s00134-017-5004-9

SYSTEMATIC REVIEW

Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis

Tomoko Fujii[1,2], Riki Ganeko[3], Yuki Kataoka[4], Toshi A. Furukawa[5], Robin Featherstone[6], Kent Doi[7], Jean-Louis Vincent[8], Daniela Pasero[9], René Robert[10], Claudio Ronco[11] and Sean M. Bagshaw[12*]

Abstract

Purpose: Polymyxin B-immobilized hemoperfusion (PMX-HP) is an adjuvant therapy for sepsis or septic shock that clears circulating endotoxin. Prior trials have shown that PMX-HP improves surrogate endpoints. We aimed to conduct an evidence synthesis to evaluate the efficacy and safety of PMX-HP in critically ill adult patients with sepsis or septic shock.

Methods: We searched for randomized controlled trials (RCTs) in MEDLINE, EMBASE, the Cochrane Library, the Health Technology Assessment Database, CINAHL, "Igaku Chuo Zasshi", the National Institute of Health Clinical Trials Register, the World Health Organization International Clinical Trials Registry Platform, the University Hospital Medical Information Network Clinical Trials Registry, the reference lists of retrieved articles, and publications by manufacturers of PMX-HP. The primary outcomes were 28-day all-cause mortality, the number of patients with at least one serious adverse event, and organ dysfunction scores. The GRADE methodology for the certainty of evidence was used.

Results: Six trials (857 participants; weighted mean age 62.5 years) proved eligible. Patient-oriented primary outcomes were assessed. The pooled risk ratio (RR) for 28-day mortality associated with PMX-HP was 1.03 [95% confidence interval (CI) 0.78–1.36; $I^2 = 25\%$; $n = 797$]. The pooled RR for adverse events was 2.17 (95% CI 0.68–6.94; $I^2 = 0\%$; $n = 717$). Organ dysfunction scores over 24–72 h after PMX-HP treatment did not change significantly (standardized mean difference − 0.26; 95% CI − 0.64 to 0.12; $I^2 = 78\%$; $n = 797$). The certainty of the body of evidence was judged as low for both benefit and harm using the GRADE methodology.

Conclusions: There is currently insufficient evidence to support the routine use of PMX-HP to treat patients with sepsis or septic shock.

Registration: PROSPERO International Prospective Register of Systematic Reviews (CRD42016038356).

Keywords: Sepsis, Septic shock, Polymyxin B-immobilized hemoperfusion, Systematic review, Meta-analysis

*Correspondence: bagshaw@ualberta.ca
[12] Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, 2-124 Clinical Sciences Building, 8440-112 ST NW, Edmonton, Canada T6G 2B7
Full author information is available at the end of the article

Springer

Introduction

Sepsis remains desperately fatal and septic shock has a hospital mortality rate as high as 20–50% worldwide [1–5]. Many interventions have been evaluated to improve the prognosis of sepsis, but large multi-centered trials of various therapies have failed to demonstrate consistent benefit [6]. As fundamental elements of sepsis treatment, including timely and appropriate antimicrobial therapies, adequate fluids, and vasopressors, have not changed for decades [7, 8], there currently is dire need for new and effective therapies.

Endotoxin, a principal component of the outer membrane of Gram-negative bacteria, is recognized as a potent mediator of the host response to infection and development of sepsis [9]. Studies measuring endotoxin levels in patients with septic shock have found that high levels of endotoxin activity correlated with worse clinical outcomes [10, 11]. Polymyxin B (PMX) is a cyclic cationic polypeptide antibiotic with high affinity for endotoxin. A novel strategy whereby PMX is bound and immobilized to polystyrene fibers in a hemoperfusion device was developed in Japan [12, 13]. The suggested mechanism of PMX hemoperfusion (PMX-HP) is to remove circulating endotoxin by adsorption, which modulates and limits the maladaptive host response to infection and the progression of the organ injury cascade of sepsis.

Selected clinical trials have suggested PMX-HP can improve the physiological profile of patients with sepsis [14–16]; however, it remains uncertain whether PMX-HP can reproducibly improve patient outcomes, as the trials have largely focused on surrogate endpoints or have been underpowered to detect effects on clinically important outcomes [16]. Additional studies have recently been completed evaluating PMX-HP, including two large multi-centre randomized controlled trials (RCTs) [17, 18].

We therefore conducted an up-to-date systematic review and evidence synthesis evaluating the impact of PMX-HP as an adjuvant therapy for critically ill adult patients with sepsis or septic shock on clinical outcomes and health services utilization. We hypothesized that use of PMX-HP would improve survival among adult critically ill patients with sepsis or septic shock.

Methods

Protocol and registration

This systematic review was conducted using guidelines in the Cochrane Collaboration and Centre for Reviews and Dissemination and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [19]. The protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews; registration number CRD42016038356, and published in full elsewhere [20].

Eligibility criteria

All relevant RCTs that investigated the effect of PMX-HP for patients with sepsis or septic shock were included. The primary research question was "what is the efficacy, effectiveness and potential harm of PMX-HP compared with standard therapy?" We obtained all relevant studies irrespective of language or publication status. Adults aged 18 years or older with sepsis, severe sepsis or septic shock were included. The diagnosis of sepsis was based on clinically suspected or documented systemic infection with any signs of systemic inflammatory response syndrome. Septic shock was classically defined as hypotension resistant to fluid administration and requiring norepinephrine or other vasopressors [21]. The intervention was use of the PMX-HP for the adjuvant treatment of sepsis or septic shock. The comparison was standard treatment only or sham hemoperfusion. Primary outcomes were 28-day all-cause mortality, the number of patients with at least one serious adverse event, and organ dysfunction scores [22] over 24–72 h after the treatment. Secondary outcomes included 90-day all-cause mortality, mean arterial blood pressure over 24–72 h after the treatment, endotoxin levels over 24–72 h after the treatment, duration of vasopressor therapy or vasopressor-free days, the receipt of renal replacement therapy (RRT), costs related to health services, and total mortality defined as mortality at 28 days or any follow-up duration when available.

Information sources

The search strategy was developed in collaboration with an experienced health research librarian. We searched MEDLINE (from the inception to Oct 2017), EMBASE, the Cochrane Library, the Health Technology Assessment Database, Cumulative Index to Nursing and Allied Health Literature, Pubmed, and "Igaku Chuo Zasshi" of the Japan Medical Abstract Society (from the inception to June 2016). The search strategies for MEDLINE were developed and were modified for searching all the other databases (eMethod 1). The search strategies were further peer-reviewed by a second research librarian [23]. For ongoing trials, we searched the National Institute of Health Clinical Trials Register, the World Health Organization International Clinical Trials Registry Platform, and the University Hospital Medical Information Network Clinical Trials Registry. We also searched citations from all included studies. We contacted experts in the field of critical care nephrology and selected commercial entities

that develop or license PMX-HP to identify additional unpublished and/or on-going trials.

Study selection

Two authors independently screened titles and abstracts of all trial reports we identified by the search to code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. The full texts of reports classified as 'retrieve' were reviewed independently according to predetermined eligibility criteria. Discrepancies were resolved through discussion with a third reviewer, as required. We identified and excluded duplicates of the same study.

Data collection process

Two reviewers independently extracted data using standardized and piloted data extraction sheets. We abstracted the following information: study characteristics, patient characteristics, sample size, interventions, comparators, potential biases in the conduct of the trial, outcomes, methods of statistical analysis, and funding support. Agreement between the two reviewers concerning the primary outcome and the risk of bias for the primary outcome was reported as percentage agreement with an intra-class correlation coefficient, and percentage agreement with a weighted kappa, respectively.

Assessment of risk of bias in individual studies

Two reviewers independently assessed the risk of bias of the included studies using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions [24], which consists of eight domains (eTable 1). The risk of bias assessment was done at the outcome level for the primary outcomes. When the original reports provided insufficient details, we made direct inquiry of the study authors. When the assessors disagreed, the final rating was decided through discussion or with the involvement of another member of the review group, if necessary. The key domain of risk of bias for 28-day mortality was allocation concealment. The overall risk of bias was also summarized in further subgroup analyses. More details of assessment of risk of bias is provided in the protocol [20].

Summary measures

As the measure of treatment effect for dichotomous outcomes, we used the risk ratio (RR) and its 95% confidence interval (CI). Continuous outcomes were pooled by calculating the mean difference (MD) with a 95% CI except for organ dysfunction scores. As the data for the organ dysfunction scores were available in the sepsis-related organ failure assessment (SOFA) score [25] or multiple organ dysfunction score [26] (MODS), we pooled standardized mean differences (SMDs) with a 95% CI [27].

Synthesis of results

We analyzed data from the included studies using Review Manager [28]. The proportion of treatment failure was calculated according to the intention-to-treat (ITT) principle. All randomized patients for whom outcome data were not available were assumed as no events. The effect of imputation was explored by a sensitivity analysis. Given the clinical heterogeneity including variability in the etiologies of sepsis in the population of interest, we used a random-effects model in all analyses [29]. We assessed overall heterogeneity by visual inspection of the forest plots, and statistical heterogeneity using the I^2 statistic and Chi-squared test. I^2 values above 50% were considered to represent substantial statistical heterogeneity. To assess reporting bias, we constructed funnel plots, and visual inspection was performed to investigate the asymmetry. Certainty of the body of evidence was assessed using the grading of recommendations assessment, development and evaluation (GRADE) framework [30]. The GRADE framework characterizes the certainty of a body of evidence on the basis of study limitations, imprecision, inconsistency, indirectness, and other considerations. The starting point for certainty in each estimate is high, but is downgraded according to the assessments of these five domains if there are serious concerns. When the effect estimates were affected substantially by the risk of bias of included studies, then we downgraded the certainty of the evidence in a domain of risk of bias.

Additional analyses

To test the robustness of the effect estimates of PMX-HP, and to explain heterogeneity, we used sensitivity analyses and subgroup analyses. We planned the following sensitivity analyses for 28-day mortality: (1) risk of bias; we included only trials with low risk of bias in allocation concealment; (2) imputed missing data; we imputed missing data on 28-day mortality in two ways: assuming the missing outcomes as events (death) in the PMX-HP group, and as no event in the control group (worst-case scenario); and assuming the missing outcomes as no event in the PMX-HP group, and as event in the control group (best-case scenario); (3) per protocol; and (4) statistical method; we used a fixed-effect model. We performed a priori subgroup analyses for the participant group and the intervention if sufficient detail was present in the eligible studies with the following hypotheses: (1) participants with abdominal sepsis, culture-confirmed sepsis, gram-negative infections, surgery, acute kidney injury (AKI), or septic shock will show greater treatment effect than patients without those conditions; and (2)

greater dose of intervention (i.e., longer duration; more than one treatment) will show greater treatment effect. eMethod 2 explains changes from the protocol [20].

Post hoc analyses

Trial sequential analysis (TSA) was done with a diversity-adjusted information size calculated using a two-sided alfa of 0.05, a power of 80%, an anticipated relative risk reduction of 20.0%, and a control event rate of 35.0%. TSA viewer version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, DE. 2016) was used. An additional sensitivity analysis including zero total event studies using continuity correction was done using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria. 2017). We added post hoc subgroup analysis for the overall risk of bias with a different criterion of assessment in the included studies, and the maximum time window from the onset of sepsis/septic shock or surgery to the first therapy.

Results

Of the 1700 citations identified from electronic and hand searches, 12 reports were identified for the review, and after exclusion of ongoing trials or inadequate reports (eTable 2), we included 6 unique trials [14, 15, 17, 18, 31, 32] in the meta-analysis (Fig. 1). The agreement of eligibility between the two reviewers was 90% [Cohen's weighted kappa: 0.79 (95% CI 0.62–0.97)]. Table 1 shows the characteristics of the trials included in the meta-analysis. All the trials used a PMX B-immobilized hemoperfusion device (Toraymyxin 20R). The number of participants across trials ranged between 16 and 450. The weighted mean age of study participants was 62.5 years (range 56.0–69.7). Sixty-one percent were male. Agreement for the primary outcome and the risk of bias items between the two reviewers was 100% (intra-class correlation coefficient: 1).

Primary outcomes

For 401 patients involved in the 5 studies [14, 15, 17, 18, 31] and contributing to 28-day mortality data (representing 83% of the included participants), the pooled RR was 1.03 (95% CI 0.78–1.36; $I^2 = 25\%$; $n = 797$; Table 2, Fig. 2a). All five trials were adjudicated as low risk of bias for the outcome (eTable 3a). The number of patients with at least one serious adverse event was reported in three studies [14, 17, 18]. The pooled RR was 2.17 (95% CI 0.68–6.94; $I^2 = 0\%$; $n = 717$; Fig. 2b). Cruz et al. [15] reported only device-related adverse events in the PMX-HP group (eTable 4). Five studies [14, 15, 17, 18, 31] reported either organ dysfunction scores at 24–72 h after the treatment or their changes over 24–72 h after the treatment. Only the EUPHRATES trial [18] reported MODS, and the others [14, 15, 17, 31] reported SOFA score. For 797 patients in the 5 studies [14, 15, 17, 18, 31], the SMD for the organ dysfunction scores was − 0.26 (95% CI − 0.64 to 0.12; Fig. 2c). The heterogeneity between the 5 trials was high ($I^2 = 78\%$).

Secondary outcomes

Among 232 patients in the ABDO-MIX trial [17] that reported 90-day mortality, PMX-HP did not reduce 90-day mortality (RR, 1.41: 95% CI 0.93–2.13; Table 2). Four trials [14, 15, 18, 31] reported mean arterial pressure. Pooled results found a statistically significant relationship between PMX-HP and increase in mean arterial pressure (MD, 5.23; 95% CI 2.75–7.72; $I^2 = 0\%$; $n = 565$; Table 2, eFigure 1). Three trials [14, 31, 32] involving 109 patients reported endotoxin levels (pg/mL) over 24–72 h after treatment measured by limulus amebocyte lysate assay (MD, − 40.77: 95% CI − 118.53 to 36.99; $I^2 = 96\%$; Table 2, eFigure 2). There were no differences in vasopressor-free days at 28 days ($n = 283$, 3 trials, eFigure 3), ICU length of stay ($n = 347$, 4 trials, eFigure 4), or the receipt of RRT ($n = 565$, 4 trials, eFigure 5; Table 2). Two studies [15, 18] provided data for duration of RRT (5.2 days for PMX-HP vs. 5.6 days for standard; $p = 0.03$) [15] and RRT-free days to day 28 (14.7 vs. 15.0 days; $p = 0.81$) [18].

One study [33] performed an economic analysis using data collected in the EUPHAS trial involving 64 patients [15] and suggested PMX-HP was cost-effective. They adopted the Italian healthcare provider's perspective and showed a mean incremental cost-effective ratio of EUR 2558 per incremental undiscounted life-year gained and EUR 3864 per incremental discounted life-year gained [33]. For 856 patients involved in the 6 studies [14, 15, 17, 18, 31, 32] contributing mortality data at 28 days or any follow-up duration, the pooled RR for death among patients treated with PMX-HP was 0.85 (95% CI 0.58–1.26; $I^2 = 64\%$; Table 2, eFigure 6).

Sensitivity and subgroup analyses

None of the 5 studies contributing to 28-day mortality [14, 15, 17, 18, 31] was rated at high risk of bias in allocation concealment. Sensitivity analyses with imputation of missing data with the worst-case scenario (pooled RR, 1.05: 95% CI 0.74–1.50; $I^2 = 47\%$, eFigure 7a) and with the best-case scenario (pooled RR, 1.02: 95% CI 0.84–1.24; $I^2 = 0\%$, eFigure 7b), and sensitivity analysis using a fixed-effect model (pooled RR, 1.07: 95% CI 0.88–1.31; $I^2 = 25\%$, eFigure 8), and per-protocol mortality (pooled RR, 0.89: 95% CI 0.62–1.29; $I^2 = 46\%$, eFigure 9) attested to the robustness of the primary analysis.

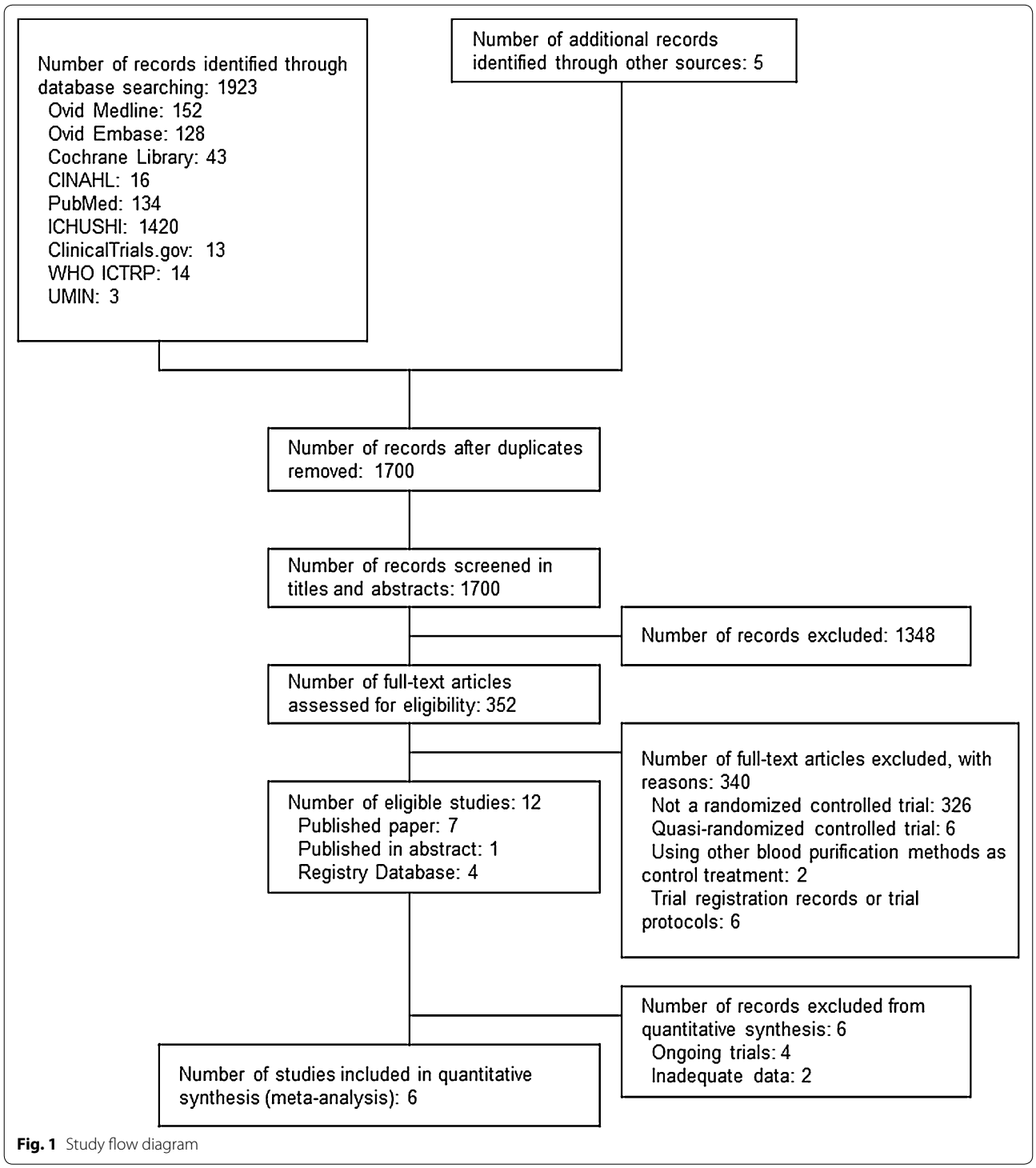

Fig. 1 Study flow diagram

Subgroup analyses for 5 studies reporting 28-day mortality [14, 15, 17, 18, 31] by trial participants with different sepsis etiologies (abdominal only vs. various etiologies including abdominal), trial participants with sepsis confirmed by culture (culture-confirmed vs. mixed or not confirmed), trial participants with gram-negative infections (culture-confirmed vs. others), trial participants with surgery (surgical vs. mixed or medical), or severity of trial participants (septic shock only vs. sepsis or septic shock) did not show any subgroup interaction

Table 1 Characteristics of the trials included in the meta-analysis

Source	Country	Study cites	Funding	Total no. of patients	Exclusion from ITT analysis	Age, mean (SD), years	Sex, male, female, *n*	Patient status	Duration, no. of sessions	Primary outcome
Nakamura 2003 [32]	Japan	NA	Investigator-initiated	60	0	56 (NA)	40, 20	Culture-positive sepsis	2 h, twice	Unclear[b]
Vincent 2005 [14]	Six countries in Europe	Multicenter	Industry-sponsored	35	0	57.7 (15.6)[a]	22, 13	Abdominal sepsis, surgical	2 h, once	The SOFA score
Cantaluppi 2008 [31]	Italy	Two centers	Investigator-initiated	16	0	60 (11.3)	12, 4	Confirmed gram-negative sepsis	2 h, twice	Viability of renal cell cultures
Cruz 2009 [15], Berto 2011 [33]	Italy	Multicenter	Industry-sponsored	64	0	63.8 (14.2)[a]	42, 22	Abdominal sepsis, surgical	2 h, twice	MAP and vasopressor requirement
Payen 2015 [17]	France	Multicenter	Industry-sponsored	243	11	69.7 (11.6)	134, 98	Abdominal sepsis, surgical, septic shock	2 h, twice	28-day mortality
EUPHRATES 2017 [18], Klein 2014 [34]	USA, Canada	Multicenter	Industry-sponsored	450	0	59.8 (14.9)[a]	273, 177[a]	Septic shock, high endotoxin activity assay	2 h, twice	28-day mortality

ITT Intention to treat, *SD* standard deviation, *NA* not available, *SOFA* sequential organ failure assessment, *MAP* mean arterial pressure

[a] Data provided by the study authors

[b] Reported endotoxin levels after treatment, survival at unknown follow-up period, adverse events

Table 2 Outcome measures

	Studies	Study reference no.	PMX-HP	Standard	Effect estimate (95% CI)	I^2 (%)
Primary outcomes						
28-day mortality	5[a]	14, 15, 17, 18, 31	135/402	124/395	Pooled RR, 1.03 (0.78, 1.36)	25
Number of patients with at least one serious adverse event	3[a]	14, 17, 18	8/360	3/357	Pooled RR, 2.17 (0.68, 6.94)	0
Change in organ dysfunction scores over 24–72 h after treatment	5[a]	14, 15, 17, 18, 31			SMD, − 0.26 (− 0.64, 0.12)	78
Secondary outcomes						
90-day all-cause mortality	1	17	40/119	27/113	RR, 1.41 (0.93, 2.13)	NA
Change in mean arterial blood pressure over 24–72 h after the treatment	4[a]	14, 15, 18, 31			MD, 5.23 (2.75, 7.72)	0
Endotoxin levels measured by LAL assay over 24–72 h after the treatment	3[a]	14, 31, 32			MD, − 40.77 (− 118.53, 36.99)	96
28-day vasopressor-free days	3[a]	14, 17, 31			MD, − 1.10 (− 4.05, 1.85)	10
ICU length of stay	4[a]	14, 15, 17, 31			MD, − 1.95 (− 7.91, 4.00)	70
The need for RRT	4[a]	14, 15, 18, 31			Pooled RR, 0.76 (0.33, 1.71)	61
Mortality at 28 days or any follow-up duration	6[a]	14, 15, 17, 18, 31, 32	144/436	140/420	Pooled RR, 0.85 (0.58, 1.26)	64

CI Confidence interval, *RR* risk ratio, *NA* not available, *SMD* standardized mean difference, *MD* mean difference, *ICU* intensive care unit

[a] Includes data provided from the study authors

(Table 3, Fig. 2a, eFigure 10–13). The subgroup of patients with AKI was not reported for their 28-day mortality in any of the included studies.

Certainty of evidence

The visual inspection of the funnel plot for the 28-day mortality suggested no apparent publication bias, but there were few studies to assess for asymmetry (eFigure 14). The certainty of evidence for the three primary outcomes was downgraded by one level each for risk of bias and imprecision, and were all considered low (Table 4).

Post hoc analyses

TSA showed the adjusted CI for 28-day mortality was 0.58–1.82 (I^2 = 25%; n = 797). The required information size to show a relative riskreduction (RRR) of 20% was 2744 (eFigure 15), and to show 2-point reduction of organ dysfunction scores was 895. An additional analysis including zero total event studies using continuity correction showed the pooled RR of the number of patients with at least one serious adverse event as 2.03 (95% CI 0.67–6.17; I^2 = 0%; n = 733). Post hoc subgroup analyses did not show subgroup interaction for the efficacy and safety outcomes. Assessment of overall risk of bias with different criteria did not affect our results (eFigures 16–18).

Discussion

Summary of key findings

The current systematic review showed that PMX-HP did not reduce 28-day mortality or organ dysfunction scores of adult sepsis or septic shock patients, and did not appear to significantly increase the risk of adverse events. PMX-HP did not reduce 90-day mortality, or significantly reduce the utilization of health resources.

Context with prior literature

Early experimental or clinical studies evaluating blood purification in sepsis have largely focused on methods of hemofiltration [35–37]. Meanwhile, large multi-centered clinical trials have found intensity of RRT beyond conventionally recommended doses does not improve survival of patients with AKI and sepsis [37–41]. Moreover, the early application of continuous venovenous hemofiltration (CVVH) was implied to worsen the severity of organ dysfunction in severe sepsis [41]. These observations suggest that alternative strategies to better target blood purification and improved survival in sepsis are necessary.

Previous systematic reviews implied that the use of PMX-HP was associated with a survival benefit, improvements in hemodynamics, and reduction in circulating endotoxin levels [16, 42, 43]. In our up-to-date systematic review, we excluded six studies where randomization was not rigorous (e.g., in five studies, allocation was alternating; and in one study, allocation was performed through discussion with patients) following direct inquiry with the study authors [44–49]. Five out of the six excluded studies [45–49] that showed large beneficial effect with relatively small sample sizes were included in previous systematic reviews [16, 42, 43]. We included two newly completed high-profile randomized trials [17, 18], and found no apparent benefit on survival.

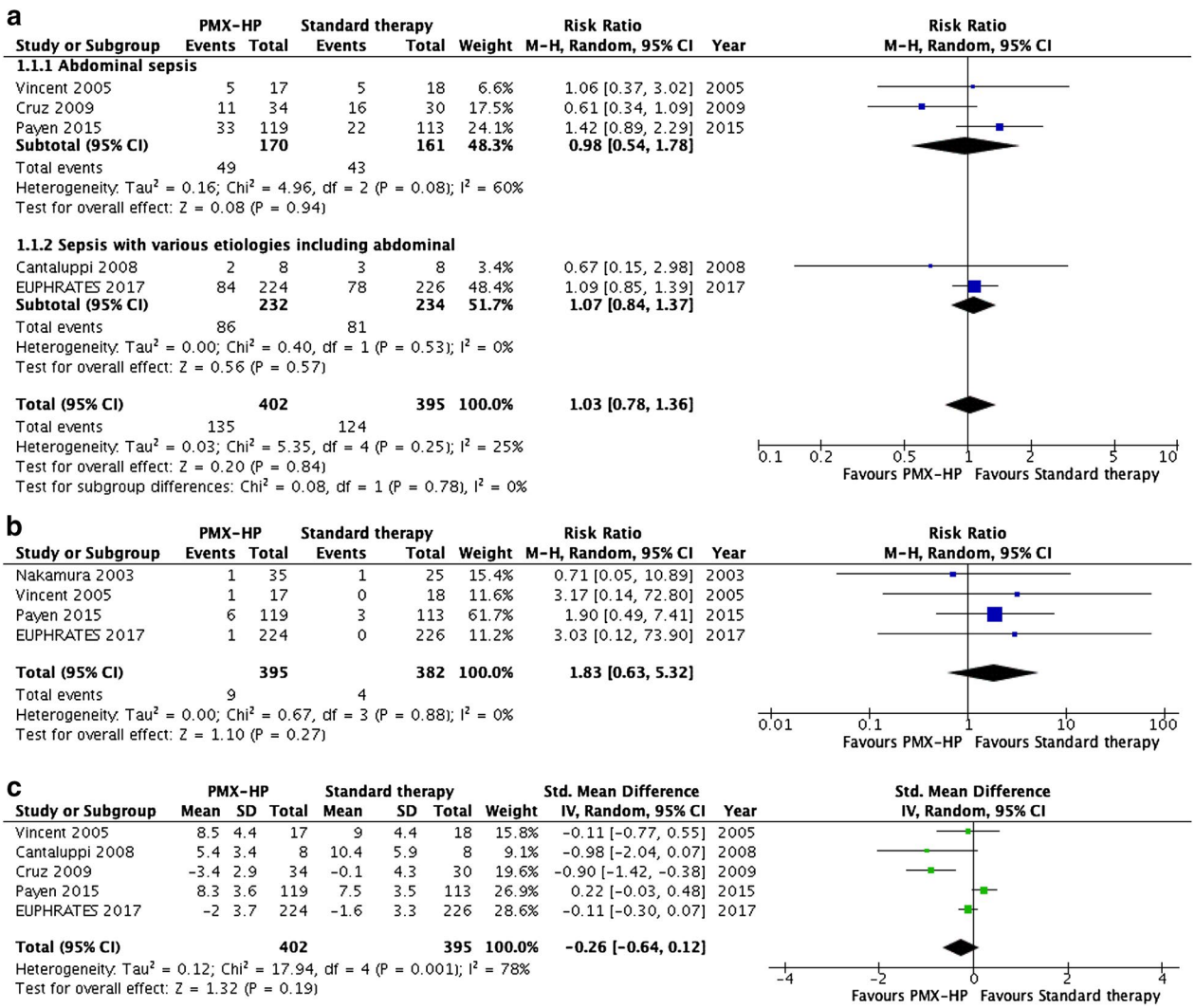

Fig. 2 Forest plot of comparison: PMX-HP versus standard therapy. *PMX-HP* polymyxin B-immobilized hemoperfusion. † Reported change data. * Data provided by the study author

There might be several possible explanations for our findings. First, there may be no beneficial effect of using PMX-HP in patients with sepsis or septic shock. Vincent et al. [14] and a post hoc analysis of ABDO-MIX study [50] measured cytokines after completion of PMX-HP treatment, including TNF-alfa, interleukins, and IFN-gamma, and no significant differences were found [50]. These results imply PMX-HP treatment may not significantly remove endotoxin and/or suppress inflammatory cytokines sufficiently to modify the course of organ dysfunction and risk of death.

Second, the pooled analysis with 797 patients may still lack sufficient statistical power to detect small but clinically meaningful effects of PMX-HP treatment, as shown in the TSA. If we assume an absolute risk reduction of 15% (i.e., 43% RRR) with an estimated baseline mortality of 35%, as adopted in the EUPHRATES trial [34], we have already accumulated sufficient information to conclude a null effect. Kaukonen et al. showed mortality in patients with severe sepsis has declined considerably over the last decade [1], likely in part implying substantial temporal progress in the overarching care provided to critically ill patients. The effect of PMX-HP, if any, could be heterogeneous and much smaller than expected, possibly due largely to PMX-HP being only an adjuvant therapy in the context of multiple interventions used to manage adult critically ill patients with sepsis.

Third, patient selection and case mix may have influenced the expected outcomes. Biologically targeted therapy is sensible to enrich the trial population with patients most likely to derive benefit from the intervention; however, the EUPHRATES trial, the only study that adopted

Table 3 Subgroup analyses of 28-day mortality related to polymyxin B-immobilized hemoperfusion

Subgroup	Studies	Patients	Pooled risk ratio	I^2 (%)	*p* value
Participants: culture	5	797		0	0.57
Culture-positive sepsis	1[a]	16	0.67 [0.15, 2.98]		
Not confirmed	4[a]	781	1.04 [0.76, 1.42]		
Participants: gram-negative infection	5	797		0	0.57
Confirmed gram-negative infection	1[a]	16	0.67 [0.15, 2.98]		
Not confirmed gram-negative	4[a]	781	1.04 [0.76, 1.42]		
Participants: surgical	5	797		0	0.78
Surgical	3	331	0.98 [0.54, 1.78]		
Mixed or medical	2[a]	466	1.07 [0.84, 1.37]		
Participants: severity of sepsis	5	797		72	0.06
Septic shock	2[a]	682	1.15 [0.92, 1.43]		
Sepsis or septic shock	3[a]	115	0.69 [0.42, 1.12]		
Intervention: no. of sessions	5	797		0	0.93
Single session	1	35	1.06 [0.37, 3.02]		
Two sessions	4[a]	762	1.01 [0.72, 1.42]		
More than two sessions	0	0	NA		

NA Not available

[a] Includes data provided from the study authors

endotoxin activity as an eligibility criterion, may still have been too small to detect a small but clinically important difference. There are three ongoing trials measuring endotoxin activity at the inclusion of the trials (eTable 2); however, the sample sizes of these trials are also likely to be too small to likely detect a clinically important effect of PMX-HP or to change the overall conclusions of sequential meta-analyses.

Strengths and limitations

We have conducted a rigorous peer-reviewed literature search to identify relevant randomized trials, including a database in Japan where the PMX-HP filter was developed. Furthermore, we have directly contacted all the study authors to assess the eligibility and the quality of each trial to minimize bias in our effect estimation. The inclusion of two new and larger studies [17, 18] has empowered the pooled analysis and enabled the up to date evidence synthesis. We have also performed several predefined sensitivity analyses to confirm the robustness of the findings. However, there are several limitations for this review. Limited numbers of studies did not allow detailed analysis and interpretation to address the issue of heterogeneity in the case mix and in treatment effect in response to PMX-HP. Second, as we conducted meta-analysis with aggregated data, we could not classify participants involved in the studies into complementary subgroups at each patient level. Third, we observed considerable heterogeneity in several analyses. Practice variation across the included studies may have contributed to heterogeneity. Similarly, there may be a biological basis for responsiveness to PMX-HP among a heterogeneous population of patients with sepsis that is incompletely understood. Fourth, as we have performed multiple analyses in this systematic review, we recommend caution when interpreting significant findings, such as the modest increase of mean arterial pressure. Finally, we have made some changes from our original protocol, due largely to the availability of the data.

Implications for clinicians, policy, and future research

Our review would suggest there is no definitive evidence to support the routine use of PMX-HP for adult critically ill patients with sepsis or septic shock. While there was no significant difference in risk shown in our review, the potential risk of serious adverse events with use of PMX-HP should be considered. The available evidence did not prove its efficacy for improved survival, and as such, performing an economic evaluation may not be justified.

The imprecision of the results does not preclude further trials to assess the efficacy of PMX-HP. In the EUPHRATES trial, post hoc exploratory per-protocol analyses showed a beneficial effect among adult patients with a MODS greater than 9 [18], a finding warranting further verification. Future clinical trials should aim to explore specific patient populations with adequate sample size, for example, those with elevated blood endotoxin level, or high organ dysfunction scores, if any clinical effect of PMX-HP is to be detected.

Table 4 Evidence table of the systematic review

Quality assessment							No. of patients		Effect		Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PMX-HP	Standard therapy	Relative (95% CI)	Absolute (95% CI)	
28-day mortality											
5	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	135/402 (33.6%)	124/395 (31.4%)	RR 1.03 (0.78–1.36)	9 more per 1000 (from 69 fewer to 113 more)	⨁⨁◯◯ LOW
The number of patients with at least one serious adverse event											
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	8/360 (2.2%)	3/357 (0.8%)	RR 2.17 (0.68–6.94)	10 more per 1000 (from 3 fewer to 50 more)	⨁⨁◯◯ LOW
Organ dysfunction score over 24–72 h after treatment											
5	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	402	395	–	SMD 0.26 lower (0.64 lower to 0.12 higher)	⨁⨁◯◯ LOW

CI Confidence interval, *RR* risk ratio, *SMD* standardized mean difference

[a] One trial was at high risk of bias in the blinding and sponsorship domains

[b] Because of the wide confidence interval

Conclusions

Among adult patients with sepsis or septic shock, use of PMX-HP compared with standard therapy alone was not proven to reduce 28-day mortality or to reduce organ dysfunction scores, or significantly increase the risk of serious adverse events. Considering the certainty of the body of evidence was low for both benefit and harm, to date, there is no strong evidence to support the routine use of PMX-HP as an adjuvant therapy in critically ill adult patients with sepsis or septic shock.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-017-5004-9) contains supplementary material, which is available to authorized users.

Author details

[1] Department of Epidemiology and Preventive Medicine, Kyoto University Graduate School of Medicine, Yoshida Hon-machi, Sakyo-ku, Kyoto, Japan. [2] Japan Society for the Promotion of Science, 5-3-1 Kojimachi, Chiyoda-ku, Tokyo, Japan. [3] Department of Surgery, Kyoto University Hospital, 54 Kawahara-cho, Syogoin, Sakyo-ku, Kyoto, Japan. [4] Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Higashi-Naniwa-Cho 2-17-77, Amagasaki, Hyogo, Japan. [5] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine, Yoshida Konoe-cho, Sakyo-Ku, Kyoto, Japan. [6] Department of Pediatrics, Alberta Research Center for Health Evidence (ARCHE), University of Alberta, 11405-87 Avenue Edmonton, Alberta, Canada. [7] Department of Emergency and Critical Care Medicine, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. [8] Department of Intensive Care, Erasme University Hospital, Unversité Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium. [9] Department of Anesthesia and Intensive Care Medicine, San Giovanni Battista Hospital, University of Turin, Via Giuseppe Verdi, 8, 10124 Turin, Italy. [10] Service de Réanimation Médicale, CHU-Poitiers, University of Poitiers, 86000 Poitiers, France. [11] Department of Nephrology Dialysis and Transplantation, International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Viale Rodolfi 37, 36100 Vicenza, Italy. [12] Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, 2-124 Clinical Sciences Building, 8440-112 ST NW, Edmonton, Canada T6G 2B7.

Acknowledgements

We thank Mr. Toshiyuki Suwa at Osaka University for his assistance with the search strategy design in Japanese databases, Ms. Tara Landry at Montreal General Hospital, McGill University Health Centre, for her peer review of the MEDLINE search strategy, Prof. Vladimir Saenko at Nagasaki University for helping to review trial reports in Russian, Ms. Ayumi Horie at Hyogo Prefectural Amagasaki General Medical Center for obtaining the Japanese full-text articles, Toray Industries, Inc. for providing the list of published/unpublished trials and conference proceedings, assisting to get contact with an author of the included study, and all the corresponding persons of ongoing trials for providing information of the current status of the trials. No specific compensation was provided to these individuals.

Author contributions

Drs. TF and SMB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: TF, SMB, RG, YK, RF, and TAF. Acquisition of data: TF, SMW, KD, RG, YK, RF, JV, DP, RR, and CR. Analysis and interpretation of data: TF, SMB, YK, TAF, JV, DP, RR, and CR. Drafting of the manuscript: TF, TAF, SMB, and KD. Critical revision of the manuscript for important intellectual content: RF, RG, YK, JV, DP, RR, CR. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

Compliance with ethical standards

Funding

TF is supported by the Japan Society for the Promotion of Science (JSPS) and has received a grant from JSPS. This study was funded in part by Grant-in-Aid for JSPS Research Fellow JP16J10320 to TF. SMB is supported by a Canada Research Chair in Critical Care Nephrology and is a steering committee member of the EUPHRATES trial. He has consulted and received speaking fees from Baxter Healthcare Corp. TAF has received lecture fees from Eli Lilly, Janssen, Meiji, Mitsubishi-Tanabe, MSD, and Pfizer. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mitsubishi-Tanabe and Mochida. KD received lecture fees from Asahi Kasei Medical Crop, Baxter Healthcare Corp., and Toray Medical Corp. JLV, DP, RB, and CR were engaged in the clinical trials included in this review, and provided some of the data not reported in their published papers. None of these funding organizations have contributed to the study design; collection, management, analysis, and interpretation of data; writing of the report, or the decision to submit the report for publication. Toray Industries provided some of the data included in this review, as noted in the body of the article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Received: 30 September 2017 Accepted: 22 November 2017
Published online: 04 December 2017

References

1. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA 311:1308–1316
2. Rhee C, Dantes R, Epstein L et al (2017) CDC prevention epicenter program: benchmarking the incidence and mortality of severe sepsis in the United States. JAMA. https://doi.org/10.1001/jama.2017.13836 **(Epub ahead of print)**
3. Quenot JP, Binquet C, Kara F et al (2013) The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. Crit Care 17:R65
4. Leligdowicz A, Dodek PM, Norena M, Co-operative Antimicrobial Therapy of Septic Shock Database Research Group et al (2014) Association between source of infection and hospital mortality in patients who have septic shock. Am J Respir Crit Care Med 189:1204–1213
5. Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801–810
6. Suffredini AF, Munford RS (2011) Novel therapies for septic shock over the past 4 decades. JAMA 306:194–199
7. Dellinger RP, Carlet JM, Masur H, Surviving Sepsis Campaign Management Guidelines Committee et al (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32:858–873
8. Dellinger RP, Levy MM, Rhodes A, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup et al (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41:580–637
9. Danner RL, Elin RJ, Hosseini JM, Wesley RA, Reilly JM, Parillo JE (1991) Endotoxemia in human septic shock. Chest 99:169–175
10. Casey LC, Balk RA, Bone RC (1993) Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. Ann Intern Med 119:771–778
11. Marshall JC, Foster D, Vincent JL, MEDIC study et al (2004) Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. J Infect Dis 190:527–534
12. Shoji H, Tani T, Hanasawa K, Kodama M (1998) Extracorporeal endotoxin removal by polymyxin B immobilized fiber cartridge: designing and antiendotoxin efficacy in the clinical application. Ther Apher 2:3–12
13. Shoji H (2003) Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin). Ther Apher Dial 7:108–114
14. Vincent JL, Laterre PF, Cohen J et al (2005) A pilot-controlled study of a polymyxin B-immobilized hemoperfusion cartridge in patients with severe sepsis secondary to intra-abdominal infection. Shock 23:400–405

15. Cruz DN, Antonelli M, Fumagalli R et al (2009) Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 301:2445–2452
16. Cruz DN, Perazella MA, Bellomo R et al (2007) Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. Crit Care 11:R47
17. Payen DM, Guilhot J, Launey Y, ABDOMIX Group et al (2015) Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med 41:975–984
18. Dellinger P (2016) EUPHRATES: evaluating the use of polymyxin B hemoperfusion in a randomized controlled trial of adults treated for endotoxemia and septic shock. Canadian Critical Care Forum, Toronto
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
20. Fujii T, Ganeko R, Kataoka Y, Featherstone R, Bagshaw S, Furukawa TA (2016) Polymyxin B-immobilised haemoperfusion and mortality in critically ill patients with sepsis/septic shock: a protocol for a systematic review and meta-analysis. BMJ Open 6:e012908
21. Levy MM, Fink MP, Marshall JC, International Sepsis Definitions Conference et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Med 29:530–538
22. Vincent JL, de Mendonça A, Cantraine F et al (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26:1793–1800
23. Sampson M, McGowana J, Cogob E, Grimshaw J, Moherd D, Lefebvre C (2009) An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 62:944–952
24. Higgins JPT, Green S (2008) Cochrane handbook for Systematic Reviews of Interventions. John Wiley & Sons, Chichester (UK)
25. Vincent JL, Moreno R, Takala J et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
26. Cook R, Cook D, Tilley J, Lee K, Marshall J, Canadian Critical Care Trials Group (2001) Multiple organ dysfunction: baseline and serial component scores. Crit Care Med 29:2046–2050
27. da Costa BR, Nüesch E, Rutjes AW et al (2013) Combining follow-up and change data is valid in meta-analyses of continuous outcomes: a meta-epidemiological study. J Clin Epidemiol 66:847–855
28. Review Manager (RevMan) [Computer program] (2014) Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen
29. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
30. Guyatt G, Oxman AD, Akl EA et al (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64:383–394
31. Cantaluppi V, Assenzio B, Pasero D et al (2008) Polymyxin-B hemoperfusion inactivates circulating proapoptotic factors. Intensive Care Med 34:1638–1645
32. Nakamura T, Ushiyama C, Suzuki Y et al (2003) Combination therapy with polymyxin B-immobilized fibre haemoperfusion and teicoplanin for sepsis due to methicillin-resistant Staphylococcus aureus. J Hosp Infect 53:58–63
33. Berto P, Ronco C, Cruz D, Melotti RM, Antonelli M (2011) Cost-effectiveness analysis of polymyxin-B immobilized fiber column and conventional medical therapy in the management of abdominal septic shock in Italy. Blood Purif 32:331–340
34. Klein DJ, Foster D, Schorr CA, Kazempour K, Walker PM, Dellinger RP (2014) The EUPHRATES trial (evaluating the use of polymyxin B hemoperfusion in a randomized controlled trial of adults treated for endotoxemia and septic shock): study protocol for a randomized controlled trial. Trials. 15:218
35. Honore PM, Jamez J, Wauthier M et al (2000) Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 28:3581–3587
36. Bellomo R, Kellum JA, Gandhi CR et al (2000) The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediators in canine endotoxemia. Am J Respir Crit Care Med 161:1429–1436
37. Cornejo R, Downey P, Castro R et al (2006) High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med 32:713–722
38. VA/NIH Acute Renal Failure Trial Network (2008) Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359:7–20
39. RENAL Replacement Therapy Study Investigators (2009) Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361:1627–1638
40. Van Wert R, Friedrich JO, Scales DC et al (2010) High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis. Crit Care Med 38:1360–1369
41. Payen D, Mateo J, Cavaillon JM et al (2009) Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. Crit Care Med 37:803–810
42. Zhou F, Peng Z, Murugan R, Kellum JA (2013) Blood purification and mortality in sepsis: a meta-analysis of randomized trials. Crit Care Med 41:2209–2220
43. Chang T, Tu YK, Lee CT et al (2017) Effects of polymyxin b hemoperfusion on mortality in patients with severe sepsis and septic shock: a systemic review, meta-analysis update, and disease severity subgroup meta-analysis. Crit Care Med 45:e858–e864
44. Nemoto H, Nakamoto H, Okada H et al (2001) Newly developed immobilized polymyxin B fibers improve the survival of patients with sepsis. Blood Purif 19:361–368
45. Nakamura T, Kawagoe Y, Matsuda T, Koide H (2004) Effect of polymyxin B-immobilized fiber on bone resorption in patients with sepsis. Intensive Care Med 30:1838–1841
46. Nakamura T, Ushiyama C, Suzuki S et al (2000) Effect of polymyxin B-immobilized fiber hemoperfusion on sepsis-induced rhabdomyolysis with acute renal failure. Nephron 86:210
47. Nakamura T, Ushiyama C, Shoji H, Koide H (2002) Effects of hemoperfusion on serum cardiac troponin T concentrations using polymyxin B-immobilized fibers in septic patients undergoing hemodialysis. ASAIO J 48:41–44
48. Nakamura T, Ushiyama C, Suzuki Y, Shoji H, Shimada N, Koide H (2002) Hemoperfusion with polymyxin B immobilized fibers for urinary albumin excretion in septic patients with trauma. ASAIO J 48:244–248
49. Nakamura T, Ushiyama C, Suzuki Y et al (2003) Hemoperfusion with polymyxin B-immobilized fiber in septic patients with methicillin-resistant Staphylococcus aureus-associated glomerulonephritis. Nephron 94:c33–c39
50. Coudroy R, Payen D, Launey Y, ABDOMIX Group et al (2017) Modulation by polymyxin-B hemoperfusion of inflammatory response related to severe peritonitis. Shock. 47:93–99