



## Management of septic shock with a norepinephrine-based haemodynamic algorithm<sup>☆</sup>

Glenn Hernandez<sup>a,\*</sup>, Alejandro Bruhn<sup>b</sup>, Carlos Romero<sup>a</sup>, Francisco Javier Larrondo<sup>b</sup>,  
Rene De La Fuente<sup>a</sup>, Luis Castillo<sup>a</sup>, Guillermo Bugedo<sup>a</sup>

<sup>a</sup> Programa de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Marcoleta 367, Tercer Piso, Santiago Centro, Chile

<sup>b</sup> Facultad de Medicina, Pontificia Universidad Católica de Chile, Marcoleta 367, Tercer Piso, Santiago Centro, Chile

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### Abstract

Management of septic shock (SS) with a norepinephrine (noradrenaline)-based haemodynamic algorithm.

**Introduction:** The choice of the best vasopressor for haemodynamic management of septic shock is controversial. Nevertheless, very few studies have been focused on evaluating different management algorithms. The aim of this study was to evaluate the performance of a norepinephrine (NE)-based management protocol. Experience with NE as the initial vasopressor, even if not comparative, could bring relevant data for planning future trails. We also wanted to evaluate the compliance of critical care physicians and nurses with haemodynamic management protocol.

**Patients and method:** A norepinephrine-based algorithm for the management of septic shock that commands different sequential interventions according to its requirements, was applied prospectively to 100 consecutive septic shock patients.

**Results:** Norepinephrine was used as the first vasoactive drug in all patients with a maximum dose of  $0.31 \pm 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$  and an ICU mortality of 33%. Physicians applied correctly all the steps of the algorithm in 92% of the patients. Applying the algorithm, avoided the use of pulmonary artery catheter in 31 patients and led to use of lower doses of vasoactive agents than in many other clinical experiences.

**Conclusion:** In conclusion, our data support extended use of an algorithm based on norepinephrine for treating septic shock patients. This is the first clinical study that uses NE as the initial vasopressor drug systematically, and although not comparative, the mortality rates adjusted to APACHE II, are comparable to other studies. It also gives support for future clinical trials comparing norepinephrine with dopamine in this setting.

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**Keywords:** Catecholamines; Norepinephrine; Septic shock

### 1. Introduction

Septic shock is the most severe consequence of an infection and despite advances in therapy, associated mortality remains around 50%, ranging in subgroups from 30 to 80% [1–7]. This wide range suggests that septic shock patients constitute a highly heterogeneous population with different therapeutic requirements and prognosis [8].

The primary goal of the haemodynamic management of septic shock is to correct circulatory abnormalities that lead to hypoxia, multiple organ failure and death. Nevertheless, there are many controversial and unresolved issues in this subject, including the most effective vasopressor management.

The choice of the best catecholamine for the initial approach to septic shock treatment is controversial [9–13]. A drug with  $\alpha$  and  $\beta$  activity such as dopamine or norepinephrine (nor-adrenaline) (NE) has been recommended [9,10]. Nevertheless, these drugs have different effects on cardiac function and regional flow [9–15], and they are possibly not equivalent in clinical efficacy. While dopamine is

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\* Corresponding author. Fax: +562 6327620.

E-mail address: glenn@med.puc.cl (G. Hernandez).

preferred world-wide for the initial management of hypotension in sepsis [9,10], this practice is not supported by any single clinical study. In contrast, a recent study suggests that earlier use of NE may be associated with a better outcome [6].

During the last decade, at least 30 prospective, randomized, placebo-controlled, multi-centre studies, directed at modulating the excessive inflammatory response, failed to improve survival from septic shock. In contrast, there is a lack of prospective studies on basic aspects such as the optimal vasopressor drug or evaluation of different haemodynamic management algorithms.

Standardisation of haemodynamic protocols could eliminate an important and confounding variable, for which there has been no accountability in previous studies of septic shock. Protocols for management may have contributed to success in recent trials involving early goal-directed therapy [16] or tight control of blood sugar [17].

Protocols are essential to ensure efficient integration of new therapies. An increase in compliance with evidence-based recommendations through the use of protocols may decrease error and enhance patient safety [18].

The aim of this study was to test the performance of a norepinephrine-based management algorithm. Experience with NE as the initial vasopressor for septic shock management, even if not comparative, could bring relevant data for planning a future randomized, controlled trial on vasoactive drugs. As a secondary objective, we wanted to evaluate the compliance of critical care physicians and nurses with a haemodynamic management protocol.

## 2. Materials and methods

We conducted a prospective observational study in the surgical intensive care unit of the Hospital Clínico de la Universidad Católica de Chile from December 1999 to June 2001. All adult patients with a diagnosis of septic shock according to the ACCP/SCCM Consensus Conference [19] admitted during this period were managed with our NE-based algorithm, and therefore included in the study. Only patients with conservative management decided previously were excluded. The study was approved by the Ethical Committee of the Universidad Católica de Chile, and all patients or their relatives signed an informed consent to be treated in the ICU according to the standard care including this algorithm.

## 3. Norepinephrine-based haemodynamic algorithm

A norepinephrine-based algorithm for the management of septic shock patients based on clinical decision and different sequential interventions, was developed. The algorithm is aimed to achieve a mean arterial pressure (MAP) goal  $\geq 70 < 80$  mmHg and sequential steps are undertaken each time the MAP falls below this value:

- (1) The first step is fluid administration. At least 1 litre of normal saline is infused in the first hour and continued until a central venous pressure  $> 10$  mmHg, or a pulmonary arterial occlusion pressure in the range of 14–16 mmHg is achieved.
- (2) If the MAP remains below 70 mmHg despite fluid administration, NE infusion is started at  $0.05 \mu\text{g kg}^{-1} \text{min}^{-1}$ , with  $0.05 \mu\text{g kg}^{-1} \text{min}^{-1}$  increments until the MAP goal is achieved.
- (3) A pulmonary artery catheter (PAC) is placed, whenever NE requirements exceed  $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$  (if not previously indicated for preexisting congestive heart failure or concomitant acute respiratory distress syndrome).
- (4) If more than  $0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$  of NE are needed with a cardiac index (CI)  $< 3.0 \text{ l min}^{-1} \text{m}^2$ , epinephrine (adrenaline) is added (initial dose:  $0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ ), and regional perfusion monitoring (gastric tonometry) and mechanical ventilation (if not in place), are considered.
- (5) The norepinephrine infusion rate is adjusted by the nursing staff (at least every hour) to the minimal dose necessary to maintain the predetermined MAP goal, so that the infusion rate becomes physician-independent. Pulmonary arterial occlusion pressure is also re-evaluated every hour, adjusting fluids to achieve a level of 14–16 mmHg.
- (6) Dobutamine (initial dose:  $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) is added in the case of significant cardiac dysfunction (CI  $< 2.5 \text{ l min}^{-1} \text{m}^2$ ) or persistent hypoperfusion (persistent lactic acidosis, mixed or central  $\text{O}_2$  venous saturation  $< 65\%$ , oliguria or poor skin perfusion).

Dobutamine is titrated with  $2 \mu\text{g kg}^{-1} \text{min}^{-1}$  increments until the hypoperfusion and/or cardiac index criteria are corrected or the heart rate exceeds 130 BPM. The algorithm is presented in Fig. 1.

### 3.1. Data collection

All patients included in this study were followed until death or hospital discharge. The following variables were collected: age, underlying disease, admission diagnosis, APACHE II (at 24 h of admission to ICU); primary site of infection and positive cultures; vasoactive drugs (maximum and total dose, and duration of treatment for each drug); pulmonary artery catheter derived haemodynamic variables (cardiac index, left ventricular stroke work index, pulmonary arterial occlusion pressure, central venous pressure); peak values for lactate, C reactive protein, serum creatinine, and bilirubin; the lowest value for platelet count and  $\text{PaO}_2/\text{FiO}_2$ ; maximum SOFA score [20]; ventilator days; ICU and hospital length of stay.

### 3.2. Statistical analysis

The results are expressed as mean  $\pm$  S.D. and a probability value  $< 0.05$  was considered as statistically significant.

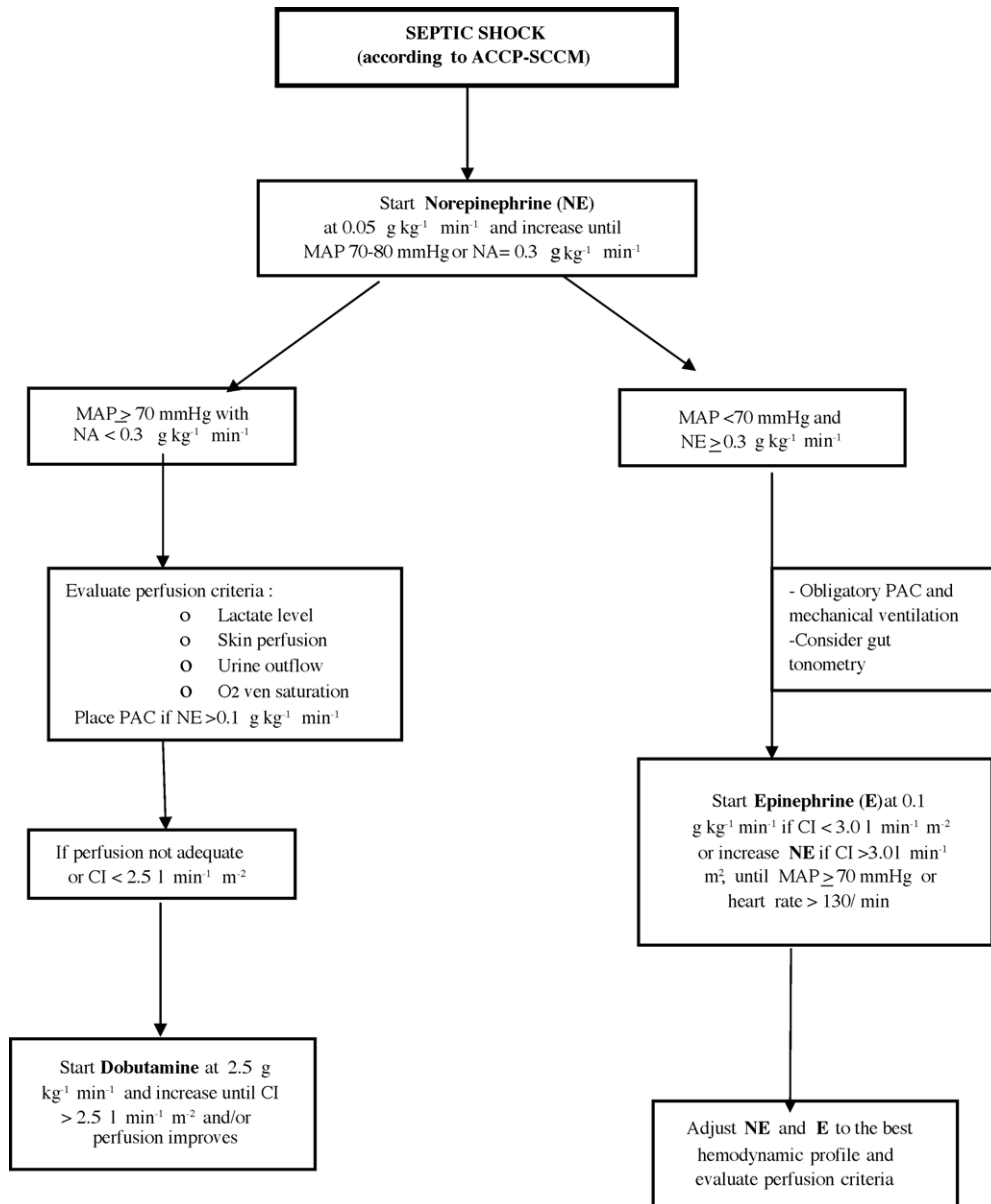


Fig. 1. Norepinephrine-based algorithm for the management of septic shock.

Subgroup characteristics were compared by two-tailed Student's *t*-test and Chi-square test.

#### 4. Results

A total of 100 patients were included in the study (50 M, 50 F; age  $63 \pm 18$  years) and their main characteristics are shown in Table 1.

Abdominal infection was the cause of septic shock in 52 patients (52%), pulmonary infections in 30 (30%), and there were miscellaneous aetiologies in the remaining 18 patients (18%).

Eighty patients (80%) were mechanically ventilated, 69 patients were monitored with a pulmonary artery catheter, 16 with a gastric tonometer (Tonocap<sup>®</sup>), and three with a venous suprahepatic catheter. Forty-seven patients (47%) developed

Table 1  
Main characteristics of the population

Admission APACHE II	$19 \pm 7.2$
Maximum SOFA	$8.75 \pm 3.7$
Mechanical ventilation (days)	$4.4 \pm 5.1$
Peak arterial lactate (mmol/l)	$4.43 \pm 3.49$
Maximal C reactive protein (mg/dl)	$27.7 \pm 11.5$
Maximal serum creatinine (mg/dl)	$2.41 \pm 1.98$
ICU mortality (%)	33 (33%)

renal failure (serum creatinine > 2 mg/dl), while 12 required haemodialysis and/or haemofiltration.

All patients were managed according to the algorithm. Nevertheless, in retrospective analysis we identified eight protocol violations in the sequence of vasoactive drugs: in four cases, epinephrine was not started despite reaching the  $NE > 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$  threshold and in another four patients, epinephrine was started with  $NE < 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$ . In every other patient, the algorithm was correctly applied.

Norepinephrine was used as the first vasoactive drug in all patients with a maximum dose of  $0.31 \pm 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$  (range:  $0.05\text{--}1.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ ). The patient distribution according to algorithm is shown in Fig. 2. Patients who required peak NE dose  $> 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$  had more severe disease with a higher mortality as shown in Table 2.

Of the 67 patients treated with peak NE dose  $< 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$ , 27 met criteria for starting dobutamine (15 with  $CI < 2.5 \text{ l min}^{-1} \text{m}^2$ , nine with poor skin perfusion and three with persistent lactic acidosis). Nine of these 67 patients died (13.4%). In no patient was dobutamine associated with an arrhythmia or hypotension requiring withdrawal of the drug.

Table 2

Comparison between patients who used peak norepinephrine doses  $>$  or  $<$  to  $0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$

Characteristics	$< 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$	$> 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$	<i>p</i>
No.	67	33	
Age (years)	$64.44 \pm 18.99$	$61.05 \pm 16.45$	NS
APACHE II	$17.06 \pm 6.62$	$22.15 \pm 7.06$	$< 0.05$
Maximal SOFA	$7.16 \pm 2.97$	$11.32 \pm 3.29$	$< 0.05$
Peak lactate (mmol/l)	$2.84 \pm 1.92$	$7.04 \pm 3.9$	$< 0.05$
Mechanical ventilation (days)	$4.27 \pm 5.65$	$4.71 \pm 4.12$	NS
Maximal creatinine (mg/dl)	$2.2 \pm 2.14$	$2.41 \pm 1.98$	NS
Mortality (%)	9/67 (13.4%)	24/33 (72.7%)	$< 0.05$

Twenty-four of 33 patients with peak NE dose  $> 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$ , died (72.7%).

## 5. Discussion

To our knowledge, this is the first clinical study that uses NE as the initial vasopressor drug systematically. Even in Martin's study [6], all patients were treated initially

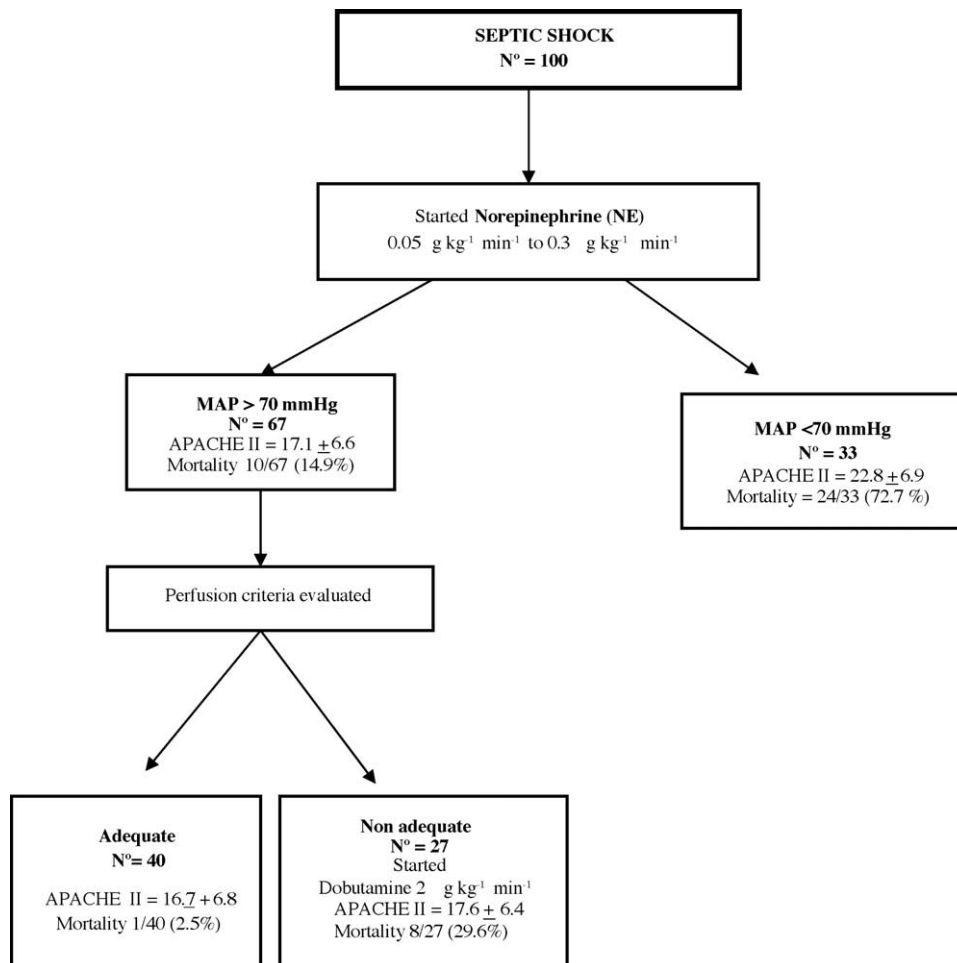


Fig. 2. Patients distribution according to norepinephrine-based algorithm.

with moderate dose dopamine. If hypotension persisted, the dopamine dose was increased or NE was added [6]. Our data may support future trials, comparing NE to other vasoactive drugs to establish the best treatment for septic shock.

Our overall mortality adjusted to APACHE II and SOFA score is comparable to that reported by other groups [1]. So, we could demonstrate the feasibility and safety of using norepinephrine as the exclusive initial vasopressor drug.

We also demonstrated the feasibility of applying a standardized management of septic shock with a 92% strict compliance among physicians and nurses. The only recorded minor protocol violations were in relation to epinephrine use. In a few cases this drug was started too early or too late in relation to the required NE threshold.

Clinical experience with norepinephrine in septic shock patients suggests that this drug can increase blood pressure successfully without causing deterioration in cardiac index or organ function [10]. Nevertheless, the final effect on individual organ blood flow may result from a balance between two opposite effects: direct vasoconstriction and the improvement in systemic perfusion pressure. When individual organs lose flow autoregulation, the final perfusion depends directly on MAP. Since norepinephrine exhibits dose-dependent  $\alpha$  adrenergic activity and may also induce adverse effects such as a decrease on splanchnic or renal blood flow [9,10], it should be used at the lowest dose to restore normal values of MAP [10]. An essential step in our management algorithm is permanent monitoring of the relation between the NE dose and MAP. Norepinephrine infusion rate is adjusted by the nursing staff (at least every hour) to the minimum dose necessary to maintain the predetermined MAP goal. This task requires training and reinforcement but it is essential to avoid excessive and potentially harmful norepinephrine doses. The same occurs with dobutamine where the gradual increase in dose until correction of hypoperfusion and/or cardiac index criteria, or heart rate  $> 130$  BPM, can avoid excessive and deleterious adrenergic stimulation [21]. In fact, our mean norepinephrine and dobutamine doses are lower than in most published papers [6,9,10,22–25].

Norepinephrine is probably more effective than dopamine at reversing hypotension in septic shock patients, but a prospective, randomized clinical trial is still required to assess whether the use of norepinephrine in septic shock patients affects mortality compared to other vasopressors.

Furthermore, there are many potential reasons for choosing norepinephrine instead of dopamine, as the initial vasopressor drug in septic shock patients that can be summarized as follows:

- (1) The haemodynamics of septic shock requires a vasoactive drug with moderate  $\beta_1$  and strong  $\alpha$  effect [9,10].
- (2) Dopamine produces a higher  $\beta_1$  adrenergic stimulation, which is probably unproductive and deleterious, before reaching a satisfactory  $\alpha$  effect [9].
- (3) The probability of improving splanchnic and renal perfusion may be higher with NE than with dopamine,

although this subject is controversial [10,11,13,26].

- (4) The protective effect of dopamine over splanchnic and renal blood flow has never been proven [27,28]. Dopamine could have a detrimental effect over gastric mucosal flow as assessed by laser doppler flowmetry [14].
- (5) Starting treatment with dopamine could delay obtaining the MAP goal, and eventually may produce cardiac overstimulation (tachycardia, risk of ischaemia).

The use of the pulmonary artery catheter has been matter of controversy [29]. In order to provide a more rational approach, we established clear indications depending on the severity of shock (as assessed by NE requirements  $> 0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) or in the presence of pre-existing congestive heart failure or concomitant acute respiratory distress syndrome. Using this approach, we avoided pulmonary artery catheter placement in 31% of the septic shock patients with the corresponding savings.

Dobutamine has been recommended by guidelines and consensus as the inotrope of choice [9,10] to increase flow when restoration of MAP is insufficient to produce normal tissue perfusion in septic shock. Nevertheless, efforts to increase oxygen delivery to supra-normal levels have been abandoned because of increased harm or lack of effect [21,25]. Considering this, we titrated dobutamine only to reach a normal cardiac index ( $> 2.5 \text{ l min}^{-1} \text{ m}^2$ ) or to correct specific hypoperfusion markers.

The usefulness of epinephrine in the management of septic refractory hypotension is controversial [9,10]. In patients who fail to respond to other vasopressors, epinephrine can increase MAP by increasing CI or stroke volume. Nevertheless, epinephrine has detrimental effects on splanchnic blood flow and has been associated with increases in systemic and regional lactate concentrations. We restricted epinephrine use to patients unresponsive to  $\text{NE} = 0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$ . This subgroup of patients exhibited a very high mortality and the benefit of epinephrine was questionable.

The optimal MAP level for septic shock has not been established by any randomized clinical trials and is controversial [2,30]. It is probably safe to manage a MAP between 65 and 80. Nevertheless, we chose 70 mmHg considering that this MAP goal has been used by recent major trials [31,32].

Standardization of haemodynamic protocols will eliminate important uncontrolled and confounding variables for which there has been no accountability in previous studies in septic shock. A standard vasopressor approach will decrease the variability and confusion that at present typify the management of septic shock. Several management protocols or algorithms including sedation, analgesia, mechanical ventilation [33–36] or initial approach to septic shock [24,25] have been applied successfully in clinical trials. Very recently a flow diagram for guidance in management decisions in septic shock [37] has been proposed but this needs to be evaluated in future trials.

Clinical experience with haemodynamic management algorithms should be encouraged. We have demonstrated that a simple, but evidence based, haemodynamic management protocol for septic shock can be applied in an ICU setting with good compliance from nurses and physicians. Titrating norepinephrine as an exclusive initial vasopressor drug and dobutamine as an inotrope against specific goals proved to be safe and feasible. With this method we could use both drugs in doses below the average reported in many published papers and thus avoid the harmful effects of adrenergic  $\alpha$  or  $\beta$  overstimulation.

Clinical algorithms must be periodically updated. We recently incorporated low doses of hydrocortisone in the treatment of all patients with NE requirements  $>0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$  [38] and consider using drotrecogin alfa in patients with NE requirements  $>0.3 \mu\text{g kg}^{-1} \text{min}^{-1}$  [31].

In conclusion, our data support extended use of an algorithm based on NE for treating septic shock patients. This is the first clinical study that uses NE as the initial vasopressor drug systematically, and although not comparative, the mortality rates adjusted to APACHE II, are comparable to other studies. The application of a standardized management for septic shock is feasible with a 92% strict compliance among physicians and nurses. Compliance with the management protocol can lead to a more rational use of the pulmonary artery catheter and to the use of lower and potentially less harmful doses of vasoactive agents. Our data may support future trials, comparing norepinephrine to other vasoactive drugs to establish the best treatment for septic shock.

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