Effect of norepinephrine on the outcome of septic shock

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Objective: **Despite increasingly sophisticated critical care, the mortality of septic shock remains elevated. Accordingly, care remains supportive. Volume resuscitation combined with vasopressor support remains the standard of care as adjuvant therapy, and many consider dopamine to be the pressor of choice. Because of fear of excessive vasoconstriction, norepinephrine is considered to be deleterious. The present study was designed to identify factors associated with outcome in a cohort of septic shock patients. Special attention was paid to hemodynamic management and to the choice of vasopressor used, to determine whether the use of norepinephrine was associated with increased mortality.**

Design: **Prospective, observational, cohort study.**

Setting: **Intensive care unit of a university hospital.**

Patients: **Ninety-seven adult patients with septic shock.**

Measurements and Main Results: **Data from these patients were examined to select variables independently and significantly associated with outcome during the hospital stay. Nineteen clinical, biological, and hemodynamic variables were collected at study entry or during the first 48–72 hrs and analyzed for each patient. A stepwise logistic regression analysis and a model building strategy were used to identify variables independently and significantly associated with outcome. The overall hospital mortality was 73% (71 patients). Five variables were significantly associated with outcome. One factor was strongly associated with a favorable outcome: the use of norepinephrine as part of the hemodynamic support of the patients. The 57 patients who were treated with norepinephrine had significantly lower hospital mortality (62% vs. 82%, $p < .001$; relative risk = 0.68; 95% confidence interval = 0.54–0.87) than the 40 patients treated with vasopressors other than norepinephrine (high-dose dopamine and/or epinephrine). Four variables were associated with a poor outcome and significantly higher hospital mortality: pneumonia as a cause of septic shock (82% vs. 61%, $p < .03$; relative risk = 1.47; 95% confidence interval = 1.07–1.77), organ system failure index ≤ 3 (92% vs. 60%, $p < .001$; relative risk = 1.47; 95% confidence interval = 1.17–1.82), low urine output at entry to the study (88% vs. 60%, $p < .01$; relative risk = 1.44; 95% confidence interval = 1.06–1.87), and admission blood lactate concentration > 4 mmol/L (91% vs. 63%, $p < .01$; relative risk = 1.60; 95% confidence interval = 1.27–1.84).**

Conclusions: **Our results indicate that the use of norepinephrine as part of hemodynamic management may influence outcome favorably in septic shock patients. The data contradict the notion that norepinephrine potentiates end-organ hypoperfusion, thereby contributing to increased mortality. However, the present study suffers from some limitation because of its nonrandomized, open-label, observational design. Hence, a randomized clinical trial is needed to clearly establish that norepinephrine improves mortality of patients with septic shock, as compared with high-dose dopamine or epinephrine. Pneumonia as the cause of septic shock, high blood lactate concentration, and low urine output on admission are strong indicators of a poor prognosis. Multiple organ failure is confirmed as a reliable predictor of mortality in septic patients. (Crit Care Med 2000; 28:2758–2765)**

KEY WORDS: dopamine; norepinephrine; septic shock; vasopressors

Despite major advances in monitoring and therapy, the mortality rate from septic shock remains elevated and is often >70% in patients presenting with severe forms of shock (1–3). Several factors are known to be associated with outcome: underlying disease, source of infection, and neutropenia (4–6). However, these factors cannot be influenced by the action of the clinician in charge of the patients. Inadequacy of antibiotic therapy also is strongly associated with mortality (4–6). Biotechnology offers numerous new and expensive investigational drugs for the treatment of septic shock (7). However, the results of trials of antibody and nonantibody substances directed against mediators of septic shock have been disappointing, with no significant effect on mortality (8). The complex nature of the pathophysiological processes in septic shock probably is related to the difficulty of modern intensive care to notably impact outcome. Mechanical ventilation, hemodynamic monitoring, antimicrobial therapy, and volume resuscitation combined with vasopressor support for refractory cases remain the standard of care for distributive/septic shock. Dopamine is considered by many as the vasopressor of choice when hypotension persists despite adequate fluid resuscitation (9–11). On the other hand, norepinephrine is considered to be deleterious. Because of fear of excessive vasoconstriction, many contend that this drug potentiates end-organ hypoperfusion, thereby contributing to increased mortality.

The aim of the present study was to identify factors associated with outcome in a cohort of septic shock patients. We paid special attention to the hemodynamic management and to the choice of the vasopressor used, to determine whether the use of norepinephrine could be associated with increased mortality.

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MATERIALS AND METHODS

Patient Eligibility

The study was approved by the Hospital Ethics Committee of our institution. During a 31-month period, 97 consecutive patients with septic shock were prospectively studied. These patients were consecutively admitted to the 16-bed general intensive care unit (ICU) of Nord Hospital, Marseilles University Hospital System. No patients were excluded from the study. Patients were included in the study on admission to the ICU, and we carefully followed up until discharge from the hospital.

Septic shock, according to the American College of Chest Physicians/Society for Critical Care Medicine Consensus Conference on sepsis and organ failure (12), was defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction (oliguria < 30 mL/hr, lactic acidosis, and alteration in mental status evaluated without sedative drugs). Sepsis was defined by two or more of the following conditions: temperature $> 38°C$ or $< 36°C$; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or the need for mechanical ventilation; and white blood cell count $> 12{,}000$ cells/mm^3 or $< 4{,}000$ cells/mm^3.

Monitoring

Heart rate, arterial pressure via an arterial catheter, central venous pressure, pulse oxymetry (SpO_2), and end-tidal CO_2 were continuously monitored in all patients. Urine was collected via an indwelling bladder catheter.

Data Collection

The following variables were collected on inclusion in the study: age, gender, underlying disease, arterial pH, urine flow, blood lactate, body temperature, blood creatinine, heart rate, and mean arterial pressure (MAP). Other variables were collected within 24–48 hrs: Acute Physiology and Chronic Health Evaluation (APACHE) II score (24 hrs); use of norepinephrine, dobutamine, dopamine, or other vasopressor (24 hrs); source of infection (48 hrs); bacteremia (48 hrs); documented infection (48 hrs); and presence of organ failure (72 hrs). The organ system failure index (OSFI) was derived from that described by Goris et al. (13). One point was given for dysfunction of each organ system by using the following definitions: renal, creatinine > 170 μmol/L; hepatic, a rise in the total bilirubin concentration to >34 μmol/L; respiratory, positive pressure ventilation with positive end-expiratory pressure > 10 cm H_2O and/or $FIO_2 > 0.4$; hematologic, platelets $< 50 \times 10^9$/L; central nervous system, clearly diminished responsiveness without sedation; cardiac, dopamine $> 10 \mu g \cdot kg^{-1} \cdot min^{-1}$ and/or the use of norepinephrine.

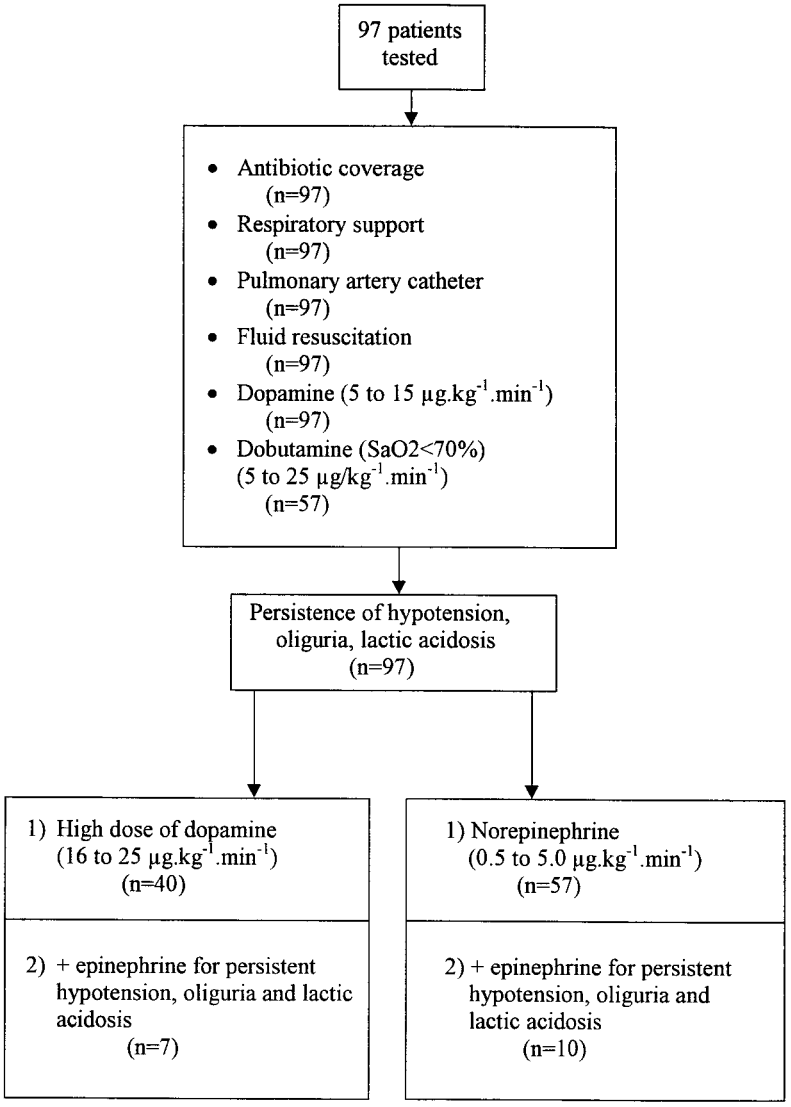

Figure 1. Trial profile. Decision tree for prescribing vasopressors in the study patients.

The type of hemodynamic management protocol used in each patient was prospectively noted. Patients were considered as survivors when they were discharged from the hospital.

General Supportive Measures

All patients received broad-spectrum antibiotic coverage, usually a beta-lactam and an aminoglycoside. Vancomycin was added when methicillin-resistant staphylococci were suspected. When culture results were obtained, the antibiotic regimen was adjusted. Antimicrobial therapy was considered adequate when all the strains isolated and presumably responsible for infection were susceptible to at least one of the antibiotics used. None of these patients received corticosteroids. Respiratory support was needed in all patients because of severe hypoxemia. Acute pneumonia was found in 55 patients and adult respiratory distress syndrome in the remaining patients. Tidal volume, respiratory rate, and FIO_2 were adjusted with the objective to keep $PaO_2 > 70$ mm Hg.

Hemodynamic Management

Initially patients with low ventricular preload (estimated from pulmonary artery occlusion pressure [PAOP]) were given fluid resuscitation with colloid (hydroxyethyl starch, in 6% solution of normal saline) and crystalloid (lactated Ringer's solution) with the objective to raise PAOP between 12 and 15 mm Hg. Blood hematocrit was maintained ±30% with packed red cell transfusions. In some patients, fluid infusion was discontinued before the targeted PAOP was reached: when at a given level, additional fluid infusion was no longer

accompanied by an increase in cardiac index, or when SpO_2 significantly decreased. During fluid challenge, but after ≥12 mL/kg of fluid had been given, vasopressor therapy (dopamine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) could be required although cardiac filling pressures were not yet adequate to maintain perfusion in face of very severe hypotension. After fluid challenge, all patients remained in clinical shock with oliguria and a MAP ≤ 65 mm Hg. Then dopamine was started in all patients at a dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ followed by 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increments, up to a dose of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Dobutamine was added at a dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increments if venous oxygen saturation was <70% (provided that SpO_2 was >95% and blood hematocrit >30%). The aim of therapy was to achieve and maintain MAP >70 mm Hg, venous oxygen saturation ≥70%, and urine flow >0.7 $mL \cdot kg^{-1} \cdot hr^{-1}$. If hypotension persisted with this treatment, dopamine was increased up to 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (high-dose dopamine 16–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$), or dopamine was kept at an infusion rate of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and norepinephrine was added, started at a dose of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with 0.3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ increments, up to a maximal dose of 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If the treatment failed to correct abnormalities in MAP, epinephrine was added (Fig. 1).

When hemodynamic status of patients was stable for at least 24 consecutive hours, progressive weaning of the drugs was begun.

Statistical Analysis

Univariate Analysis. Results are shown as mean ± SD. Normal distribution of data was checked for each variable by chi-square analysis. A univariate analysis was performed by analysis of variance or chi-square test. Homogeneity of variances was determined by the Bartlett's test. Kaplan-Meier survival curves were constructed and compared by a log-rank statistic (14). Statistical significance was attributed to $p < .05$.

To evaluate the influence of the different variables on outcome (survival during hospital stay evaluated on day 7, on day 28, and on hospital discharge), we examined the distribution of clinical characteristics in relation to outcome of the patients by using categorical data analysis, and we calculated the corresponding chi-square statistic. The relative risk and 95% confidence intervals were used as measures of association between a clinical factor and death risk. For continuous variables, cutoff points were determined before the analysis and were defined as follows: age > 75 yrs, urine flow < 10 $mL \cdot hr^{-1}$, blood lactate ≥ 4 $mmol \cdot L^{-1}$, MAP < 50 mm Hg, blood creatinine > 200 $\mu mol \cdot L^{-1}$, body temperature < 36°C, and arterial pH < 7.1.

Multivariate Analysis. To further evaluate the influence of the different variables on survival during hospital stay, we performed a multivariate procedure on the studied qualitative variables. The aim of this analysis was to determine the concomitant effects of the quantitative variables on hospital survival or death. For that purpose, the last step in the analysis was to develop a logistic regression analysis. A logistic regression model was developed to predict survival while controlling for other potential confounding factors. The aim was to find the best model and then to test whether the inclusion of the selected variables added significant power.

To determine the independent contribution of the variables to outcome, we used a logistic regression analysis and a model building strategy (15, 16). The goal was to select those variables that result in a "best" model to predict outcome of septic shock patients. On completion of the univariate analysis, those variables whose univariate test had a $p < .25$ were considered candidates for the multivariate model (15, 16). The use of a more traditional level (such as .05) often fails to identify variables of importance. Use of larger level has the disadvantage of including variables that are of questionable importance (16). We then performed stepwise selection of variables (multivariate analysis by stepwise logistic re-

Table 1. Hospital mortality rates observed according to the studied variables (univariate analysis)

Variables	Mortality Rate (% yes/no)	*p* Value
Age, >75 yrs	87/67	.07
Male	70/69	.97
Underlying disease	86/64	.08
Pneumonia	82/61	.03
Peritonitis	71/64	.41
Bacteremia	68/73	.90
Documented infection	67/76	.41
Heart rate, >130 beats·min^{-1}	73/68	
Mean arterial pressure, <50 mm Hg	61/72	.24
Urine flow, <10 ml·hr^{-1}	88/61	.01
Arterial pH, <7.1	74/67	.83
Blood lactate, >4 mmol·L^{-1}	91/63	.01
Creatinine > 200 $\mu mol \cdot L^{-1}$	77/68	.31
Organ system failure index score, ≥3	92/60	.001
Use of norepinephrine	62/84	.001
Use of high-dose dopamine	66/74	.54
Use of dobutamine	65/73	.52
Use of epinephrine	71/63	.52

Table 2. Distribution and relative risk for outcome-related risk or protective factors in patients with septic shock

	Relative Risk (Confidence Limit, 95%)	*p* Value
Protective factor	0.68 (0.54–0.87)	.03
Use of norepinephrine		
Risk factors		
Lactate, >4 mmol·L^{-1}	1.60 (1.27–1.84)	.002
Urine flow <10 mL·hr^{-1}	1.44 (1.06–1.87)	.005
Pneumonia	1.47 (1.07–1.77)	.04
Organ system failure index, ≥3	1.47 (1.17–1.82)	.01
Indifferent factors		
Underlying disease	0.93 (0.74–1.23)	NS
Creatinine, >200 $\mu mol \cdot L^{-1}$	0.84 (0.54–1.21)	NS
MAP, <50 mm Hg	1.11 (0.84–1.43)	NS
Bacteremia	0.77 (0.64–1.28)	NS
Peritonitis	0.91 (0.68–1.20)	NS
Age, >75 yrs	0.77 (0.53–1.30)	NS
Documented infection	1.29 (0.93–1.60)	NS
Body temperature, <36°C	1.10 (0.39–2.54)	NS
Heart rate, >130 beats/min	0.80 (0.63–1.27)	NS
Arterial pH, <7.1	0.84 (0.71–1.27)	NS
Use of high-dose dopamine	1.04 (0.74–1.57)	NS
Use of epinephrine	0.94 (0.67–1.35)	NS
Use of dobutamine	0.84 (0.59–1.74)	NS

MAP, mean arterial pressure.

gression; SAS/STAT Program, SAS Institute, Cary, NC). This provided an effective means to screen a large number of variables and to simultaneously fit a number of logistic regression equations. Final multivariate logistic model included only the factors that remained independently and significantly associated with outcome during hospital stay after adjustment for the effects of all other variables. When variables independently related to outcome were determined and the predictive model was established, we calculated the association of predicted probabilities and observed clinical responses.

RESULTS

The 97 patients were 29 women and 68 men with a mean age of 53 ± 12 yrs; the mean APACHE II score was 28 ± 4. All patients needed mechanical ventilation. Causes of septic shock were 50 pneumonia (52%), 33 peritonitis (34%), and 14 miscellaneous etiologies (11%). The hospital mortality was 73% (70 patients). All patients with peritonitis had positive cultures of abdominal fluid. Antibiotic selection was appropriate to all strains of *Enterobacteriaceae* isolated. Coverage of anaerobic bacteria was obtained by the use of a betalactam antibiotic + inhibitor (piperacilin-tazobactam) or imipenem. Nine patients with pneumonia had negative bronchoalveolar lavage cultures. The other patients with pneumonia had positive bronchoalveolar lavage cultures. In three of these patients, the initial antibiotic regimen was not appropriate and treatment was modified on day 2, according to the culture results. For other infections (skin infections, five patients; urinary tract infections, seven patients; catheter-related infections, two patients), cultures were all positive and the antibiotic treatment was appropriate to the isolated pathogens.

Tables 1 and 2 present the prognostic values of the variables possibly related to outcome (univariate analysis). The use of norepinephrine as part of the hemodynamic support was strongly related to a favorable outcome and was considered as a protective factor that markedly decreased hospital mortality. Four factors were considered as risk factors and were associated with unfavorable outcome: elevated lactate concentration (≥ 4 mmol·L^{-1}), low urine flow (<10 mL·hr^{-1}), pneumonia as the cause for septic shock, and OSFI ≥ 3 (Tables 1 and 2). Other tested factors including the use of high-dose dopamine and of epinephrine were of minor importance and did not significantly influence outcome.

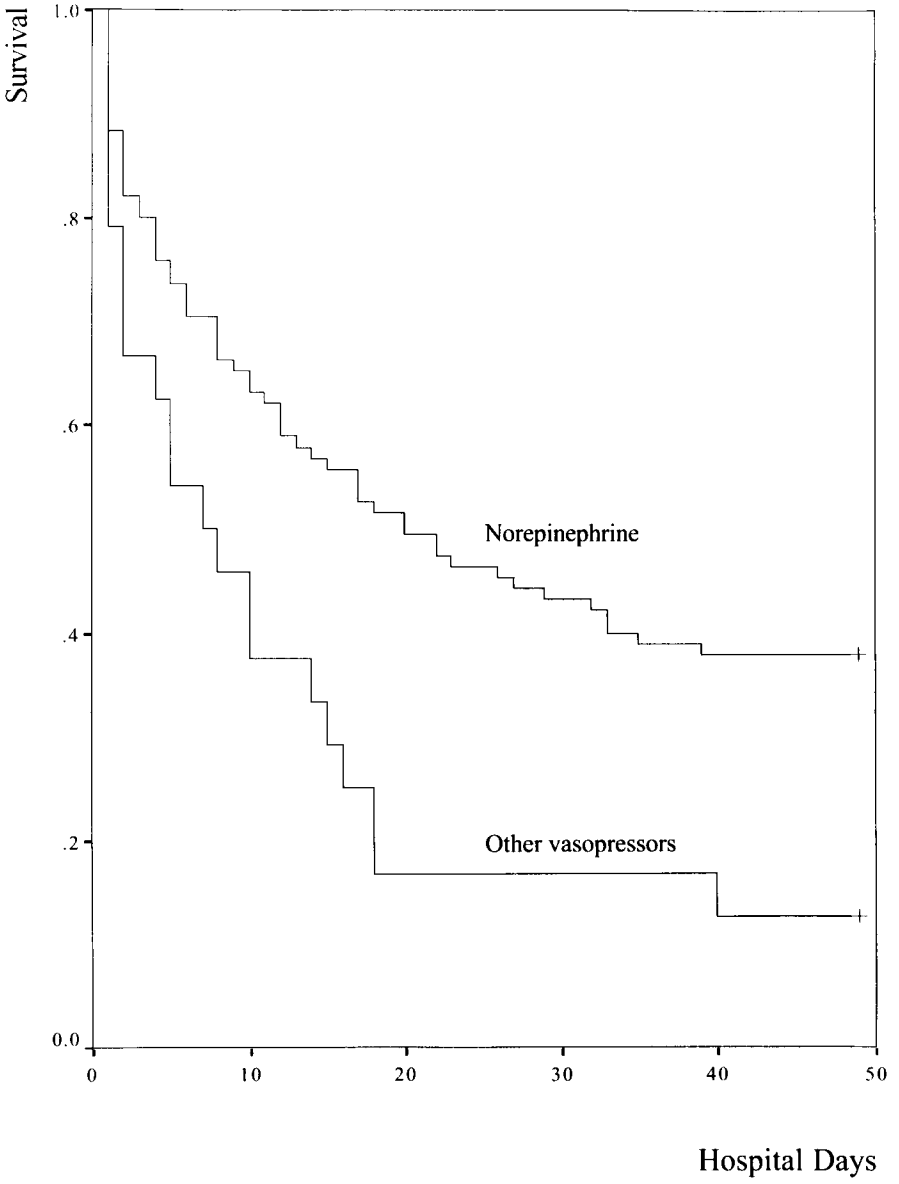

Figure 2. Survival Kaplan-Meier curves for patients treated according to the use of norepinephrine or other vasopressors. A significantly better survival (log-rank test) was observed for patients treated with norepinephrine. ($p < .001$).

Figure 2 shows a significantly ($p < .001$) better survival for patients treated with norepinephrine as part of their hemodynamic support (Kaplan-Meier survival curves). Mortality was lower in these patients on day 7 (28% vs. 40%, $p < .005$), on day 28 (55% vs. 82%, $p < 0.001$), and on hospital discharge (62% vs. 84%, $p < 0.001$). In Table 3, patients treated with norepinephrine were compared with patients not treated with norepinephrine, to exclude potential differences that might have explained the difference in survival. Table 3 shows that the patients had similar characteristics. Table 4 shows the hemodynamic support used in patients treated or not with norepinephrine. Five out of the seven patients who received epinephrine in addition to high-dose dopamine died in intractable shock. Seven out the ten patients who received epinephrine in addition to norepinephrine also died in intractable shock.

The multivariate analysis and model building are presented in Table 5. Once again, the use of norepinephrine as part of the hemodynamic support was the only factor associated with a favorable outcome. Four factors were independently and significantly associated with an unfavorable outcome in the multivariate logistic model: pneumonia as the cause for septic shock ($p < .05$), low urine flow and

Table 3. Characteristics of patients according to the presence or absence of norepinephrine in hemodynamic support

	Patients Who Received Norepinephrine (n = 57)	Patients Who Did Not Receive Norepinephrine (n = 40)
Age (yrs)	54 ± 12	57 ± 15
Male (%)	37 (65)	31 (77)
APACHE II score	28 ± 4	28 ± 3
Lactate ($mmol \cdot L^{-1}$)[a]	5.4 ± 1.7	5.7 ± 1.9
Urine flow ($mL \cdot hr^{-1}$)[a]	14 ± 12	17 ± 13
Heart rate (beats/min)[a]	124 ± 17	125 ± 13
MAP (mm Hg)[a]	54 ± 7	56 ± 9
Creatinine ($\mu mol \cdot L^{-1}$)[a]	216 ± 184	197 ± 167
Causes of septic shock (%)		
Peritonitis	20 (35)	13 (32)
Pneumonia	30 (53)	20 (50)
Other infections	7 (12)	7 (18)
Documented infections (%)	52 (91)	36 (90)
Underlying diseases (%)	57 (100)	37 (93)
Multiple trauma	15 (26)	10 (27)
Complicated vascular surgery	15 (26)	11 (30)
Complicated abdominal surgery	17 (30)	12 (32)
Cancer	10 (18)	4 (11)
Neutropenia	0 (0)	0 (0)

APACHE, Acute Physiology and Chronic Health Evaluation; MAP, mean arterial pressure.
[a]At study entry. No significant differences were observed for the studied variables.

Table 4. Therapies used to treat septic shock with regard to the hemodynamic management used

	Patients Who Received Norepinephrine (n = 57)	Patients Who Did Not Receive Norepinephrine (n = 40)
Fluid expansion (mL) (initial fluid resuscitation)	1827 ± 673	1742 ± 717
Norepinephrine (patients)	57	—
Maximal dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	2.27 ± 2.10	—
Duration (days)	7 ± 3	—
Dobutamine (patients)	32	25
Maximal dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	18 ± 10	15 ± 7
Duration (days)	6 ± 4	4 ± 7
Dopamine (patients)	57	40
Maximal dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	13 ± 5	22 ± 7[a]
Duration (days)	3 ± 3	3.5 ± 6
Epinephrine (patients)	10	7
Maximal dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	2.7 ± 3.1	2.9 ± 2.9
Duration (days)	2.1 ± 2.2	3.1 ± 2.9

—, not applicable.
[a]$p < .01$.

high lactate concentration before treatment was started ($p < .001$), and OSFI ≥ 3 ($p < .001$). The efficiency of the predictive model was high as shown by the 86% concordance between probabilities predicted by the model and observed clinical responses of individual patients (2,916 pairs of data were evaluated).

DISCUSSION

The present data show that mortality in the study patients was strongly associated with high blood lactate concentration and low urine output at time of onset of septic shock, with pneumonia as a cause for septic shock, and with OSFI ≥3. Mortality was favorably influenced by the use of norepinephrine as part of the hemodynamic management.

Early studies showed that norepinephrine could be effective, but because of the lack of routine hemodynamic monitoring and the fear of excessive vasoconstriction, this drug is not used widely (15–19). Indeed, the inappropriate use of potent vasopressor agents in hypovolemic situations leads to tissue hypoperfusion and severe ischemia of vital organs (20). Many clinicians are reluctant to use norepinephrine because of findings from dated studies with no relevance to our current understanding of the hemodynamic management of patients with septic shock. Thus, many consider dopamine to be the pressor of choice when hypotension persists in septic shock patients despite fluid resuscitation (21–23). However, several studies have shown that an adequate tissue perfusion pressure cannot be obtained in many patients with the use of dopamine, even at doses as high as 80 μg/kg/min (24–27). In these studies, norepinephrine was found to be beneficial, with improvement in arterial blood pressure, urine flow, oxygen delivery, and consumption. Our critical care team has observed many favorable outcomes from the use of norepinephrine, which may be attributable, in part, to the special attention paid to achieving effective circulating volume replacement before prescribing the vasopressor agents. These subjective observations needed confirmation from more scientific data, which led to the multivariate analysis performed in the present study. We hypothesized that norepinephrine could increase blood pressure without impairing organ perfusion and hence could contribute to a better outcome.

Several investigators have demonstrated the ability of norepinephrine to raise arterial pressure and systemic vas-

Mortality in the study patients was strongly associated with high blood lactate concentration and low urine output at time of onset of septic shock, with pneumonia as a cause for septic shock, and with organ system failure index ≥3. Mortality was favorably influenced by the use of norepinephrine as part of the hemodynamic management.

Table 5. Multivariate logistic model including the factors that remained independently and significantly associated with outcome

Variables	Coefficient (C)	Standard Error (SE)	C:SE Ratio	*p* Value
Protective factor				
Use of norepinephrine	2.3718	0.8019	2.95	.003
Risk factors				
Organ system failure index = 3	0.0723	0.0212	3.41	.001
Pneumonia	1.1576	0.5003	2.31	.05
Lactate > 4 mmol·hr^{-1}	0.3422	0.1350	2.53	.001
Urine flow < 10 mL·hr^{-1}	−0.0418	0.0239	1.74	.08

The ratio of coefficient to standard error (C:SE) can be read roughly as *t* statistics. Absolute value >2 indicates variable of significant effect on outcome in the presence of other variables.

cular resistance while preserving cardiac function in patients with septic shock (24–26, 28–30). Septic shock is characterized by depression of both left and right ventricular function. Vasopressor infusion should not be considered in patients with high systemic vascular resistance because elevated cardiac afterload obtained by straining the myocardium could be deleterious in cases of severe cardiac dysfunction. This point is crucial: A potent vasopressor such as norepinephrine must be used only to restore normal values of systemic vascular resistance and/or systemic arterial blood pressure in patients with severe and documented vasodilation. We demonstrated that although norepinephrine markedly increased biventricular afterload conditions, a significant improvement in right ventricular function was observed in septic shock patients treated with norepinephrine (31). This was explained in part by beta-1 stimulation and to a greater extent by a correction of systemic hypotension followed by an increase in coronary perfusion pressure.

Studies have demonstrated the beneficial effects of norepinephrine on renal function during septic shock (25, 28, 32, 33). In patients with hypotension and hypovolemia (e.g., during hemorrhagic shock), the use of vasopressors should be avoided for the following reasons: Despite the constant improvement in blood pressure, renal blood flow decreases and renal vascular resistance rises (19). The situation is different in hyperdynamic septic shock. It is speculated that urine flow decreases mainly as a result of lowered glomerular perfusion pressure. Because norepinephrine has a greater effect on efferent than on afferent arteriolar resistance (33) and increases the filtration fraction, normalization of renal vascular resistance could effectively reestablish urine flow. Schaer et al. (34) demonstrated in dogs that when cardiac index is normal or elevated, norepinephrine increases renal vascular resistance but renal blood flow remains stable or even increases. The increase in urine output observed in patients treated with norepinephrine also could be explained by a decrease in antidiuretic hormone release, which, through different mechanisms, favors water retention (35). Cardiac and sinoaortic baroreceptors are sensitive to pressure, and in case of low intravascular pressure, they activate the sympathic system and increase antidiuretic hormone secretion. Restoration of adequate systemic and central pressures in patients with septic shock probably inhibited vasopressin secretion (36).

Fears of excessive vasoconstriction and accentuated organ hypoperfusion may lead to concern about splanchnic ischemia. This concern also appears to be unwarranted. Marik et al. (37) showed that the use of norepinephrine resulted in a significantly greater increase in phi than dopamine, suggesting an uncompensated increase in oxygen requirement with dopamine and an improvement in splanchnic oxygen utilization with norepinephrine. Likewise, Meier-Hellman et al. (38) showed a significant increase in splanchnic blood flow and oxygen delivery in patients treated with norepinephrine. One also could speculate that norepinephrine infusion might contribute to the progression of multiple organ failure by potentiating end-organ hypoperfusion, thereby increasing mortality. Indices of hypoperfusion like splanchnic blood flow, phi, or glomerular filtration rate were not measured in the present study, but the relationship between the use of norepinephrine and the development of multiple organ dysfunction syndrome was carefully examined by Goncalves et al. (39). The conclusion of their multivariate analysis was that the use of norepinephrine failed to predict mortality although APACHE III score and multiple organ dysfunction score did. Their data clearly contradict the notion that norepinephrine facilitates the development of multiple organ dysfunction. Nonsurvivors succumbed secondary to the severity of their illness and underlying conditions, and not as a result of norepinephrine therapy (39).

One point should be discussed in more detail: Should we use dopamine or norepinephrine as the "first-line" inotropic agent? The first point is that during the initial therapy of septic patients who have clinical signs of shock despite initial fluid resuscitation, vasopressor therapy should be started to support organ function, sometimes before the adequacy of intravascular volume can be ensured (11). In this setting, dopamine, which can increase both pressure and flow, is the first choice (at a dose range of 5–10 15μg·kg^{-1}·min^{-1}, as in the present study). In patients who receive adequate fluid resuscitation and remain hypotensive despite the use of dopamine, the present study clearly shows that norepinephrine is superior to high-dose dopamine. This conclusion is supported by a previous randomized clinical trial that also favored norepinephrine over dopamine in a small group of patients with hyperdynamic septic shock. Presently we do not have the data to make firm recommendations for the therapy of hemodynamically unstable patients. The present study underscores some benefits of the use of norepinephrine in adequately fluid resuscitated patients.

Epinephrine also was used in the study patients when norepinephrine or high-dose dopamine failed. This was the case in 17.5% of patients in each group. Five out of the seven patients who received epinephrine in addition to high-dose dopamine died in intractable septic shock. Seven out of ten patients who received epinephrine in addition to norepinephrine also died in intractable septic shock. Epinephrine did not appear as a significant factor in the multivariate analysis, probably for two reasons: a) an inadequate sample size (seven and ten patients); and b) a prescription in very severe forms of septic shock resistant to fluid loading, dobutamine, high-dose dopamine, or norepinephrine.

We also observed that blood lactate concentrations are reliable prognostic indicators. This confirms results from previous investigators (40–42). The time-course of lactate under treatment is of great interest, but high concentrations at the onset of septic shock are also interesting to consider. Hyperlactatemia requires careful interpretation, which is beyond the scope of this study. However, it can be considered as a simple bedside prognostic index that enables the clinician to identify patients early with a high risk of fatality.

As expected, multiple organ dysfunction was an independent predictor of poor outcome (12). Almost all the nonsurvivors in the present study had dysfunction of at least three organ systems, whereas survivors generally had dysfunction of two or one organ systems.

Other studies (4–6, 40–42) have aimed to identify prognostic variables in human sepsis. The present study provides new insight because of its design. Indeed, our ICU serves as a referral center, and thus only patients with severe forms of septic shock were treated. Severity can be assessed by the high APACHE II score, the fact that most patients had underlying diseases (cancer, complicated surgery, trauma), and the fact that respiratory failure led to the use of mechanical ventilation for all patients. Mortality related to septic shock was high in the study patients; however, this is in accordance with other studies on patients with severe forms of septic shock (1, 3). Hence, it is likely that studying such patients accounts for the rather high mortality observed, and we cannot eliminate some bias attributable to the selection of the patients. Because of the possibility that the underlying disease itself could lead to early mortality, we evaluated mortality at three different time points: 7 days, 28 days, and hospital discharge. On these three time points, mortality was significantly lower in the norepinephrine group than in the other group (see Results section and Fig. 2)

In conclusion, within the limits of this study, five variables were independently and significantly associated with outcome of septic shock patients. Four factors were associated with a poor outcome: pneumonia as a cause of septic shock, OSFI ≥ 3, and low urine output and high blood lactate concentration at the time of onset of septic shock. One factor, the use of norepinephrine as part of the hemodynamic support, was associated with a highly significant decrease in hospital mortality. The data contradict the notion that norepinephrine potentiates end-organ hypoperfusion through excessive vasoconstriction, thereby increasing mortality. However, the present study suffers from some limitations because of its nonrandomized, open-label, observational design. Hence, whether norepinephrine clearly affects mortality of septic shock patients, as compared with high-dose dopamine or epinephrine, should be confirmed by a randomized trial.

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