Implementation of a Norepinephrine-based Protocol for Management of Septic Shock: A Pilot Feasibility Study

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Background: The subject of the best vasopressor for hemodynamic management of septic shock (SS) is controversial. One of the difficulties in planning such studies is that physicians are reluctant to use one vasopressor exclusively, and there is considerable variation in practice. The aim of this study was to test the feasibility of implementing a single pressor-based algorithm (in this case, norepinephrine [NE]).

Methods: A NE-based algorithm was applied prospectively to 100 consecutive SS patients. A formal training program was implemented before starting the protocol and applied to 72 physicians and nurses involved in intensive care unit (ICU) patient care. Compliance, protocol violations, probable adverse effects, and outcome were evaluated on a daily basis by an independent group of fellows and a research nurse.

Results: In 100 patients, there were 7,139 hours of algorithm use. Only 13 protocol violations were observed, mostly in the timing of inotropic drugs. Senior staff physicians or busy night shifts accounted for most of these violations. ICU mortality was 33%, which is comparable to that predicted by Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores. Adverse events probably related to NE were not observed.

Conclusions: The present algorithm, applied after a strict training program, obtained an overall good acceptance and compliance with very few protocol violations in more than 7,000 hours of use. Safety was demonstrated by a global mortality comparable to that predicted by severity scores and absence of specific drug-related morbidity. The implementation of a single pressor-based algorithm for SS is feasible and safe.

Key Words: Clinical algorithm, Norepinephrine, Septic shock.

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The subject of the best vasopressor drug for the initial management of septic shock is controversial. Dopamine (DA) and norepinephrine (NE), the two most commonly used vasopressors, are associated with theoretical advantages and disadvantages and may not be equivalent in terms of outcome and adverse effects.1–3 The necessity of a large prospective randomized trial comparing both drugs and aimed at establishing the best standard vasopressor approach has been emphasized.1 We were interested in designing and launching a DA versus NE comparative trial. However, clinicians have been reluctant to use one or the other drug, exclusively. In a previous observational study, without any protocol guideline, our staff physicians and residents spontaneously employed eight different vasoactive combinations to treat 22 septic shock patients (Acute Physiology and Chronic Health Evaluation [APACHE] II score, 20.15 ± 7.0; Sequential Organ Failure Assessment [SOFA] score, 9.9 ± 4.9) with a hospital mortality of 49%. Of these patients, 20 patients eventually required NE.4

This variation in practice makes formal evaluation of efficacy difficult. So, before we could initiate the trial, we first had to establish a standard protocol for care using just one of the two drugs. Therefore, we designed a pilot study of a single pressor (in this case, NE) algorithm for treatment of septic shock. The study was not intended as a comparison study. Rather, we wanted to determine whether we were able to implement the algorithm reliably, and to ensure the algorithm was tolerated by clinicians and not associated with outcomes that were worse than historical controls or predicted mortality. If this feasibility study was successful, we intend to launch a multicentric study comparing two protocols for managing septic shock, where the only difference in protocols will be the choice of DA or NE as the single initial pressor.

Our main objective was to test the acceptance (compliance and protocol violations) of a single pressor-based algorithm for hemodynamic management of septic shock. As a secondary objective we wanted to test safety of this algorithm approach evaluating mortality (compared with mortality predicted by common intensive care unit [ICU] severity scores) and morbidity (evaluating the incidence of probably drug related adverse effects).

MATERIALS AND METHODS

We developed a NE-based algorithm for the management of septic shock patients based on clinical decision and different sequential interventions, aimed at maintaining a
mean arterial pressure (MAP) between 70 and 80 mm Hg and normalizing perfusion criteria (Fig. 1). Sequential steps are undertaken each time MAP is lower. The main characteristics of the algorithm are:

1. The first step is fluid administration. At least 1 L of normal saline is infused in the first hour and continued until achieving a central venous pressure (CVP) /H1102210 mm Hg, or a pulmonary arterial occlusion pressure (PAOP) in the range of 14 to 16 mm Hg.

2. If MAP is <70 mm Hg despite fluid administration, NE infusion is started at 0.05 μg · kg⁻¹ · min⁻¹, with 0.05 μg · kg⁻¹ · min⁻¹ increments until MAP goal is achieved.

3. A pulmonary artery catheter (PAC) is placed, whenever NE >0.1 μg · kg⁻¹ · min⁻¹ is required (if not previously indicated for preexisting congestive heart failure [CHF] or concomitant acute respiratory distress syndrome [ARDS])

4. With persistent hypotension despite >0.3 μg · kg⁻¹ · min⁻¹ of NE and cardiac index (CI) <3.0 l · min⁻¹ · m⁻², epinephrine (E) is added (initial dose: 0.1 μg · kg⁻¹ · min⁻¹), and regional perfusion monitoring (gastric tonometry) and mechanical ventilation (if not in place), are considered.

5. NE 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. PAOP is also re-evaluated every hour, adjusting fluids to the 14- to 16-mm Hg level.

6. In patients with stable MAP ≥70 mm Hg, dobutamine (DOB) (initial dose: 2.5 μg · kg⁻¹ · min⁻¹) is added in case of significant cardiac dysfunction (CI < 2.5 l · min⁻¹ · m⁻²) or persistent hypoperfusion (persistent lactic acidosis, mixed or central O₂ venous saturation <65%, oliguria or poor skin perfusion). Dobutamine is titrated with 2 μg · kg⁻¹ · min⁻¹

Fig. 1. Norepinephrine-based algorithm for management of septic shock. MAP, mean arterial pressure; PAC, pulmonary artery catheter; CI, cardiac index.
increments until correcting the first hypoperfusion and/or CI criteria or heart rate $>$130 bpm.

To improve compliance with the algorithm, we implemented an educational intervention. The algorithm was taught to all nurses, residents, fellows, and staff physicians of the surgical intensive care unit (SICU), using different educational tools such as lectures, written statements, and web-based educational interventions. Knowledge of the algorithm was finally assessed with a written test applied to all nurses and residents. Specific reinforcements were later implemented on an individual basis.

Subsequently, we conducted a pilot observational feasibility study in the SICU from December 1999 to June 2001. Adult patients with a diagnosis of septic shock according to the ACCP/SCCM Consensus Conference$^5$ admitted during this period were eligible for management with the protocol, unless they exhibited some exclusion criteria. Patients with a terminal illness (disseminated neoplasm) or irreversible neurologic impairment according to their head physicians, and in whom life-prolonging treatments were limited, 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 approving to be treated in the ICU according to standard care including this algorithm.

Our measures of feasibility were training time, compliance (number of patients treated with the algorithm over all septic shock patients admitted in the period), and number of protocol violations. Our measures of safety were mortality and morbidity. Mortality was compared with APACHE II$^6$ and SOFA$^2$ predicted mortality. Morbidity was assessed evaluating probable NE adverse effects. Probable related morbidities included acute coronary syndromes, digital necrosis, arrhythmias, and acute abdomen due to mesenteric ischemia or NE dependant splanchnic ischemia.

An independent group of fellows (not involved in patients care) and a research nurse evaluated compliance, violations of protocol, probable drug-related adverse effects, and outcome on a daily basis until ICU discharge and then assessed hospital mortality.

### Statistical Analysis

The results are expressed as means $\pm$ SD and a probability value $<0.05$ was regarded as statistically significant. To compare our observed mortality with that predicted by APACHE II and SOFA scores, test and CI for one proportion was used (MINITAB 13.2 STAT TRANSF MED CALC). Subgroup characteristics were compared by two-tailed Student’s $t$ test and $\chi^2$ test.

### RESULTS

The number of nurses and physicians that were trained in the use of the algorithm was 25 and 47, respectively. They were trained for a total of 21 hours (8 hours of direct lectures, 8 hours of practical training, 2 hours for a written test, and 3 hours for reinforcement).

During the study period, 825 patients were admitted to the SICU. In all, 114 patients met the criteria for septic shock. Of these, 14 patients were excluded because of advanced cancer (11 cases) or irreversible neurologic impairment due to massive stroke (3 cases). In these 14 patients, full treatment was withheld or limited, or do-not-resuscitate status decided. One hundred patients (50 males and 50 females; age 63 $\pm$ 18 years) were finally treated with the algorithm and some general characteristics are shown in Table 1. As general data, abdominal infection was the cause of septic shock in 52 patients (52%), pulmonary infections in 30 (30%), and miscellaneous etiologies in the remaining 18 patients (18%). Eighty patients (80%) were mechanically ventilated, 69 were monitored with a pulmonary artery catheter (PAC), 16 with a gastric tonometer (Tonocap), and three with a supraphepatic venous catheter. Twelve patients required renal replacement therapy.

In these 100 patients, there were 7,139 hours of algorithm use. Every patient received NE as the initial vasopressor and none received DA at any point. Mean peak NE dose was $0.31 \pm 0.3 \, \mu g \cdot kg^{-1} \cdot min^{-1}$ (0.05 to 1.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and the drug was used for 71.9 $\pm$ 79.4 hours. Dobutamine (mean peak dose $4.0 \pm 1.8 \, \mu g \cdot kg^{-1} \cdot min^{-1}$) and epinephrine (mean peak dose $0.31 \pm 0.27 \, \mu g \cdot kg^{-1} \cdot min^{-1}$) were added in 45 and 33 patients, respectively, as stated by the algorithm. Nevertheless, during the study period, 13 algorithm violations were observed in 10 patients, which consisted in 10 cases of wrong step sequence or timing in the use of dobutamine or epinephrine (too early or too late in relation to the protocol guideline), two cases of unjustified pulmonary artery catheter placement, and one case of no further assessment of persistent lactic acidosis. Interestingly, when we analyzed the source of these violations (13 in 10 patients), they corresponded in 11 cases to two staff physicians with more than 15 years of on-call duties including night shifts, compared with only two in which ICU residents were responsible. Also interesting is the fact that 9 of 13 violations were at night shifts with high bed occupation rates.

Events probably related to side effects of pressors, such as digital necrosis or clinically demonstrated mesenteric ischemia, were not observed in this study. Acute coronary syndromes (ACS) were suspected in three cases (ST alterations

### Table 1 Main Characteristics of the Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean $\pm$ SD or n (%)</th>
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<tbody>
<tr>
<td>Admission APACHE II</td>
<td>19 $\pm$ 7.2</td>
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<tr>
<td>Maximum SOFA</td>
<td>8.75 $\pm$ 3.7</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>4.4 $\pm$ 5.1</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
</tr>
<tr>
<td>Peak arterial lactate</td>
<td>4.43 $\pm$ 3.49</td>
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<tr>
<td>(mmol/L)</td>
<td></td>
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<tr>
<td>Maximal C-reactive</td>
<td>27.7 $\pm$ 11.5</td>
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<tr>
<td>protein (mg/dL)</td>
<td></td>
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<tr>
<td>Maximal serum creatinine</td>
<td>2.41 $\pm$ 1.98</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
</tr>
<tr>
<td>ICU mortality (%)</td>
<td>33 (33%)</td>
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</tbody>
</table>

*Note: Values are included as mean $\pm$ SD or n (%).

*Abbreviations: NE, norepinephrine; APACHE, acute physiology and chronic health evaluation; SOFA, systemic inflammatory response syndrome.

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with moderate troponin rising) but these abnormalities resolved spontaneously in a mean of 3 days. Six cases of atrial fibrillation were observed (four transient and two persistent) on patients in whom DOB or epinephrine had been added to NE according to algorithm. There were no cases of arrhythmia or hypotension associated with the use of DOB, requiring drug withdrawal.

The hospital mortality rate was 33%, which is comparable to that predicted by APACHE II score (35% for 19 points) or maximum SOFA score (26% for a score in the range of 8 to 9) \( p = 0.754 \) and 0.137, respectively, with a 95% CI of 0.23 to 0.43. Interestingly, patients who required peak NE dose \( >0.3 \mu g \cdot kg^{-1} \cdot min^{-1} \) exhibited a much higher mortality compared with those with peak NE dose \( <0.3 \mu g \cdot kg^{-1} \cdot min^{-1} \) (24 of 38 [63.15%] versus 9 of 62 [14.51%]; \( p < 0.05 \)), but this was compatible with more severe disease, also reflected by higher peak arterial lactate levels (7.04 \( \pm \) 3.9 versus 2.84 \( \pm \) 1.92 mmol/L; \( p < 0.05 \)) and maximum SOFA scores (11.32 \( \pm \) 3.29 versus 7.16 \( \pm \) 2.97; \( p < 0.05 \)).

**DISCUSSION**

The present algorithm obtained an overall good acceptance and exhibited a favorable feasibility and effectiveness under conditions of an open, observational design. Our goal was not to obtain conclusions on the efficacy of this algorithm-guided hemodynamic treatment of septic shock compared with standard treatment as usual, but to assess its feasibility and compliance. Only a study with a randomized controlled design can prove that an algorithm-guided treatment procedure results in higher efficacy in terms of treatment outcome.

Tension between a detailed protocol (sometimes described as “rigid”) and physician judgment (widely believed to be inherently flexible) is commonly used as a framework for discussion and may lead to nonacceptance or compliance by individual physicians. This was not the case in our SICU setting and the algorithm was well accepted. In general, physicians and nurses involved in the management of ICU patients cooperated and tried to apply the protocol to individual patients. Very few protocol violations were observed, mainly involving wrong steps in the sequence of vasoactive drugs. As we described above, these violations occurred mainly in busy night shifts or under the staffing of senior physicians. This suggests that compliance with this kind of algorithm may be worse in busy or understaffed ICUs especially during night shifts or in ICUs staffed with older and eventually tired physicians. In fact, the two staff physicians involved in protocol violations had successfully completed the training program and when requested to explain the violations, argued that they occurred in extremely busy shifts. So, we are not sure of the applicability of this kind of algorithm in other centers because, despite its simplicity, it requires discipline and commitment by all physicians and nurses involved in patient care and also some objective conditions such as an adequate ICU staffing.

Nevertheless, we do believe that training and education of the physicians who will use the algorithm are important issues and can influence results. We trained a group of 47 physicians (residents, fellows, and staff physicians) and 25 ICU nurses for a total of 21 hours. The success of training was assessed with a written test including specific reinforcements according to results. We started applying the algorithm only after the former process was finished. From another point of view, success of this approach is reflected by the occurrence of only 13 protocol violations in 10 of > 100 patients treated and >7,000 hours of algorithm application. Adequately explicit and detailed protocols that use complex rule sets have been associated with 90 to 95% clinician compliance in clinical trial settings. Our results are comparable with those experiences.

Safety of this protocolized, single-pressor approach is demonstrated by a mortality rate comparable to that predicted by APACHE II or SOFA score and probably better than our previous experience with a nonprotocolized hemodynamic management or unregulated clinical practice. Safety is also demonstrated by the nonoccurrence of probable NE-related adverse effects such as myocardial infarction or bowel necrosis. Furthermore, the incidence of atrial fibrillation is the same as expected for acutely ill patients.

The major limitation of this pilot study is that we only assessed compliance and feasibility in a single institution. It is possible that compliance will decline when used in more hospitals, as we discussed above. Nevertheless, these data have now been used to promote acceptance of a protocolized, single-pressor approach to septic hypotension in our hospital.

The assumption behind the development of systematic treatment algorithms is that decreasing the variance and increasing the appropriateness of treatment strategies may result in enhanced patient outcomes. It has been suggested that algorithms may provide an effective means to optimize outcome with clinical benefit and cost savings. Organized management with goal-directed therapy could reduce unnecessary variation in clinical practice and may have influenced favorable changes on patient outcome.

We have shown that the otherwise highly variable hemodynamic treatment of septic shock can be managed following an organized protocol, with good compliance and no obvious increase in mortality or morbidity compared with predicted risk estimates. This study provides further example of the ability of protocolized care algorithms to help critical care clinical researchers and will serve as the basis for initiating a multicentric trial comparing NE versus DA in the management of septic shock.

**REFERENCES**


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