Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial: study protocol and statistical analysis plan

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ABSTRACT

Background: Septic shock is associated with poor outcomes. Vitamin C (ascorbic acid) is a cellular antioxidant and has anti-inflammatory properties. Whether the combination therapy of vitamin C, thiamine and hydrocortisone reduces vasopressor dependency in septic shock is unclear.

Objectives: To describe the protocol and statistical analysis plan of a multicentre, open-label, prospective, phase 2 randomised clinical trial evaluating the effects of vitamin C, thiamine and hydrocortisone when compared with hydrocortisone monotherapy on the duration of vasopressor administration in critically ill patients with septic shock.

Methods: VITAMINS is a multicentre cardiovascular efficacy trial in adult patients with septic shock. Randomisation occurs via a secure website with stratification by site, and allocation concealment is maintained throughout the trial. The primary outcome is the duration of time alive and free of vasopressor administration at Day 7. Secondary outcomes include feasibility endpoints and some patient-centred outcomes. All analyses will be conducted on an intention-to-treat basis.

Conclusion: The VITAMINS trial will determine whether combination therapy of vitamin C, thiamine and hydrocortisone when compared with hydrocortisone increases vasopressor-free hours in critically ill patients with septic shock. The conduct of this study will provide important information on the feasibility of studying this intervention in a phase 3 trial.

Trial registration: ClinicalTrials.gov, identification No. NCT03333278.

Crit Care Resusc 2019; 21 (2): 119-125

Sepsis is a dysregulated host response to infection. Adjunctive therapies targeting the inflammatory cascade are being increasingly explored, although, to date, they have failed to demonstrate consistent benefit, and sepsis and septic shock continue to lead to poor outcomes. Hospital mortality in patients with septic shock remains as high as 22% in Australia and New Zealand.[1] From a global perspective, perhaps 50 million patients with sepsis are treated in hospitals every year.[2]

Moreover, the mortality from sepsis and septic shock in middle and low income countries is reported to be as high as 60%.[3-5] In addition, patients with sepsis have numerous short and long term complications and are at increased risk of death for up to several years following the acute event.[6-9] Thus, effective, low cost and safe treatment strategies are urgently needed.

In animal models, exogenous vitamin C (ascorbic acid) has been reported to attenuate the inflammatory cascade, reduce the endothelial injury characteristic of sepsis, enhance the release of endogenous catecholamines, and improve vasopressor responsiveness.[10-15] These effects have resulted in reduced organ injury and increased survival in some models. However, their effects in critically ill humans are unclear due to insufficient clinical data.[16]

Relative thiamine deficiency frequently occurs in critically ill patients with sepsis.[17] Thiamine increases the conversion of glyoxylate, a by-product of vitamin C metabolism, to oxalate. Oxalate is excreted by the kidney, and serum concentrations will increase with renal impairment.[18] In patients with renal impairment receiving high dose vitamin C, supersaturation of serum with oxalate may result in tissue deposition as well as crystallisation in the kidney. Also, thiamine can reverse oxidative stress that is not related to thiamine deficiency, suggesting that thiamine may act as a site-directed antioxidant.[19] Exogenous thiamine may, therefore, limit oxidative injury and restore energy production.[20]

A single-centre retrospective before-and-after study of 94 patients supported the concept that administration of high dose intravenous vitamin C (1.5 g four times per day), together with high dose intravenous thiamine (200 mg twice a day) and hydrocortisone (50 mg four times per day) may be useful. The combination therapy was reported to reduce the time of vasopressor administration and mortality in patients with severe sepsis and septic shock.[21] In this study, hydrocortisone was administered to ≈ 60% of patients in the control group. Since this study was published, the ADRENAL (Adjunctive Corticosteroid Treatment in Critically

Ill Patients with Septic Shock) trial established that the duration of vasopressor is reduced with hydrocortisone administration.[22]

The Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial is a multicentre pilot feasibility randomised clinical trial to further evaluate the role of vitamin C and thiamine. The VITAMINS trial is managed by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) at Monash University and is supported by the Intensive Care Foundation (www.intensivecarefoundation.org.au). This report presents the trial protocol and the statistical analysis plan. The VITAMINS trial is registered with ClinicalTrials.gov (identification No. NCT03333278)

Objectives

The primary aim of the VITAMINS trial is to determine whether the intravenous administration of vitamin C, thiamine and hydrocortisone in patients with septic shock increases the duration of time alive and free of vasopressor administration at Day 7 after randomisation compared with hydrocortisone alone.

Methods

Study design and participants

This is a multicentre, open-label, prospective, phase 2 randomised clinical trial. Patients admitted to a study intensive care unit (ICU) with a primary diagnosis of septic shock will be screened for inclusion.

Study population

Inclusion criteria

All diagnostic criteria for septic shock (based on the Sepsis-3 consensus[23]) have to be fulfilled simultaneously within a 24-hour period before enrolment. In addition, the patient must be receiving a vasopressor infusion continuously at the time of enrolment.

Thus, inclusion criteria include:

- suspected or documented infection;
- acute increase of ≥ 2 Sequential Organ Failure Assessment (SOFA) points due to the infection;
- need for vasopressor therapy to maintain the mean arterial pressure (MAP) > 65 mm Hg for > 2 hours; and
- lactate > 2 mmol/L, despite adequate fluid resuscitation.

Exclusion criteria

Patients will be excluded from the study if any of the criteria listed in Table 1 apply.

Randomisation

Allocation concealment

A permuted block randomisation method with variable block sizes of 2, 4 and 6 and stratified by site was developed. The random allocation sequence was generated centrally using a computer software program at the coordinating centre, the ANZIC-RC. This was then embedded into the Research Electronic Data Capture (REDCap) system, which is a secure web application for managing online data collection.[24] ICU patients are allocated to either group in a 1:1 ratio as soon as possible after fulfilling the eligibility criteria, and randomisation is performed using the REDCap system at each study site. To limit selection bias, site investigators, site research coordinators, and statisticians cannot access the allocation sequence.

Blinding

The VITAMINS trial is an open-label study; accordingly, all site personnel are aware of the study intervention assigned to the participants.

Study interventions

Intervention group

Patients in the intervention group receive intravenous vitamin C (1.5 g, every 6 hours), thiamine (200 mg, every 12 hours), and hydrocortisone (50 mg, every 6 hours). Vitamin C is diluted in a 100 mL solvent of either 0.9% saline or 5% dextrose in water and infused over one hour. For patients in whom the treating clinician wishes to restrict fluid administration, vitamin C (1.5 g) can be diluted into 50 mL of solvent. Thiamine (200 mg) is added to a 100 mL solvent of either 0.9% saline or 5% dextrose in water and infused over 30–60 minutes. For patients in whom the treating clinician wishes to restrict fluid administration, thiamine can be diluted into 50 mL of solvent. Hydrocortisone is administered by slow intravenous injection over at least 30 seconds. Hydrocortisone can be stopped or tapered after the completion of study treatment as per the treating clinician. We recommend a taper of 3 days.

Control group

Patients in the control arm of the study receive hydrocortisone 50 mg intravenous every 6 hours.[22,25] Hydrocortisone is administered by slow intravenous injection over at least 30 seconds. Hydrocortisone can be stopped or tapered after the completion of study treatment as per the treating clinician. Patients also receive thiamine if clinically indicated at the discretion of the attending ICU clinician. As the administration of intravenous vitamin

Table 1. Exclusion criteria of the VITAMINS trial

- Age < 18 years
- Pregnancy
- DNR (do not resuscitate)/DNI (do not intubate) orders
- Death is deemed to be imminent or inevitable during this admission, and either the attending physician, patient or substitute decision maker is not committed to active treatment
- Patients with known human immunodeficiency virus (HIV) infection
- Patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Patients transferred from another intensive care unit or hospital with a diagnosis of a septic shock for > 24 hours
- Patients with a diagnosis of a septic shock for > 24 hours
- Patients with known or suspected
  - history of oxalate nephropathy or hyperoxaluria
  - short bowel syndrome or severe fat malabsorption
  - acute beri-beri disease
  - acute Wernicke encephalopathy
  - malaria
  - scurvy
  - Addison disease
  - Cushing disease
- Clinician expects to prescribe systemic glucocorticoids for an indication other than septic shock (not including nebulised or inhaled corticosteroid)
- Patient is receiving treatment for systemic fungal infection or has documented *Strongyloides* infection at the time of randomisation
- Patient with known chronic iron overload due to iron storage and other diseases
- Patient previously enrolled in this study
- Clinician expects to prescribe high dose vitamin C for another indication

C is not the usual practice currently in Australian or New Zealand ICUs, administration of intravenous vitamin C to patients allocated to the control groups is not allowed and will be reported as a protocol deviation.

Duration of the interventions

The study intervention continues until one of the following criteria for treatment cessation is met:

- all vasopressors are discontinued for 4 consecutive hours in the presence of a MAP > 65 mmHg or a target MAP set by the clinician in charge of the patient's care; or
- for the intervention group, 10 days of vitamin C and thiamine have been administered;
- for the control group, 7 days of hydrocortisone (and a taper of 3 days, if applicable) have been administered; or
- the patient is discharged from ICU; or
- contraindications to vitamin C, thiamine or hydrocortisone therapy arise; or
- death occurs; or
- serious adverse events suspected to be related to a study medication develops; or
- any permanent withholding criteria occur (consent withdrawn or consent to continue not granted).

Data collection and monitoring

All study data are collected by trained staff at each study site from source records (medical and/or nursing documentation) and entered into REDCap. Data collection includes baseline demographics, primary diagnoses, physiological parameters and pathology, interventions and documentation of deaths and other serious adverse events. The study timelines, procedures and assessments are shown in Table 2.

All data entry is monitored at the coordinating centre with site visits for source data verification conducted on an as-needed basis.

Outcomes

The primary outcome is the duration of time alive and free of vasopressor administration at Day 7 (168 hours) after randomisation. This is defined by the patient being alive at discontinuation of all vasopressors for at least 4 hours in the presence of a MAP > 65 mmHg or target MAP set by clinicians for the same 4-hour period as recorded in the ICU chart and censored at 7 days. If a patient dies while receiving vasopressor therapy following their initial septic shock episode, this patient will be assigned zero vasopressor-free hours. Once discontinuation has occurred, the patient

is considered vasopressor-free even if the patient dies after discontinuation of vasopressors for at least 4 hours before Day 7. This outcome was chosen because it has been previously used in ICU studies as an appropriate outcome for research into the resolution of septic shock.[21] Feasibility endpoints comprise important secondary outcomes; these include time from meeting eligibility criteria to the first dose of the main study drug, monthly recruitment rate, number of patients screened, randomised to the screened patient ratio, reasons for exclusion, and intervention protocol compliance. Patient-centred outcomes are listed in Table 3.

Statistical analysis plan

Sample size

In the absence of definitive data pertaining to the standard deviation of the primary outcome, our sample size calculations were done in two stages. Firstly, based on available data external to Australia and New Zealand, and secondly, based on the pooled standard deviation (SD) of the first 60 patients enrolled in this study. Assuming a conservative SD of 42 hours, a sample size of 120 patients was initially calculated to provide 90% power (two-sided $P = 0.05$), to detect a clinically relevant increase of 25 hours alive and vasopressor-free at Day 7 (eg, increase from 113 to 138 hours[21]) in the intervention group. We added a margin of one hour to 24 hours to ensure that the difference will be more than one day. Subsequently, we planned to recalculate the sample size utilising the pooled SD from the first 60 patients enrolled in the study. Because data used for this calculation were pooled, an adjustment of α level for interim analysis is unnecessary.[26] The pooled standard deviation of 51.6 was found to be substantially higher than originally anticipated. Thus, a sample size of 180 was calculated to provide 90% power to detect a 25-hour difference, with a two-sided $P = 0.05$. As the distribution of the primary outcome is not expected to follow a normal distribution, we have inflated our sample size by 15% to account for non-normality[27] and have allowed a further 5% to account for patients dropping out, resulting in a total of 216 patients required. The SD of our pooled population was further confirmed after 108 patients were recruited and found to be consistent with the SD from the first 60 patients.

Baseline characteristics and primary outcomes

All data will be assessed for normality and presented by treatment allocation. Categorical variables will be presented as frequency (%) and compared using the χ^2 tests for equal

Table 2. Study timelines and procedures — SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram

		Study period						
		Enrolment	Allocation	Post-allocation				Close-out
Timepoint		Up to -24 h	0	Every 6 h Up to 15 days	Once daily Up to 15 days	28 days or ICU discharge	Hospital discharge	90 days
Enrolment	Eligibility screen	X						
	Informed consent	Prospectively or consent to continue						
	Baseline data	X						
	Allocation		X					
Intervention	Vitamins group	Until vasopressor discontinued for 4 h or up to 10 days in the ICU						
	Control group							
Assessments	Vital status					X	X	X
	Vasopressor agents			X		X		
	Mechanical ventilation and RRT				X	X		
	Pathology				X			
	SOFA score				Up to 7 days			
	Fluid, urine output				Up to 7 days			

ICU = intensive care unit. RRT = renal replacement therapy. SOFA = Sequential Organ Failure Assessment.

Table 3. Study outcome measures

Primary outcome	▪ The duration of time alive and free of vasopressor administration at Day 7 (168 hours) after randomisation for the initial septic shock ▸ This is defined by the patient being alive at discontinuation of all vasopressors for at least 4 hours in the presence of a MAP > 65 mmHg or target MAP set by clinicians for the same 4-hour period as recorded in the ICU charts and censored at 7 days. If a patient dies of the initial septic shock while receiving vasopressor therapy, this patient will be assigned zero alive and vasopressor-free time
Feasibility outcomes	▪ Time from meeting eligibility criteria to the first dose of the main study drugs ▪ Monthly recruitment rate ▪ Number of patients screened ▪ Randomised to the screened patient ratio ▪ Reasons for exclusion ▪ Compliance with drug administration protocol
Patient-centred outcomes	▪ 28-day ICU-free days ▪ ICU mortality ▪ Hospital mortality ▪ 28-day mortality ▪ 90-day mortality ▪ Delta SOFA score at Day 3 ▪ Hospital length of stay ▪ 28-day cumulative vasopressor-free days ▪ 28-day cumulative mechanical ventilation-free days ▪ 28-day RRT-free days ▪ Acute kidney injury defined by KDIGO criteria (safety outcome) ▪ Vasopressor dose (noradrenaline equivalent dose)

ICU = intensive care unit. KDIGO = Kidney Disease: Improving Global Outcomes. MAP = mean arterial pressure. RRT = renal replacement therapy. SOFA = Sequential Organ Failure Assessment.

proportion. Continuous variables will be presented as the mean (SD) or median (interquartile range [IQR]) and compared using a Student *t* test for normally distributed variables, and a Wilcoxon rank-sum test otherwise.

All statistical analysis will be conducted on an intention-to-treat basis. No imputation will be applied to any missing data for the primary analysis, and the number of observations analysed will be reported. The primary outcome will be analysed using a Wilcoxon rank-sum test with results reported as median (IQR) and a Hodges–Lehmann estimate of absolute difference reported with 95% confidence interval (CI). Sensitivity to baseline imbalance and known covariates will be performed using quartile regression, while sensitivity to missingness will be determined using multiple imputation.

Other outcomes

Binary outcomes will be summarised using the proportions in each treatment group. Continuous outcomes will be summarised using means (SD) or medians (IQR) where appropriate.

Twenty-eight-day ICU-free days will be defined as the number of days alive and out of the ICU to Day 28. Delta SOFA score will be defined as the Day 3 SOFA score minus the pre-randomisation SOFA score. Twenty-eight-day cumulative vasopressor-free days will be defined as the total number of days that a patient was not on vasopressor support. This outcome will, therefore, include any recurrence of vasopressor requirements by summing up time being alive at discontinuation of all vasopressors in the presence of a MAP > 65 mmHg or target MAP by Day 28 after the vasopressor has been ceased at least 4 hours for initial septic shock. Adrenaline and vasopressin dose will be converted to the equivalent noradrenaline dose using the conversion scale, which has been used in previous critical care research.[28] The total vasopressor dose will be calculated as the sum of noradrenaline dose and the converted doses. The time course of vasopressor dosing will be graphed for each treatment group and compared using linear mixed effects modelling clustered at the individual patient level to examine the difference in vasopressor dose

over time. For estimation of the incidence of death by Day 28, Kaplan–Meier curves will be calculated and plotted for each of the intervention arms. For comparison of the incidence of death, as a log-rank test (two-sided) will be used, and for quantifying intervention effect, the hazard ratio of death with 95% CI will be provided based on a Cox regression model.

A two-tailed $P < 0.05$ will be used for indicating statistical significance in all analyses. Independent senior statisticians at Monash University will perform the data analysis.

Ethical considerations

Ethics and governance approvals for all aspects of the trial were obtained before commencing recruitment at each study site. In Australia, the process for obtaining consent is according to the following hierarchy:

- **Informed consent from the participant or substitute or medical treatment decision maker.** Where possible, and as authorised by law, which varies between jurisdictions, consent should be obtained from the participant or their legal surrogate, if the patient lacks decision making capacity.
- **Consent to continue.** Where it is not possible or practicable for the patient or the legal surrogate to consider the study and give consent immediately, the patient may be enrolled with a waiver of consent (for emergency medical research procedures in Victoria) and consent obtained from the participant's legal surrogate as soon as possible, provided the procedure is in accord with the requirements of the local ethics committee and applicable legislation. When appropriate, the participant's legal surrogate and, in turn, the participant will be informed of the study and will be able to withdraw consent for ongoing participation at any time.
- **Verbal/telephone consent.** In cases in which the participant's legal surrogate cannot attend the hospital to sign the consent form within the time constraints of the study, consent for patient participation in the study may be obtained over the telephone following local guidelines. The telephone conversation must be documented in the patient's medical record. As soon as the participant's legal surrogate is able to attend the hospital, they will be asked to sign a consent form and note that telephone consent was already provided.

The participant's legal surrogate will be able to withdraw their consent for the patient to participate in the study at any time without any reduction in quality of care, and if they choose to withdraw the patient, permission will be asked to use the data collected up to that time. Once subjects are recovered and are able to consider the information sheet, they will be offered the opportunity to withdraw from the study follow-up. If the patient chooses to withdraw from the study, they will be asked for permission to use their data up to the time of withdrawal.

In New Zealand, the approach to obtain consent will be consistent with the Health and Disability Code, which outlines the framework for providing treatment to patients who are unable to consent for themselves. The specific approach will be:

- to consider whether the study treatment and study participation is in the best interest of each patient; and
- to seek the advice of persons interested in the patient's welfare — as soon as it is practical and reasonable — to establish that study participation is consistent with the patient's wishes.

All participants who recover sufficiently will be given the opportunity to provide informed consent for ongoing study participation and the use of data collected for the study.

Conclusion

The VITAMINS trial is an ongoing multicentre, open-label, prospective, phase 2 randomised clinical trial to evaluate whether intravenous vitamin C, thiamine and hydrocortisone lead to more rapid resolution of vasopressor administration when compared with hydrocortisone alone in patients with septic shock. If the combination therapy suggests a degree of benefit in terms of the primary outcome and some patient-centred outcomes and the trial is shown to be feasible, these data will inform the physiological rationale of undertaking a subsequent phase 3 trial to determine the effects of this therapy on patient-centred outcomes.

Acknowledgements: All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work. The VITAMINS trial is supported by a grant from the Intensive Care Foundation (www.intensivecarefoundation.org.au). Tomoko Fuji is supported by the Japan Society for the Promotion of Science. Andrew Udy greatly acknowledges the support of the National Health and Medical Research Council of Australia (Early Career Fellowship, GNT1124532). Paul Young is supported by a Clinical Practitioner Fellowship from the Heath Research Council of New Zealand. None of these funding organisations has 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.

Competing interests

None declared.

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References

1 Kaukonen KM, Bailey M, Suzuki S, et al: Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* 2014, 311: 1308-16.
2 Fleischmann C, Scherag A, Adhikari NK, et al; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016, 193: 259-72.
3 Silva E, Pedro Mde A, Sogayar AC, et al: Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care* 2004, 8: R251-60.
4 Sales Júnior JA, David CM, Hatum R, et al: [An epidemiological study of sepsis in Intensive care units: sepsis Brazil study] [Portuguese]. *Rev Bras Ter Intensiva* 2006, 18: 9-17.
5 World Health Organization. The top 10 causes of death: leading causes of death by economy income group 2012. WHO factsheets. http://www.who.int/mediacentre/factsheets/fs310/en/index1.html (viewed Apr 2019).
6 Wang HE, Szychowski JM, Griffin R, et al. Long-term mortality after community-acquired sepsis: a longitudinal population-based cohort study. *BMJ Open* 2014, 4: e004283.
7 Prescott HC, Osterholzer JJ, Langa KM, et al: Late mortality after sepsis: propensity matched cohort study. *BMJ* 2016; 353: i2375.
8 Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; 304: 1787-94.
9 Shankar-Hari M, Ambler M, Mahalingasivam V, et al. Evidence for a causal link between sepsis and long-term mortality: a systematic review of epidemiologic studies. *Crit Care* 2016; 20: 101.
10 Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med* 2011, 39: 1454-60.
11 Han M, Pendem S, Teh SL, et al. Ascorbate protects endothelial barrier function during septic insult: role of protein phosphatase type 2A. *Free Radic Biol Med* 2010, 48: 128-35.
12 Kim SR, Ha YM, Kim YM, et al. Ascorbic acid reduces HMGB1 secretion in lipopolysaccharide-activated RAW 264.7 cells and improves survival rate in septic mice by activation of Nrf2/HO-1 signals. *Biochem Pharmacol* 2015, 95: 279-89.
13 Bornstein SR, Yoshida-Hiroi M, Sotiriou S, et al. Impaired adrenal catecholamine system function in mice with deficiency of the ascorbic acid transporter (SVCT2). *Faseb J* 2003, 17: 1928-30.
14 Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. *Biofactors* 2009, 35: 5-13.
15 Fisher BJ, Kraskauskas D, Martin EJ, et al. Attenuation of sepsis-induced organ injury in mice by vitamin C. *JPEN J Parenter Enteral Nutr* 2014, 38: 825-39.
16 Putzu A, Daems AM, Lopez-Delgado JC, et al. The effect of vitamin C on clinical outcome in critically ill patients: a systematic review with meta-analysis of randomized controlled trials. *Crit Care Med* 2019. doi: 10.1097/CCM.0000000000003700. [Epub ahead of print]
17 Donnino MW, Andersen LW, Chase M, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. *Crit Care Med* 2016; 44: 360-7.
18 Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. *Kidney Int* 2009; 75: 1264-71.
19 Gibson, GE; Zhang, H. Interactions of oxidative stress with thiamine homeostasis promote neurodegeneration. *Neurochem Int* 2002; 40: 493-504.
20 Marik PE. Hydrocortisone, ascorbic acid and thiamine (HAT Therapy) for the treatment of sepsis. Focus on ascorbic acid. *Nutrients* 2018; 10: 1762.
21 Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J: Hydrocortisone, Vitamin C and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest* 2017; 151: 1229-38.
22 Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378: 797-808.
23 Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016, 315: 801-10.
24 Paul A Harris, Robert Taylor, Robert Thielke, et al. Research electronic data capture (REDCap) — a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377-81.
25 Venkatesh B, Myburgh J, Finfer S, et al; ANZICS CTG investigators. The ADRENAL study protocol: adjunctive corticosteroid treatment in critically ill patients with septic shock. *Crit Care Resusc* 2013; 15: 83-8.
26 Pocock SJ. Current controversies in data monitoring for clinical trials. *Clin Trials* 2006; 3: 513-21.
27 Lehmann EL. Nonparametrics: statistical methods based on ranks, revised. Pearson Education [Facsimile edition], 1998, pp. 76-81.
28 Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377: 419-30.