## **Supplemental Online Content**

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eAppendix. Calculation of Norepinephrine Equivalent (NEE)

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eReference.

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

## eAppendix. Calculation of Norepinephrine Equivalent (NEE)

NEE = Noradrenaline dose (mcg/kg/min) + Adrenaline dose (mcg/kg/min) +  $1/100 \times$  dopamine dose (mcg/kg/min) + 0.1 if noted to be on vasopressin

Note that the dose of vasopressin was not recorded in the ADRENAL study. The above adjustment was based on the typical starting dose of vasopressin 0.04u/min, and a conversion factor of 2.5. (1)

eTable 1: Outcomes for those requiring KRT

Variables	<b>KRT</b> N = 701	<b>No KRT</b> N = 2,460	p-value
Days alive and out of the ICU, mean	40.6 (36.3)	65.1 (31.3)	< 0.001
(SD)			
Days alive and out of the hospital,	25.8 (29.2)	46.0 (31.3)	< 0.001
mean (SD)			
90-day mortality	312 / 698 (44.7%)	486 / 2442 (19.9%)	< 0.001
6-month mortality	328 / 695 (47.2%)	561 / 2407 (23.3%)	< 0.001
Hospital Readmission Rates	38 / 701 (5.4%)	201 / 2460 (8.2%)	0.02
Quality of life scores			
6-month QoL EQ5D5L Utility score	0.3 (0.4)	0.5 (0.4)	< 0.001
(mean, SD) <sup>1</sup>			
QoL Utility scores with deceased	0.6 (0.4)	0.7 (0.3)	0.36
patients excluded (sensitivity analysis) <sup>2</sup>			
ED5D5L Visual Analogue Scale	70.9 (20.4)	71.2 (20.9)	0.78
(mean, SD) <sup>3</sup>			

- 1) Deceased patients coded '0', for this primary analysis.
- 2) Sensitivity analysis which includes only survivors.
- 3) Only survivors included

eTable 2: Sensitivity Analyses

Outcomes	Treatment allocation						
	Hydrocortisone	Placebo	**OR/MD (95% CI)**	p-value			
Adjusted analysis for other predictors of KRT requirement 1							
Use of KRT <sup>1</sup>	329 / 1,589	372 / 1,572	OR 0.81 [0.68 - 0.97]	0.02			
	(20.7%)	(23.7%)					
Number of days alive and free for	69.6 (34.0)	68.1 (35.0)	MD 1.60 [-0.73 - 3.93]	0.18			
KRT <sup>1</sup>							
Analysis excluding patients who c	Analysis excluding patients who commenced KRT <1 day after randomisation (as well as KRT at						
baseline and/or chronic dialysis re	equirement) <sup>2</sup>		·				
Use of KRT	189 / 1,449	219 / 1,419	OR 0.82 [0.66 – 1.02]	0.08			
	(13.0%)	(15.4%)					
Analysis excluding patients who commenced KRT <2 days after randomisation (as well as KRT at							
baseline and/or chronic dialysis re	equirement) <sup>2</sup>		·				
Use of KRT	114 / 1,374	144 / 1,344	OR 0.78 [0.59 – 1.01]	0.06			
	(8.3%)	(10.7%)					

<sup>1.</sup> adjusted for age, sex, APACHE II score, bilirubin at enrolment, primary site of infection, time from the onset of shock to randomization, use of vasopressin and last MAP at enrolment as fixed effects.

<sup>2.</sup> adjusted for admission type as a fixed effect, and sites as a random effect, only.

eTable 3: Other Outcomes associated with KRT Status

Variables	<b>KRT</b> N = 701	<b>No KRT</b> N = 2,460	p-value
Time to shock resolution (days, mean (SD)	6.3 (6.8)	3.7 (4.1)	<0.001
Persistent shock resolution (N, %)	525 / 701 (75%)	2,293 / 2452 (94%)	<0.001

eTable 4: Associations with days alive and free of KRT - univariate and multivariate models

Male       -2.90 (-8.74, 2.94)       -3.64 (-9.49, 2.21)         Weight (in kg)       0.22 (0.12, 0.32)       < 0.001		Univariate		Multivariate	
Sex	Variables	MD (95% CI)		MD (95% CI)	
Female	Age at randomisation (years)	-0.54 (-0.73, -0.34)	< 0.001	-0.52 (-0.72, -0.31)	< 0.001
Male       -2.90 (-8.74, 2.94)       -3.64 (-9.49, 2.21)         Weight (in kg)       0.22 (0.12, 0.32)       < 0.001       0.19 (0.08, 0.29)       < 0.001         APACHE II Score       -0.37 (-0.75, 0.02)       0.06       -0.06 (-0.47, 0.35)       0.78         High bilirubin       -0.08 (-0.15, -0.01)       0.03       -0.11 (-0.18, -0.04)       0.003         Source of admission       -0.91 (-16.64, -       -3.16 (-10.66, 4.34)			0.33		0.22
Weight (in kg)         0.22 (0.12, 0.32)         <0.001         0.19 (0.08, 0.29)         <0.001           APACHE II Score         -0.37 (-0.75, 0.02)         0.06         -0.06 (-0.47, 0.35)         0.78           High bilirubin         -0.08 (-0.15, -0.01)         0.03         -0.11 (-0.18, -0.04)         0.003           Source of admission         0.05         -0.316 (-10.66, 4.34)         0.75           Accident and Emergency Department	Female	_		_	
APACHE II Score	Male	-2.90 (-8.74, 2.94)		-3.64 (-9.49, 2.21)	
High bilirubin	Weight (in kg)	0.22 (0.12, 0.32)	< 0.001	0.19 (0.08, 0.29)	< 0.001
Source of admission	APACHE II Score	-0.37 (-0.75, 0.02)	0.06	-0.06 (-0.47, 0.35)	0.78
Accident and Emergency Department Hospital Floor (i.e. wards) -9.19 (-16.64, 3.16 (-10.66, 4.34) 1.74)  Transfer from another ICU 6.10 (-7.55, 19.75) 1.94 (-11.51, 15.38)  Transfer from another hospital (except from another ICU) 15.38  Transfer from another hospital (except from another ICU) ICU) Admitted from Theatre following EMERGENCY Admitted from Theatre following ELECTIVE surgery Admitted from Theatre following ELECTIVE surgery -7.59 (-24.94, 9.75) 3.75 (-13.60, 21.09)  Admission type Non-operative Operative -6.26 (-12.87, 0.34)  Primary site of infection Pulmonary -5.44 (-13.83, 2.94) -2.41 (-11.22, 6.39) Blood -3.41 (-11.32, 4.51) -2.52 (-10.25, 5.21) Urinary 0.20 (-7.81, 8.20) -0.05 (-8.56, 8.46) Other 11.42 (0.45, 22.39) 12.80 (1.79, 23.82)  First organism Staphylococcus Other gram positives Gram Negatives -6.93 (-23.68, 9.83) Other (incl nil identified)  Bacterneemia Absence -Presence -5.00 (-2.05, 12.06)  Use of nephrotoxic antibiotics at randomization 0.08	High bilirubin	-0.08 (-0.15, -0.01)	0.03	-0.11 (-0.18, -0.04)	0.003
Hospital Floor (i.e. wards)	Source of admission	, , ,	0.05	,	0.75
Transfer from another ICU  Transfer from another ICU  Transfer from another hospital (except from another count of the cou	Accident and Emergency Department	_		_	
Transfer from another ICU  Transfer from another hospital (except from another lCU)  Transfer from another hospital (except from another lCU)  Admitted from Theatre following EMERGENCY  Admitted from Theatre following ELECTIVE surgery  Admitted from Theatre following ELECTIVE surgery  Admission type  Non-operative  Operative  Operative  Thira abdominal  Admitted from theatre following  Blood  Thira abdominal  T	Hospital Floor (i.e. wards)			-3.16 (-10.66, 4.34)	)
Transfer from another hospital (except from another ICU)  Admitted from Theatre following EMERGENCY Surgery  Admitted from Theatre following ELECTIVE surgery  Admitted from Theatre following ELECTIVE surgery  Admission type  Non-operative Operative Operati	Transfer from another ICU				
Admitted from Theatre following EMERGENCY -6.84 (-14.51, 0.84) -3.10 (-11.58, 5.38) surgery  Admitted from Theatre following ELECTIVE surgery -7.59 (-24.94, 9.75) 3.75 (-13.60, 21.09)  Admission type 0.06  Non-operative -6.26 (-12.87, 0.34)  Primary site of infection -6.26 (-12.87, 0.34)  Primary site of infection -7.544 (-13.83, 2.94) -2.41 (-11.22, 6.39)  Blood -3.41 (-11.32, 4.51) -2.52 (-10.25, 5.21)  Urinary 0.20 (-7.81, 8.20) -0.05 (-8.56, 8.46)  Other 11.42 (0.45, 22.39) 12.80 (1.79, 23.82)  First organism -7.09 (-6.28, 20.46)  Gram Negatives -7.09 (-6.28, 20.46)  Gram Negatives -6.93 (-23.68, 9.83)  Other (incl nil identified) 3.53 (-9.05, 16.11)  Bacteraemia -6.96 (-2.05, 12.06)  Use of nephrotoxic antibiotics at randomization 0.08	Transfer from another hospital (except from another ICU)	2.53 (-7.26, 12.33)		,	
Admitted from Theatre following ELECTIVE surgery Admission type  O.06 Non-operative Operative Operative Operative Operative Operative Operative Onumber of infection Pulmonary Operative Other operative Other Other Other Other Other Other Other Other Other operative Other gram positives Offer gram positives Offer gram positives Offer operative Other operative Other operative O.07 O.11	Admitted from Theatre following EMERGENCY	-6.84 (-14.51, 0.84)	1	-3.10 (-11.58, 5.38)	)
Non-operative — 6.26 (-12.87, 0.34)  Primary site of infection — 0.07 — 0.11 Pulmonary — — — — — — — — — — — — — — — — — — —	Admitted from Theatre following ELECTIVE surgery	-7.59 (-24.94, 9.75)	ı		
Operative         -6.26 (-12.87, 0.34)           Primary site of infection         0.07         0.11           Pulmonary         —         —           Intra abdominal         -5.44 (-13.83, 2.94)         -2.41 (-11.22, 6.39)           Blood         -3.41 (-11.32, 4.51)         -2.52 (-10.25, 5.21)           Urinary         0.20 (-7.81, 8.20)         -0.05 (-8.56, 8.46)           Other         11.42 (0.45, 22.39)         12.80 (1.79, 23.82)           First organism           Staphylococcus         —           Other gram positives         7.09 (-6.28, 20.46)           Gram Negatives         4.91 (-8.36, 18.18)           Fungi         -6.93 (-23.68, 9.83)           Other (incl nil identified)         3.53 (-9.05, 16.11)           Bacteraemia         0.16           Absence         —           Presence         5.00 (-2.05, 12.06)           Use of nephrotoxic antibiotics at randomization         0.08	Admission type		0.06	,	
Primary site of infection       0.07       0.11         Pulmonary       —       —         Intra abdominal       -5.44 (-13.83, 2.94)       -2.41 (-11.22, 6.39)         Blood       -3.41 (-11.32, 4.51)       -2.52 (-10.25, 5.21)         Urinary       0.20 (-7.81, 8.20)       -0.05 (-8.56, 8.46)         Other       11.42 (0.45, 22.39)       12.80 (1.79, 23.82)         First organism       0.31         Staphylococcus       —         Other gram positives       7.09 (-6.28, 20.46)         Gram Negatives       4.91 (-8.36, 18.18)         Fungi       -6.93 (-23.68, 9.83)         Other (incl nil identified)       3.53 (-9.05, 16.11)         Bacteraemia       0.16         Absence       —         Presence       5.00 (-2.05, 12.06)         Use of nephrotoxic antibiotics at randomization       0.08	Non-operative	_			
Primary site of infection       0.07       0.11         Pulmonary       —       —         Intra abdominal       -5.44 (-13.83, 2.94)       -2.41 (-11.22, 6.39)         Blood       -3.41 (-11.32, 4.51)       -2.52 (-10.25, 5.21)         Urinary       0.20 (-7.81, 8.20)       -0.05 (-8.56, 8.46)         Other       11.42 (0.45, 22.39)       12.80 (1.79, 23.82)         First organism         Staphylococcus       —         Other gram positives       7.09 (-6.28, 20.46)         Gram Negatives       4.91 (-8.36, 18.18)         Fungi       -6.93 (-23.68, 9.83)         Other (incl nil identified)       3.53 (-9.05, 16.11)         Bacteraemia       0.16         Absence       —         Presence       5.00 (-2.05, 12.06)         Use of nephrotoxic antibiotics at randomization       0.08	Operative	-6.26 (-12.87, 0.34)	١		
Intra abdominal	Primary site of infection		0.07		0.11
Blood	Pulmonary	_		_	
Urinary       0.20 (-7.81, 8.20)       -0.05 (-8.56, 8.46)         Other       11.42 (0.45, 22.39)       12.80 (1.79, 23.82)         First organism         Staphylococcus       —         Other gram positives       7.09 (-6.28, 20.46)         Gram Negatives       4.91 (-8.36, 18.18)         Fungi       -6.93 (-23.68, 9.83)         Other (incl nil identified)       3.53 (-9.05, 16.11)         Bacteraemia       0.16         Absence       —         Presence       5.00 (-2.05, 12.06)         Use of nephrotoxic antibiotics at randomization       0.08	Intra abdominal	-5.44 (-13.83, 2.94)	١	-2.41 (-11.22, 6.39)	)
Other         11.42 (0.45, 22.39)         12.80 (1.79, 23.82)           First organism         0.31           Staphylococcus         —           Other gram positives         7.09 (-6.28, 20.46)           Gram Negatives         4.91 (-8.36, 18.18)           Fungi         -6.93 (-23.68, 9.83)           Other (incl nil identified)         3.53 (-9.05, 16.11)           Bacteraemia         0.16           Absence         —           Presence         5.00 (-2.05, 12.06)           Use of nephrotoxic antibiotics at randomization         0.08	Blood	-3.41 (-11.32, 4.51)		-2.52 (-10.25, 5.21)	)
First organism         0.31           Staphylococcus         —           Other gram positives         7.09 (-6.28, 20.46)           Gram Negatives         4.91 (-8.36, 18.18)           Fungi         -6.93 (-23.68, 9.83)           Other (incl nil identified)         3.53 (-9.05, 16.11)           Bacteraemia         0.16           Absence         —           Presence         5.00 (-2.05, 12.06)           Use of nephrotoxic antibiotics at randomization         0.08	Urinary	0.20 (-7.81, 8.20)		-0.05 (-8.56, 8.46)	
First organism         0.31           Staphylococcus         —           Other gram positives         7.09 (-6.28, 20.46)           Gram Negatives         4.91 (-8.36, 18.18)           Fungi         -6.93 (-23.68, 9.83)           Other (incl nil identified)         3.53 (-9.05, 16.11)           Bacteraemia         0.16           Absence         —           Presence         5.00 (-2.05, 12.06)           Use of nephrotoxic antibiotics at randomization         0.08	Other	11.42 (0.45, 22.39)		12.80 (1.79, 23.82)	<u> </u>
Staphylococcus         —           Other gram positives         7.09 (-6.28, 20.46)           Gram Negatives         4.91 (-8.36, 18.18)           Fungi         -6.93 (-23.68, 9.83)           Other (incl nil identified)         3.53 (-9.05, 16.11)           Bacteraemia         0.16           Absence         —           Presence         5.00 (-2.05, 12.06)           Use of nephrotoxic antibiotics at randomization         0.08	First organism		0.31		
Gram Negatives       4.91 (-8.36, 18.18)         Fungi       -6.93 (-23.68, 9.83)         Other (incl nil identified)       3.53 (-9.05, 16.11)         Bacteraemia       0.16         Absence       —         Presence       5.00 (-2.05, 12.06)         Use of nephrotoxic antibiotics at randomization       0.08	Staphylococcus	_			
Fungi	Other gram positives	7.09 (-6.28, 20.46)			
Other (incl nil identified)  Bacteraemia  Absence  Presence  0.16	Gram Negatives	4.91 (-8.36, 18.18)			
Bacteraemia 0.16 Absence	Fungi	-6.93 (-23.68, 9.83)	1		
Absence — 5.00 (-2.05, 12.06) Use of nephrotoxic antibiotics at randomization 0.08	Other (incl nil identified)	3.53 (-9.05, 16.11)			
Presence 5.00 (-2.05, 12.06) Use of nephrotoxic antibiotics at randomization 0.08	Bacteraemia		0.16		· · · · · · · · · · · · · · · · · · ·
Use of nephrotoxic antibiotics at randomization 0.08	Absence	_			
		5.00 (-2.05, 12.06)			
	Use of nephrotoxic antibiotics at randomization		0.08		
	No	_			

	Univariate	•	Multivariate	•
Variables	MD (95% CI)	p- value	MD (95% CI)	p- value
Yes	5.15 (-0.53, 10.82)			
Last MAP	0.51 (0.19, 0.83)	0.002	0.49 (0.17, 0.82)	0.003
NEE	-2.08 (-3.04, -1.11)	< 0.001	-2.09 (-3.15, -	< 0.001
			$(1.03)^1$	
MAP/NEE ratio	$0.19 (-0.12, 0.51)^2$	0.23	$-0.23 (-0.57, 0.10)^2$	0.16
Use of Vasopressin		0.51		
No	_			
Yes	2.20 (-4.39, 8.80)			
Use of Dobumatine, Milrinone or Levosimendan		0.39		
No	_			
Yes	-5.58 (-18.24, 7.07)			
Time from the onset of shock to randomisation	-0.01 (-0.04, 0.01)	0.32	-0.02 (-0.04, 0.01)	0.21
Steroid received		0.13		
No	_			
Yes	7.26 (-2.08, 16.59)			
Treatment allocation		0.75		0.65
Placebo	_		_	
Hydrocortisone	0.92 (-4.77, 6.60)		1.28-4.31, 6.87)	

<sup>1.</sup> Expressed for an increase of 0.1 unit; 2. Expressed for an increase of 100 units Multivariate model includes treatment, age, sex, weight, APACHE II score, primary site of infection, NEE, MAP/NEE, time from the onset of shock to randomisation and significant variables (p<0.05) from univariate mode

## Reference

1. Kotani Y, Di Gioia A, Landoni G, Belletti A, Khanna AK. An updated "norepinephrine equivalent" score in intensive care as a marker of shock severity. Critical Care. 2023;27(1):29.