Original article

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Intravenous thiamine as an adjuvant therapy for hyperlactatemia in septic shock patients

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Abstract

***Objective*: To assess the effectiveness of intravenous (IV) thiamine in reducing hyperlactatemia in septic shock patients.**

***Design*: Prospective, randomized controlled trial.**

***Setting*: General intensive care unit (GICU), Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur.**

***Patients and participants*: Adult patients with septic shock and hyperlactatemia (lactate ≥2 mmol/l).**

***Interventions*: IV thiamine 200 mg thrice daily for 3 days.**

***Measurements and results*: A total of 72 patients were recruited into the study. Seven patients died within 24 hours of study commencement and were dropped out. Patients were randomized into the thiamine group (TG) who received IV thiamine 200 mg diluted in 50 ml of normal saline, or placebo group (PG) who received 50 ml of normal saline infusion over 30 minutes. Arterial blood lactate samples were collected at time of enrolment, after 6, 12, 18, 24, 48, and 72 hours of study drugs administration. Relative lactate changes over 24 hours, duration of weaning off vasopressors, Sequential Organ Failure Assessment (SOFA) score changes over 72 hours, ICU length of stay (LOS) and mortality rates were compared between groups. There were no significant differences in the relative lactate changes (TG: 37.5% [4.7-59.1] vs PG: 47.8% [29.1-70.7], p=0.091), duration of vasopressors being weaned off (TG: 75.5 [48.0-131.25] vs PG: 88.0 [48.0-147.0]), SOFA score changes (TG: 3.0±3.41 vs PG: 2.7±3.3), ICU LOS (TG: 5.0 [4.0-11.0] vs PG: 6.0 [3.0-12.0]), and ICU mortality rate (TG: 14 [43] vs PG: 12 [37]). Multivariate logistic regression test showed that baseline lactate level was an independent predictor for mortality (p=0.044).**

***Conclusion*: Intravenous thiamine did not show significant improvement in relative lactate changes, time for shock reversal, SOFA scoring, ICU LOS, and mortality rate in septic shock patients with hyperlactatemia. However, baseline lactate level was shown to be an independent predictor for ICU mortality.**

Key words: Thiamine, hyperlactatemia, septic shock, intensive care unit, mortality.

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Introduction

Thiamine (vitamin B1) is an essential component in cellular metabolism. It circulates in our body as free thiamine as well as an active phosphorylated form - thiamine pyrophosphate (TPP). Thiamine pyrophosphate acts as a co-factor for mitochondrial oxidative decarboxylation process and glycolytic pathway. The deficiency or absence of thiamine causes anaerobic metabolism which could lead to lactate production with biochemical derangement. (1,2) Thiamine deficiency has been shown to be more prevalent in critically ill patients particularly in septic shock patients requiring renal replacement therapy. (3,4) The deficiency might be due to either lack of intake or increased in losses. (5)

Macro and micro-circulatory dysfunctions are often associated with septic shock patients, causing tissue hypoperfusion with elevation of serum lactate levels. (6,7) Systemic inflammatory responses in sepsis could lead to an increase in glycolysis, impairment in pyruvate dehydrogenase activity (the enzyme responsible for pyruvate entry into the glycolytic pathway) and a rise in cytoplasmic pyruvate levels. (8) A study done by Donnino et al in 2010 found that septic patients with thiamine deficiency developed lactic acidosis leading to cardiovascular adverse effects such as hemodynamic instability, myocardial depression and reduced responsiveness to inotropes and vasopressors. (3,6,7) Early lactate normalization within 6 hours, has been shown to be an independent predictor for survival in sepsis as shown by Puskarich et al in 2013. (9) Nguyen et al in 2004 also showed that early lactate clearance within 12 hours of resuscitation in severe septic patients led to the reduction of relative risk of death by two-fold. (10) Hence, the Surviving Sepsis Guidelines in 2016 had included early lactate clearance within the first 6 hours of resuscitation as the goal of treatment in resuscitation. (11)

In view of the relevance of thiamine deficiency associated with lactic acidosis in sepsis, Donnino et al in 2016 studied the use of intravenous (IV) thiamine as the metabolic resuscitator in septic shock patients. They showed no overall improvements in lactate levels in patients receiving IV thiamine 200 mg twice daily except for those with baseline thiamine deficiency. (12) The European Federation of Neurological Societies (EFNS) recommended higher doses of IV thiamine 200 mg three times a day in patients diagnosed with Wernicke encephalopathy without causing significant adverse events. (13) Similarly, DiNicolantonio et al in 2013 studied IV thiamine dose of 200 mg three times a day which showed improvement of left ventricular ejection fraction in heart failure patients. (14)

For our study, we aimed to determine if the higher effective dose of IV thiamine administration (200 mg three times a day) could achieve early normalization of serum lactate levels as well as improve the overall patient's outcome.

Materials and methods

This prospective, randomized controlled study was conducted after getting approval by the Dissertation Committee of the Department of Anaesthesiology and Intensive Care, and the Medical Research and Ethics Committee, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia Medical Center (UKMMC) (FF-2017-389). This study was conducted in the general intensive care unit (GICU) of UKMMC from December 2017 until September 2018 in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.

Seventy-two patients aged 18 years and above, with septic shock (defined as presence of two or more systemic inflammatory response syndrome [SIRS] criteria with documented or suspected infection, hypotension requiring use of vasopressors to maintain mean arterial pressure [MAP] ≥65 mmHg, and having a serum lactate ≥2 mmol/l despite adequate fluid resuscitation) (15) were recruited into the study. Written informed consent was obtained either from the patient or the patient's legal guardian prior to study inclusion. Patients with limitation of therapy, bowel or limb ischemia, liver failure (defined by the presence of coagulopathy, international normalized ratio of >1.5, and encephalopathy without preexisting cirrhosis [16] or Class C Child Pugh classification), (17) obstetric patients, patients with known allergy to the study drugs were excluded. Patients who died within 24 hours after enrolment were dropped out from the study.

Following recruitment, all patients were randomized into 2 groups, thiamine group (TG) and placebo group (PG) using computer-generated randomization. Both groups of patients were resuscitated according to the 2016 Surviving Sepsis Campaign (SSC) guidelines. (10) Patients from the TG group received IV thiamine 200 mg diluted in 50 ml of normal saline while those from the PG group received 50 ml of normal saline infusion. All of the study drugs were infused over 30 minutes, given thrice daily for a total duration of 3 days.

For the blood lactate samples, arterial blood was collected in heparinized blood-gas syringes by ICU nurses at the various study intervals. Baseline levels of lactate were taken on study enrolment (T0), after 6 hours (T6), 12 hours (T12), 18 hours (T18), 24 hours (T24), 48 hours (T48), and 72 hours (T72), and were analyzed immediately using the blood gas analyzer in ICU (ABL 800 Basic, Radiometer Medical ApS, Denmark). Severe lactic acidosis was defined as lactate levels raised >4 mmol/l with corresponding lactic acidosis (pH<7.35). (18) Full blood count, renal function, coagulation profile, and clinical variables required for the determination of Acute Physiology and Chronic Health Evaluation (APACHE) II score (**Appendix A**) and Sequential Organ Failure Assessment (SOFA) (**Appendix B**) were collected and documented.

Study outcomes which included the relative lactate changes over 24 hours [(lactate at 0 hour minus lactate at 24 hours over lactate at 0 hour) x 100%], time for shock reversal (duration of vasopressors being weaning off), relative changes of the SOFA score over 72 hours, ICU length of stay (LOS) and ICU mortality rate were also calculated, measured, and documented accordingly.

Statistical analysis

The sample size required for the study was calculated by using the 'Power and Sample Size Calculation' program, based on a previous study done by Donnino et al in 2016. (12) The power of this study was set at 80% and α-value of 0.05, whereby it was estimated that 30 patients would be required for each group. Anticipating a 20% dropout rate, 36 patients were recruited for each group.

The data was analyzed by using IBM SPSS for Windows, version 24.0 (IBM Corp, Monk, NY, USA). Demographic data such as race, gender, and comorbidities were analyzed using chi-square test and Fisher's exact test. For continuous data, normality was tested, reported as mean±SD or median±interquartile range and subsequently analyzed using independent T-test or Mann-Whitney test accordingly. Univariate and multivariate logistic regression were performed to evaluate the independent association between baseline parameter and mortality. Odds ratio (OR) with 95% confidence interval (CI) were analyzed. Statistical analysis for lactate and SOFA score trend was conducted using STATA, version 14 (College station, TX, StataCorp LP, USA). A value of $p<0.05$ was considered as statistically significant.

Results

A total of 72 patients were recruited into the study. However, 7 patients died within 24 hours of study commencement and were dropped out from the study. Therefore, sixty-five patients were included in the data analysis whereby 32 patients received IV thiamine infusion while 33 patients received normal saline infusion.

As shown in **Table 1**, both TG and PG were comparable with respect to baseline demographics, comorbidities, source of infection, baseline lactate levels and the severity of the illness. The thiamine group showed a higher baseline APACHE II score as compared to PG. However, there were no significant differences in relative lactate changes at 24 hours, duration for weaning off the vasopressors, ICU LOS, and ICU mortality between groups as shown in **Table 2**. Predictors of mortality were analyzed by using univariate and multivariate logistic regression (LR) tests and showed that only baseline lactate levels were identified as the independent predictor for ICU mortality as shown in **Table 3**.

Figure 1 shows the trend of lactate level changes over 72 hours for TG and PG. There were no significant differences in lactate level reduction at 6, 12, 18, 24, 48 and 72 hours after the study drugs were initiated ($p=0.480$). **Figure 2** showed no significant differences in SOFA scoring changes over 3 days after the study drugs were administered ($p=0.490$).

Discussion

Serum lactate is a disease severity marker and found to be an independent predictor for mortality in septic patients. (19) Hyperlactatemia has been recognized as part of the definition of septic shock in the SEPSIS-3 consensus. (20)

From our study, we were unable to observe any significant differences in the relative lactate changes between TG and PG despite using higher doses of IV thiamine. This is probably due to the complexity of the pathological mechanisms leading to hyperlactatemia in septic shock patients which include hypoperfusion with microcirculation abnormalities leading to anaerobic glycolysis, stress-induced adrenergic aerobic glycolysis producing lactate, impaired hepatic lactate clearance and mitochondrial dysfunctions limiting pyruvate metabolism. (8) Therefore, these numerous factors may lead to the irreversibility of hyperlactatemia in septic shock patients despite adequate thiamine supplementation enhancing metabolic functions. (21,22)

Based on our study results, there were no significant changes in the time for shock reversal, SOFA scoring, ICU LOS, and ICU mortality rate. This may be explained by a probable delay of IV thiamine initiation which was commenced only after ICU admission and not during early resuscitation in the emergency department. A retrospective study done by Woolum JA et al in 2018 demonstrated that early thiamine administration within a median time of 6.4 hours after hospital admission led to good lactate clearance as well as patients survival rate. (23) Similarly, a study done by Holmberg MJ et al in 2017 also showed that a median time of first thiamine administration within 9 hours in septic shock patients given in the emergency department was associated with a lower mortality rate. (24) However, we did not measure the time between hospital admission to our first

study drug administration in our study.

From our study, we identified using regression analysis, that the baseline lactate level was an independent predictor for ICU mortality. This result was comparable with findings from the Australian Resuscitation in Sepsis Evaluation (ARISE) trial in which isolated hyperlactatemia levels were shown to have worse adjusted 90 days mortality rate. (19)

There were a few limitations seen in our study. First, there was variability on the timing of first IV thiamine administration due to the different timing of a patient's admission to GICU either from the ward or casualty department. Second, we were unable to identify patients' baseline thiamine levels as plasma thiamine level measurement was not available in our center. Finally, as this study was done in a single center, the sample size was small and may not have truly reflected the changes that may be seen in a bigger study population conducted in multi-center trials.

Conclusion

Intravenous thiamine did not show any significant improvement in relative lactate changes over 24 hours, time for shock reversal, SOFA scoring trends, ICU LOS, and ICU mortality rate in septic shock patients with hyperlactatemia. However, the baseline lactate level was identified as an independent predictor for ICU mortality.

Declaration of interest

The authors declare no conflict of interest.

Acknowledgement

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Table 1. Demographics data, comorbidities, source of infection, lactate value, and the severity of illnesses between TG and PG

	PG (n=33)	TG (n=32)	p value
Demographics			
- Age (year)	67.0 [55.0-77.0]	63.5 [50.5-70.5]	0.467
- BMI (kg/m²)	26.1 [23.9-28.0]	27.9 [23.3-30.0]	0.642
- Race			
Malay	17 (26.2)	15 (23.1)	0.857
Chinese	14 (21.5)	14 (21.5)	
Indian	2 (3.1)	3 (4.6)	
- Gender			
Male	18 (27.7)	20 (30.8)	0.515
Female	15 (23.1)	12 (18.5)	
Co-morbidities			
- Coronary artery disease	4 (6.2)	4 (6.2)	0.963
- Congestive heart failure	3 (4.6)	0 (0.0)	0.081
- Hypertension	21 (32.3)	20 (30.8)	0.924
- Chronic pulmonary disease	5 (7.7)	4 (6.2)	0.757
- Diabetes mellitus	15 (23.1)	19 (29.2)	0.261
- Chronic kidney disease	8 (12.3)	7 (10.8)	0.821
Source of infection			
- Hospital acquired infection	11 (16.9)	9 (13.8)	0.649
- Community acquired infection	22 (33.8)	23 (35.4)	
Lactate values			
- Baseline lactate level, T0	3.2 [2.5-5.9]	3.6 [2.5-6.1]	0.901
- Lactate level ≥4 mmol/l at T0	14 (21.5)	14 (21.5)	0.914
Severity of illness			
- Baseline SOFA score	13.0 [10.5-14.0]	13.5 [12.0-15.0]	0.076
- Baseline APACHE II score	29.0 [23.0-34.0]	35.0 [28.3-37.8]	0.037*

Legend: Values are expressed in median [IQR] or frequency (%) as appropriate. IQR=Interquartile range; PG=placebo group; TG=thiamine group; BMI=body mass index; SOFA=Sequential Organ Failure Assessment; APACHE II=Acute Physiology and Chronic Health Evaluation II. *$p<0.05$ is considered statistically significant.

Table 2. Study outcome results

	PG (n=33)	TG (n=32)	p value
Relative lactate changes over 24 hours (%)	47.8 [29.1-70.7]	37.5 [4.7-59.1]	0.091
Duration of vasopressors (hours)	88.0 [48.0-147.0]	75.5 [48.0-131.3]	0.457
SOFA score changes over 72 hours	2.7±3.3	3.0±3.4	0.714
ICU LOS (days)	6.0 [3.0-12.0]	5.0 [4.0-11.0]	0.370
ICU mortality (%)	12 (37)	14 (43)	0.543

Legend: Values are expressed in mean±SD, median [IQR] and frequency (%) as appropriate. IQR=Interquartile range; PG=placebo group; TG=thiamine group; SOFA=Sequential Organ Failure Assessment; ICU=intensive care unit; LOS=length of stay.

Table 3. Predictor of mortality with univariate and multivariate logistic regression (LR)

	Univariate LR		Multivariate LR	
Mortality	OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Thiamine	1.361 (0.503-3.683)	0.544		
Age	0.998 (0.965-1.032)	0.894	1.007 (0.970-1.045)	0.718
Gender	0.949 (0.347-2.595)	0.918		
Comorbidities	0.364 (0.104-1.277)	0.115		
Baseline lactate	1.174 (1.002-1.376)	0.047*	1.181 (1.005-1.389)	0.044*
Baseline APACHE II score	1.033 (0.969-1.102)	0.321		

Legend: *$p<0.05$ is considered statistically significant. APACHE II=Acute Physiology and Chronic Health Evaluation II.

Figure 1. Lactate trend over 72 hours

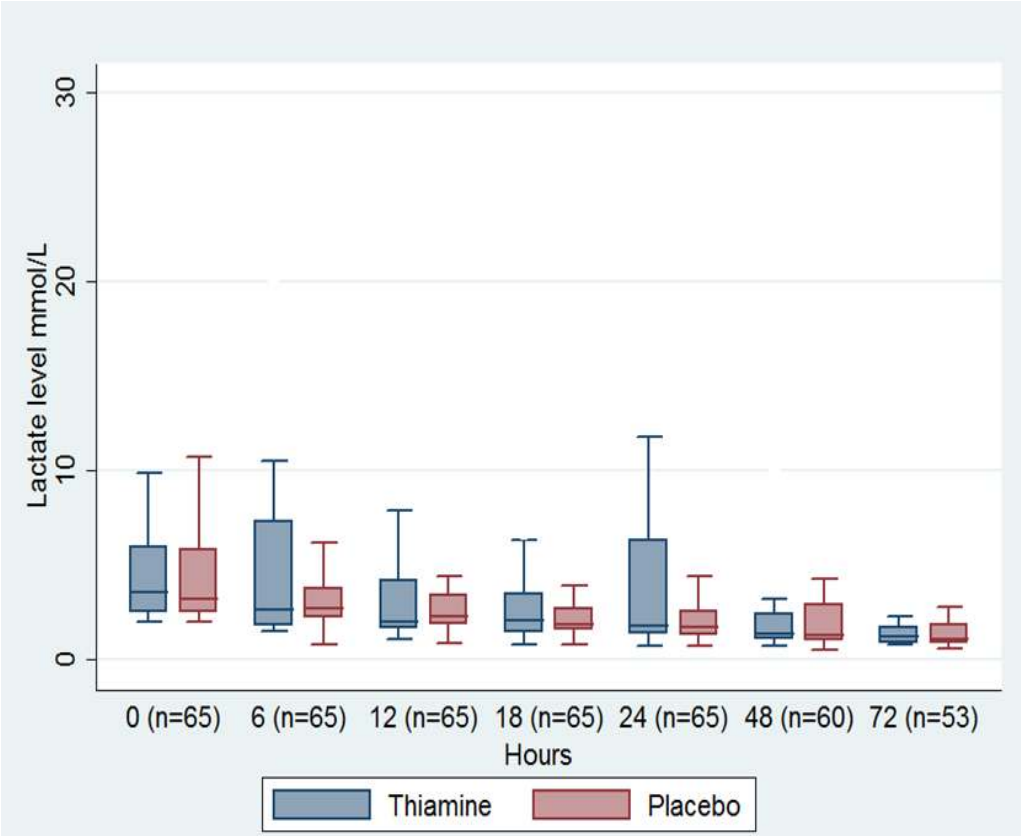
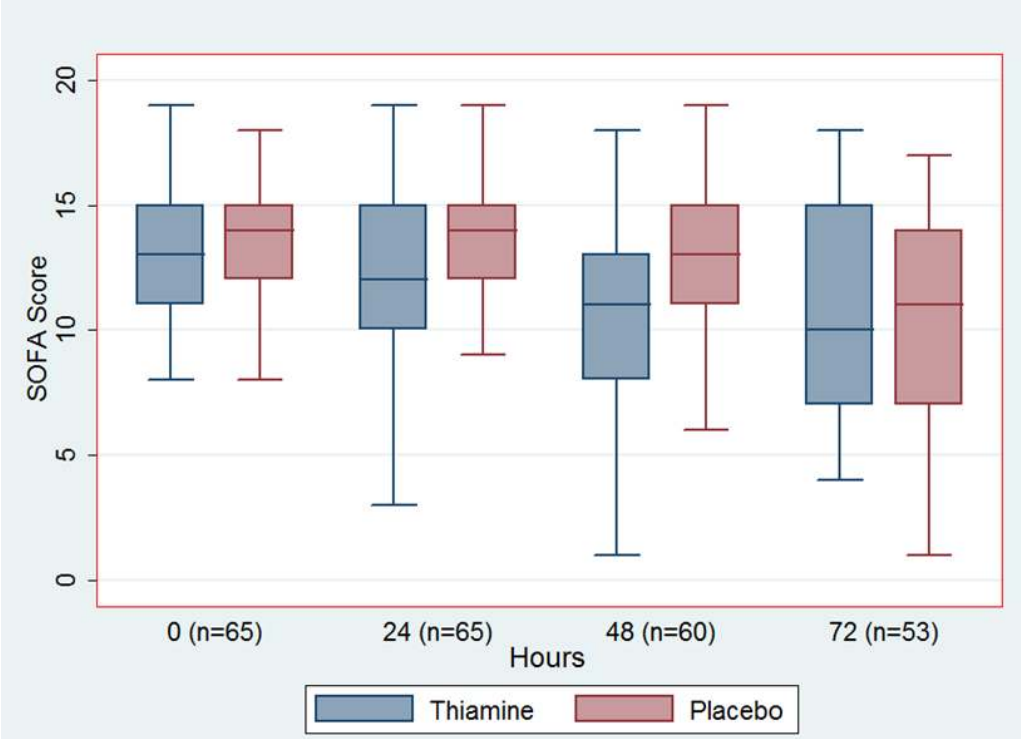


Figure 2. Trend for SOFA scoring



Appendix A. Acute Physiology and Chronic Health Evaluation (APACHE) II scoring systems

GICU UKMMC APACHE II FORM

Please complete & calculate table below with parameters measured/observed within the first 24 hours of ICU admission.

A. Acute Physiologic (APS) Points										Points
Physiologic Variable	+4	+3	+2	+1	0	+1	+2	+3	+4	
Temperature (°C)	>41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9	
Mean Arterial Pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49	
Heart rate (beats/min)	≥180	140-179	110-139		70-109		50-69	40-54	≤39	
Respiratory rate (Non-ventilated or ventilated))	≥50	35-49		25-34	12-24	10-11	6-9		≤5	
Oxygenation: AaDO2 **OR** PaO2 (mmHg)										
a. **$FiO_2 \geq 0.5$** record only $AaDO_2$	≥ 500	350-499	200-349		<200					
b. **$FiO_2 < 0.5$** record only PaO_2					>70	61-70		55-60	<55	
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15	
Serum HCO_3^- mEq/L (ABG, if none then Venous but not preferred)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15	
Serum Sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110	
Serum Potassium (mmol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5	
Serum Creatinine (μmol/L) **Double point score for Acute Renal Failure**	≥267	152-266	114-151		45-113		<45			
Haematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20	
White Blood Count (in 1000/mm^3)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1	
Glasgow Coma Scale (GCS): **Score = 15 – actual GCS**										
Total APS points										**A**
B. Age Points: Assign points to age: <44 = 0; 45-54 = 2; 55-64 = 3; 65-74 = 5; ≥75 = 6										**B**
C. Chronic Health Points: If the patient has a history of severe organ insufficiency or is immunocompromised, assign points as follows: ☐ Non operative or emergency postoperative patients = **5** points ☐ Elective postoperative patients = **2** points										**C**
DEFINITIONS: Organ insufficiency or immunocompromised state evident prior to this hospital admission and conforming to the following criteria: **LIVER:** Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma **CARDIOVASCULAR:** New York Heart Association Class IV **RENAL:** Receiving chronic dialysis					**RESPIRATORY:** Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40mmHg), or respiratory dependency **IMMUNOCOMPROMISED:** Patient has received therapy that suppresses resistance to infection, e.g. immunosupression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (e.g. leukaemia, lymphoma, AIDS)					
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic health points)										

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13(10):818-29)

Appendix B. Sequential Organ Failure Assessment (SOFA) scoring

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

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