PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Polymyxin B-immobilized Hemoperfusion and Mortality in Critically Ill Patients with Sepsis/Septic Shock: Protocol for a Systematic Review and Meta-Analysis
AUTHORS	Fujii, Tomoko; Ganeko, Riki; Kataoka, Yuki; Featherstone, Robin; Bagshaw, Sean; Furukawa, Toshi

VERSION 1 - REVIEW

REVIEWER	Masafumi Yamato Department of Nephrology, Osaka National Hospital, Osaka, Japan I received lecture fees from Baxter.
REVIEW RETURNED	25-Jun-2016

GENERAL COMMENTS	I also think your review will help guide treatment recommendations of sepsis or septic shock in the clinical practice guidelines. I have two comments to your manuscript. 1) It was reported that PMX-HP therapy given to patients with septic shock for longer than 2 hours may be more effective. In this protocol for a Systematic Review and Meta-analysis, we wonder if the duration time of PMX-HP therapy could influence on the mortality, or not. If so, we would recommend that you discuss as study limitation in discussion. 2) In septic shock, renal-replacement-therapy (RRT) for septic AKI was often required. Please tell me that you can evaluate the frequency of use or duration of RRT as secondary outcomes.

REVIEWER	Eric Schmidt University of Colorado Denver, United States
REVIEW RETURNED	23-Aug-2016

GENERAL COMMENTS	Fujili and colleagues propose a systematic review and (if appropriate) meta-analysis of polymyxin B-immobilized hemoperfusion in sepsis. This is an interesting and dynamic topic, given the promising findings of the EUPHAS study and the disappointing findings of the ABDOMIX study. Accordingly, there is need for a systematic review of the literature regarding polymyxin B-immobilized hemofiltration in sepsis. A few questions are raised. As my expertise is sepsis pathogenesis (and not statistical analysis), these questions are limited to biologic plausibility and clinical impact.

	1. The pending EUPHRATES study represents the largest randomized controlled trial of polymyxin B-immobilized hemofiltration in sepsis. As the authors are aware (one of whom is on the EUPHRATES steering committee), this study has a goal enrollment of 650 patients, nearly equaling the total enrollment of all RCTs on this topic (spanning Nakamura et al's 1999 Inflamm Res report to Payen et al's 2015 ABDOMIX study). Thus, any systematic review/meta-analysis of polymyxin B-immobilized hemofiltration in sepsis would become rapidly irrelevant without inclusion of EUPHRATES data. The performance/publication of any analyses should be deferred until these data are available for inclusion. According to Clinicatrials.gov, enrollment has completed on this study, with publication expected in 2017. 2. A major value of this systematic review is identification of specific patient "endotypes" that may have particular benefit from polymyxin B-immobilized hemofiltration, allowing for more targeted implementation of this therapy in future randomized controlled trials. Thus, the inclusion of a priori subgroup analyses (as described on page 16) is appreciated, despite recognized statistical concerns. I would recommend an additional subgroup analysis according to the presence or absence of culture-proven gram (-) infection, as a common critique levied against negative studies of polymyxin B-immobilized hemofiltration is that only certain infection types benefit from endotoxin removal. Minor comments: 1. It would be interesting to determine if there are differences between non-treated control patients (who did not receive a two-lumen catheter) and "sham" patients, who did receive a catheter. This would provide guidance for future studies, as it would reassure that use of non-treated control patients approximates the outcomes of sham-treated patients. 2. The Discussion section of the final manuscript would benefit from a brief review of why polymyxin-B-immobilized hemoperfusion is expected to benefit patients. Is it only endotoxin removal? Is there potentially clearance of activated neutrophils?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1 (Dr. Masafumi Yamato)

1) It was reported that PMX-HP therapy given to patients with septic shock for longer than 2 hours may be more effective. In this protocol for a Systematic Review and Meta-analysis, we wonder if the duration time of PMX-HP therapy could influence on the mortality, or not. If so, we would recommend that you discuss as study limitation in discussion.

Response: We agree with the reviewer. We have added duration of treatment to subgroup analyses for treatment intensity.

2) In septic shock, renal-replacement-therapy (RRT) for septic AKI was often required.
Please tell me that you can evaluate the frequency of use or duration of RRT as secondary outcomes.

Response: We have added a subgroup analysis of patients with and without AKI, and we would extract the number of patients with AKI and treated with RRT for each study.

Response to Reviewer 2 (Dr. Eric Schmidt)

1. The pending EUPHRATES study represents the largest randomized controlled trial of polymyxin B-immobilized hemofiltration in sepsis. As the authors are aware (one of whom is on the EUPHRATES steering committee), this study has a goal enrollment of 650 patients, nearly equaling the total enrollment of all RCTs on this topic (spanning Nakamura et al's 1999 Inflamm Res report to Payen et al's 2015 ABDOMIX study). Thus, any systematic review/meta-analysis of polymyxin B-immobilized hemofiltration in sepsis would become rapidly irrelevant without inclusion of EUPHRATES data. The performance/publication of any analyses should be deferred until these data are available for inclusion. According to Clinicatrials.gov, enrollment has completed on this study, with publication expected in 2017.

Response: We appreciate the Reviewer's comment. We plan to include the results of EUPHRATES trial in this SR.

2. A major value of this systematic review is identification of specific patient "endotypes" that may have particular benefit from polymyxin B-immobilized hemofiltration, allowing for more targeted implementation of this therapy in future randomized controlled trials. Thus, the inclusion of a priori subgroup analyses (as described on page 16) is appreciated, despite recognized statistical concerns. I would recommend an additional subgroup analysis according to the presence or absence of culture-proven gram (-) infection, as a common critique levied against negative studies of polymyxin B-immobilized hemofiltration is that only certain infection types benefit from endotoxin removal.

Response: We agree with the Reviewer's recommendation. We have added two subgroup analyses as below:

- Culture positive sepsis versus others
- Confirmed gram negative sepsis versus others

Minor comments:

1. It would be interesting to determine if there are differences between non-treated control patients (who did not receive a two-lumen catheter) and "sham" patients, who did receive a catheter. This would provide guidance for future studies, as it would reassure that use of non-treated control patients approximates the outcomes of sham-treated patients.

Response: This is an interesting comment by the Reviewer. We will extract details of each trials protocol for delivery the intervention for the control groups in each study, and where applicable, the use of sham hemoperfusion. The influence of sham control will be evaluated and reported.

2. The Discussion section of the final manuscript would benefit from a brief review of why polymyxin-B-immobilized hemoperfusion is expected to benefit patients. Is it only endotoxin removal? Is there potentially clearance of activated neutrophils?

Response: We appreciate the Reviewer's comment. We have now added some description of the reported mechanisms for how PMX-HP may provide benefit.

"The role of endotoxin in sepsis is well established in literature9,10. PMX-HP was developed to remove circulating endotoxin2,3, which leads to decreases in inflammatory cytokines and mediators. PMX-HP has also been reported to adsorb activated neutrophils24 and monocytes25 in septic patients. A variety of small open-label clinical trials have been published with generally promising results13. Nevertheless, data from previous studies should be considered as inconclusive, as those trials inherit high risk of bias, i.e. underpowered or unblinded. "

VERSION 2 – REVIEW

REVIEWER	Masafumi Yamato Department of Nephrology, Osaka National Hospital, Osaka, Japan
REVIEW RETURNED	21-Sep-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Eric Schmidt University of Colorado Denver, USA
REVIEW RETURNED	06-Sep-2016

GENERAL COMMENTS	The authors have satisfactorily addressed my questions. I look forward to their final systematic review.