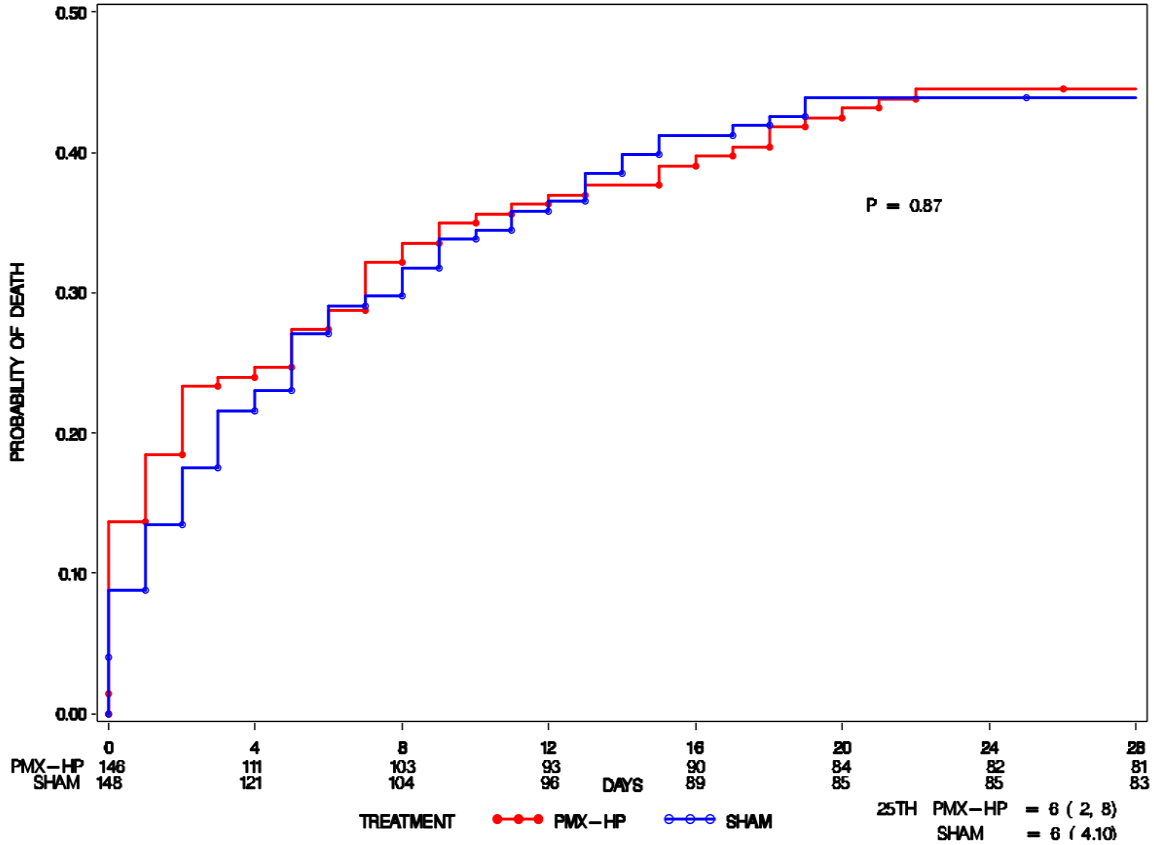
Supplementary Online Content

Dellinger RF, Bagshaw SM, Antonelli M, et al. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level:the EUPHRATES randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.14618

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1a Probability of death for all participants

Kaplan Meier curve truncated at 28 days stratified by PMX-HP and sham treatment.

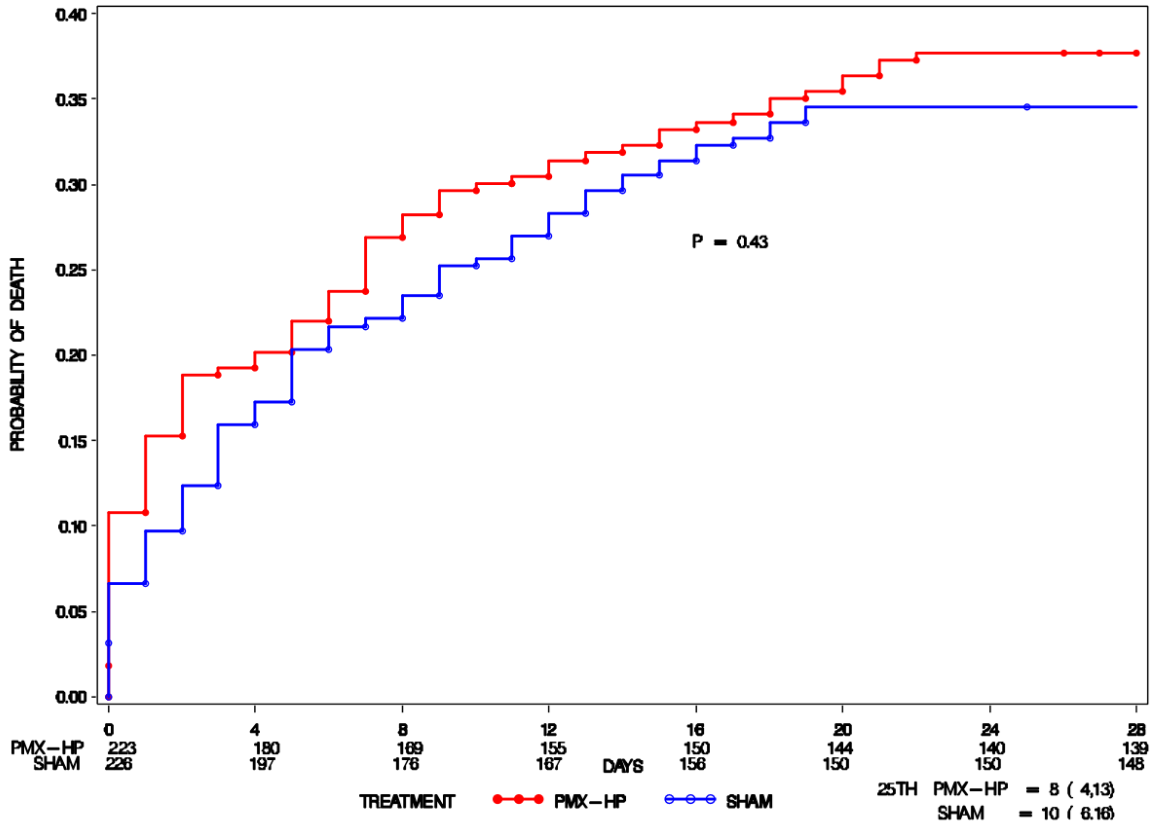


Abbreviations: PMX-HP, polymyxin B hemoperfusion

P value obtained using log-rank test

25th percentile for reaching the event (death) for the PMX group was 6 [IQR 2,8] and for sham is

eFigure 1b Probability of death for the population with multiple organ dysfunction score (MODS) >9. Kaplan Meier curve truncated at 28 days stratified by PMX-HP and sham treatment



Abbreviations: PMX-HP, polymyxin B hemoperfusion

P value obtained using log-rank test

25th percentile for reaching the event (death) for the PMX-HP group was 8 [IQR 4,13] and for sham 10 [IQR 6,16]

eTable 1. Time from randomization to receipt of intervention

	All participants[a]		MODS >9 population[a]	
	PMX-HP (n=212)	**SHAM (n=220)**	**PMX-HP (n=129)**	**SHAM (n=145)**
Time, hours: minutes, Mean (95% CI)	4:02 (3:42 to 4:24)	2:58 (2:37 to 3:21)	4:03 (3:35 to 4:33)	3:00 (2:33 to 3:27)

Abbreviations: IQR, interquartile range; MODS, multiple organ dysfunction score, PMX-HP, Polymyxin B hemoperfusion.

[a]Participants who were randomized and not treated are not included in this analysis.

eTable 2. Secondary and exploratory endpoints for the All Participants and MODS >9 populations

	All Participants Population (n=450)				MODS >9 Population (n=295)			
Secondary Endpoints[a]	**PMX-HP (n=224)**	**SHAM (n=226)**	**Difference (95% CI)**	***P* Value**[b]	**PMX-HP (n=147)**	**SHAM (n=148)**	**Difference (95% CI)**	***P* Value**[b]
Change in MODS[c] (mean [SD])	-2.2 (3.6)	-1.6 (3.3)	-0.48 (-1.1 to 0.14)	0.13	-3.0 (3.7)	-2.3 (3.3)	-0.7 (-1.6 to 0.1)	0.08
Change in MAP (mean [SD]), mmHg	9.4 (17.3)	4.1 (14.4)	5.5 (2.5 to 8.6)	<0.005	8.1 (16.0)	3.9 (14.1)	4.5 (0.7 to 8.3)	0.02
Change in serum creatinine (mean [SD]), mg/dL	0.2 (3.3)	0.0 (1.6)	0.18 (-0.3 to 0.7)	0.48	-0.1 (1.4)	0.0 (1.6)	0.2 (-0.3 to 0.8)	0.40
Exploratory Endpoints[a]								
Change in PO_2/FiO_2 ratio (mean [SD])	47 (104)	24 (129)	23 (1.3 to 44.7)	0.22	40 (104)	24 (129)	16 (-10.9 to 42.9)	0.54
Change in total bilirubin (mean [SD]), mg/dL	0.4 (3.5)	0.5 (2.2)	0.1 (-0.4 to 0.6)	0.59	0.5 (4.2)	0.8 (2.6)	0.3 (-0.5 to 1.1)	0.80
Change in platelets (mean [SD]),$10^3/\mu L$	-54 (65)	-44 (78)	10 (-3.3 to 23.3)	0.05	-51 (68)	-44 (78)	7 (-9.8 to 23.8)	0.27
Change in AKIN AKI[d] score, (n,%)	-0.02 (1.2)	0.07 (1.0)	0.09 (-0.1 to 0.3)	0.43	-0.08 (1.2)	0.2 (1.1)	0.28 (0.02 to 0.54)	0.10
Change in CVI[e] (mean [SD])	-3.9 (3.7)	-3.4 (3.9)	0.5 (-0.2 to 1.2)	0.14	-4.3 (3.7)	-3.3 (4.0)	1.0 (0.1 to 1.9)	0.07
MV-free days to day 28 (mean [SD])	12.0 (11.4)	10.7 (10.5)	1.3 (-0.7 to 3.3)	0.17	12.7 (10.9)	9.8 (10.0)	2.9 (0.5 to 5.3)	0.02
median (range)	14 (0-28)	14 (0-28)	-	-	17 (0-28)	6.0 (0-29)	-	-
RRT-free days to day 28 (mean [SD])	14.7 (13.1)	15.0 (12.7)	0.3 (-2.1 to 2.7)	0.85	12.3 (12.8)	12.3 (12.5)	0.95 (-2.9 to 2.9)	0.10
median (range)	17.0 (0-28)	16.0 (0-28)	-	-	9.0 (0-28)	10.0 (0-28)	-	-
Hospital stay, days (mean [SD])	23.2 (7.2)	23.3 (7.1)	0.1 (-1.2 to 1.4)	0.81	23.9 (6.7)	24.6 (6.2)	0.7 (-0.8 to 2.2)	0.36
median (range)	28.0 (2-28)	28.0 (5-28)	-	-	28.0 (2-28)	28.0 (5-28)	-	-
Mortality at 90-days, (n,%)	95/223 (42.6)	91/226 (40.3)	2.3 (-6.8 to 11.4)	0.56	71/146 (48.6)	72/148 (48.7)	0.0 (-11.1 to 11.4)	0.99
Mortality at 6-months, (n,%)	101/219 (46.1)	93/223 (41.7)	4.4 (-4.8 to 13.7)	0.35	75/145 (51.7)	73/146 (50.0)	1.7 (-9.8 to 13.2)	0.77
Mortality at 1-year, (n,%)	110/219 (50.2)	94/223 (42.2)	8.1 (-1.2 to 17.3)	0.10	79/145 (54.5)	74/146 (50.7)	3.8 (-7.7 to 15.3)	0.52
Type/site of infection								
Gram negative infection, (n,%)	22/53 (42)	11/30 (37)	4.8 (-16.9 to 26.6)	0.66	17/36 (47)	9/21 (43)	4.4 (-22.4 to 31.1)	0.75
Gram positive infection, (n,%)	16/49 (33)	18/51 (35)	2.6 (-21.2 to 15.9)	0.78	12/31 (39)	17/41 (41)	2.8 (-25.6 to 20.1)	0.81
Mixed infection, (n,%)	12/32 (38)	18/51 (35)	2.2 (-19.1 to 23.5)	0.84	11/21 (52)	16/33 (48)	3.9 (-23.4 to 31.2)	0.78
Pulmonary (either suspected or documented), (n,%)	28/75 (37)	33/87 (38)	0.6 (-15.6 to 14.4)	0.94	23/50 (46)	26/56 (46)	0.4 (-19.4 to 18.6)	0.96
Intra-abdominal (suspected or documented), (n,%)	25/71 (35)	24/80 (30)	5.6 (-9.3 to 20.5)	0.49	19/48 (40)	21/56 (38)	2.1 (-16.7 to 20.8)	0.83

Abbreviations: AKIN AKI=acute kidney injury network acute kidney injury; CVI= cumulative vasopressor index; ITT, intent to treat; MODS= multiple organ dysfunction score ; MAP= mean arterial pressure ; MV= mechanical ventilation ; PMX-HP= PO2/FiO2= ; RRT= renal replacement therapy ; SD= standard deviation

[a]All change endpoints are baseline to day 3.

[b]P values were calculated for continuous variables as analysis of covariance or mixed model and χ^2 for categorical variables as unless cell in the 2 by 2 table contains < 5 events, then Fishers Exact used.

[c]MODS -measure of altered organ function in acutely ill patients using 6 organ systems with weighted scores (range of score 0 is for normal to score of 4 as the most severe) of each organ system (MODS range 0 to 24). A higher score is associated with greater burden of organ dysfunction. A MODS of 9 to 12 points has a mortality of approximately 25%. Prior to the protocol amendment the MODS score was calculated at baseline. After the amendment, MODS >9 was included at the time of screening.

[d]AKIN AKI classification scheme for acute kidney injury using changes in baseline serum creatinine and urine output. Range: No AKI to Stage 3 AKI. Stage 1 AKI defined as an increase in serum creatinine (SCr) ≥ 0.3 mg/dL over 48 hours or ≥1.5 x baseline over 7 days or an episode of urine output (UO) <0.5 mL/kg/hr for ≥6 hours; Stage 2 AKI defined as an increase in SCr ≥2x baseline or UO <0.5 mL/kg/hr for ≥12 hours; Stage 3 AKI defined as an increase in SCr ≥ 3x baseline or UO <0.3 ml/kg/hr for ≥24 hours or anuria for ≥12 hours. Stage 2 and 3 are associated with increased mortality. Among patients with AKI and sepsis, mortality is approximately 30%. AKIN AKI stage was obtained at baseline.

[e]CVI score-cumulative points for equivalent doses of vasopressor support at a point in time. Dose points range from 1-4 for each vasopressor (dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin). Total CVI score range 1-20; CVI score 16-20 = 5-6 high dose vasopressors). CVI score was obtained at baseline with a single score calculated for the vasopressor dose at the time of the assessment.

eTable 3 EAA values and change from baseline for all participants, per protocol (two PMX –HP or two Sham treatments).

EAA Value	PMX-HP		Sham		Change from baseline Mean Difference (95% CI)	*P* Value[a]
	Total (n)	Mean (SD)	Total (n)	Mean (SD)		
Baseline[b] EAA value	173[e]	0.79 (0.13)	202[e]	0.77 (0.17)	--	--
Day 2[c] EAA value	163	0.71 (0.23)	201	0.71 (0.23)	0.003 (-0.04 to 0.05)	0.88
Day 3[d] EAA value	158	0.66 (0.21)	195	0.65 (0.22)	-0.007 (-0.06 to 0.05)	0.81

Abbreviations: CI, confidence interval; EAA, endotoxin activity assay; MODS, multiple organ dysfunction score; PMX-HP, Polymyxin B hemoperfusion; SD, standard deviation.
Note: All EAAs with values greater than 1 have been assigned a maximum value of 1. Patients with an undefined change from baseline, because of missing data, were excluded.

[a] Results of mixed model

[b] Baseline EAA is the screening/eligibility EAA.

[c] Day 2 EAA is the EAA approximately 10 hours (±30mins) after completion of 2nd treatment.

[d] Day 3 EAA is 24 hours after Day 2.

[e]Excludes subjects who did not receive two PMX-HP or sham treatments.

eTable 4 EAA values and change from baseline for participants with MODS >9, per protocol (two PMX –HP or two Sham treatments).

EAA Value	PMX-HP		Sham		Change from baseline Mean Difference (95% CI)	*P* Value[a]
	Total (n)	Mean (SD)	Total (n)	Mean (SD)		
Baseline[b] EAA value	115[e]	0.79 (0.12)	129[e]	0.77 (0.12)	---	---
Day 2[c] EAA value	108	0.72 (0.19)	122	0.70 (0.19)	-0.01 (-0.07 to 0.04)	0.62
Day 3[d] EAA value	110	0.67 (0.19)	128	0.65 (0.20)	0.02 (-0.03 to 0.07)	0.93

Abbreviations: CI, confidence interval; EAA, endotoxin activity assay; MODS, multiple organ dysfunction score; PMX-HP, Polymyxin B hemoperfusion; SD, standard deviation.

Note: All EAAs with values greater than 1 have been assigned a maximum value of 1. Patients with an undefined change from baseline, because of missing data, were excluded.

[a] Results of mixed model

[b] Baseline EAA is the screening/eligibility EAA.

[c] Day 2 EAA is the EAA approximately 10 hours (±30mins) after completion of 2nd treatment.

[d] Day 3 EAA is 24 hour after Day 2.

[e]Excludes subjects who did not receive two PMX-HP or sham treatments.

eTable 5. Serious adverse events among participants randomized and had treatment initiated. Reported for an occurrence of 5 events or more.

Event	**PMX-HP n=212 n (%)**	**Sham n=220 n (%)**
Subject with any SAE	**138 (65.1)**	**126 (57.3)**
Worsening sepsis	23 (10.8)	20 (9.1)
Worsening septic shock	14 (6.6)	17 (7.7)
Worsening multi organ failure	14 (6.6)	12 (5.5)
Cardiac arrest/cardio-respiratory arrest	8 (3.8)	20 (9.0)
Respiratory failure	8 (3.8)	9 (4.1)
Thrombocytopenia	6 (2.8)	4 (1.8)
Acute kidney injury	3 (1.4)	6 (2.7)

SAE=serious adverse event; PMX-HP=polymyxin-B hemoperfusion

eTable 6. Adverse events associated with the device (PMX-HP cartridge), its components, heparin and central venous catheter among patients randomized, and had treatment initiated.

	PMX-HP (n=212)	**Sham (n=220)**
	n (%)	**n (%)**
Adverse Event	**11 (5.2)**	**5 (2.3)**
Related to PMX-HP	**2 (0.9)**	**0 (0.0)**
Hypotension	2 (0.9)	0
Related to Heparin	**5 (2.4)**	**4 (1.8)**
Thrombocytopenia	3	2
Catheter site hemorrhage	1	0
Hematuria	1	1
Heparin induced thrombocytopenia	0	1
Related to Catheter	**3(1.4)**	**1(0.5)**
Insertion site hemorrhage	1	0
Deep vein thrombosis	2	0
Vena cava thrombosis	0	1

PMX-HP=polymyxin-B hemoperfusion