Influence of vasopressor agent in septic shock mortality. Results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study)*

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Objective: **Guidelines for the adrenergic support of septic shock are controversial. In patients with community-acquired septic shock, we assessed the impact of the choice of vasopressor support on mortality.**

Design: **Cohort, multiple center, observational study.**

Setting: **Seventeen Portuguese intensive care units (ICUs).**

Patients: **All adult patients admitted to a participating ICU between December 2004 and November 2005.**

Interventions: **None.**

Measurements and Main Results: **Patients were followed up during the first five ICU days, the day of discharge or death, and hospital outcome. Eight hundred ninety-seven consecutive patients with community-acquired sepsis (median age, 63 years; 577 men; and hospital mortality, 38%) were studied. Of the 458 patients with septic shock, 73% received norepinephrine and 50.5% dopamine. The norepinephrine group had a higher hospital mortality (52% vs. 38.5%, $p = 0.002$). A Kaplan–Meier survival curve showed diminished 28-day survival in the norepinephrine group (log-rank = 22.6, $p < 0.001$). A Cox proportional hazard analysis revealed that the administration of norepinephrine was associated with an increased risk of death (adjusted hazard ratio, 2.501; 95% confidence interval, 1.413–4.425; $p = 0.002$). In a multivariate analysis with ICU mortality as the dependent factor, Simplified Acute Physiology Score II and norepinephrine administration were independent risk factors for ICU mortality in patients with septic shock.**

Conclusions: **In patients with community-acquired septic shock, our data suggest that norepinephrine administration could be associated with worse outcome. (Crit Care Med 2009; 37: 410–416)**

KEY WORDS: vasopressors; catecholamines; vasoactive agents; community-acquired sepsis; septic shock; survival

Community-acquired sepsis remains a common and serious illness and a leading cause of death despite an aggressive therapeutic and supportive care.

A recent European epidemiologic study, the Sepsis Occurrence in Acutely Ill Patients (SOAP), was performed to identify the frequency of sepsis in European intensive care units (ICUs) and recognize various etiological, diagnostic, therapeutic, and prognostic factors (1). Only six Portuguese ICUs participated in the SOAP study, and, in addition, in the 2-week period of patient enrolment, only 69 patients were included, and sepsis was diagnosed in just 50. Our study, Portuguese Community-Acquired Sepsis study (Sepsis Adquirida na Comunidade e internada em Unidade de Cuidados Intensivos [SACiUCI]), was designed to characterize the epidemiology of community-acquired sepsis in patients admitted to Portuguese ICUs and, in addition, to assess the level of compliance with Surviving Sepsis Campaign recommendations (2).

Persistence of hypotension after an adequate fluid challenge should receive adrenergic support (3). The adrenergic agents are divided into inoconstrictors (norepinephrine, adrenaline, and dopamine) and inodilators (dobutamine, dopexamine, and isoproterenol) (4, 5). Dopamine has been classified by several experts as the "complete" catecholamine (6, 7) because, depending of its dose, it could have δ, β_1, β_2, and α_1 activity (2). However, randomized controlled trials evaluating the efficacy and safety of the different catecholamines in the treatment of shock, in particular, septic shock, are still lacking. As a result, according to the Surviving Sepsis Campaign guidelines, both norepinephrine and dopamine are recommended as first-line agents in the treatment of septic shock (2), although phase II trials have yielded conflicting results (8, 9).

From the SOAP database (10), the authors showed that shock patients treated with dopamine had significantly higher hospital mortality (49.9% vs. 41.7%, $p = 0.01$). However, as the authors clearly pointed out, the SOAP study is an observational study not designed to assess the efficacy and safety of vasopressor agents. The results from three large trials in patients with septic shock, comparing vasopressin vs. norepinephrine, VASST study (11), epinephrine vs. combined dobutamine and norepinephrine, CATS study (12), and dopamine vs. norepinephrine (De-Backer D, Clinical Trials NCT00314704), would hopefully bring some light to this debate (13).

The present analysis from the SACiUCI study was performed to assess

***See also p. 736.**

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the impact of vasopressor choice in septic shock mortality. In addition, the compliance and the impact of the hemodynamic-related interventions from sepsis care bundles on mortality, namely, the use of vasopressors after fluids if mean arterial pressure (MAP) <65 mm Hg and use of inotropes from the resuscitation 6-hour bundle and low-dose steroids for patients with septic shock from the management 24-hour bundle, were also investigated.

MATERIALS AND METHODS

Study Design. The SACiUCI study was a prospective, multiple center, observational study designed to evaluate the epidemiology of community-acquired sepsis in patients who are admitted in Portuguese ICUs. The ICU recruitment was by direct invitation, with no financial incentive. First, the study was submitted to the National Ethics Committee for approval. Subsequently, Local Hospital Ethics Committees approved the study design, and informed consent was waived because this was an observational study without any deviation from the current medical practice. All the patients who were ≥18 years newly admitted to the participating ICUs (see Appendix for a list of the participating ICUs) from December 2004 to November 2005 were consecutively enrolled. Patients were followed up until death or hospital discharge. Only the first ICU admission was included.

Definitions. Infection was defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by a pathogenic or potentially pathogenic microorganism (14) and/or clinically suspected infection plus the prescription of antimicrobial therapy. Community-acquired infection was defined as the onset of infection before hospital admission or not present at admission but becomes evident in the first 48 hours (15). Presence of sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria by the presence of a documented or suspected infection plus at least two of the systemic inflammatory response syndrome criteria (16). Severe sepsis was defined as sepsis complicated by organ dysfunction, and septic shock refers to a state of acute circulatory failure characterized by persistent arterial hypotension (systolic arterial pressure <90 mm Hg, a MAP <60 mm Hg, or a reduction in systolic arterial pressure of >40 mm Hg from baseline) despite adequate fluid resuscitation (14, 16). Emergency surgery was defined as a nonscheduled surgery within 24 hours before ICU admission.

Patients were classified according to their primary admission diagnosis into five categories: medical coronary, medical noncoronary, trauma, scheduled surgery, and emergency surgery. Patients with community-acquired sepsis were segregated in a cohort and divided according to mutually exclusive primary infection source: respiratory, neurologic, urologic, intra-abdominal, skin and soft tissues, gynaecologic and obstetrics, endovascular, and others. The initial management of patients with community-acquired sepsis was scrutinized according to the Surviving Sepsis Campaign guidelines to describe the compliance with the recommendations (2).

Data Collection and Management. Data were collected prospectively using preprinted case report forms, using a specific database software, or on line through the study web page. All data were collected in a central database located at the Department of Biostatistics and Medical Informatics (Serviço de Bioestatística e Informática Médica – SBIM), Medical School, University of Porto, Porto, Portugal. Detailed instructions concerning the aims of the study and data collection were given to all participating centers and were also available at the study Web site (epr.med.up.pt/sepsis/) before starting data collection and throughout the study period. A medical doctor was individually designated as responsible for data collection in each ICU. The participating centers had a constant feedback of the patients included and any problems related with the data because the program was designed to identify and reject inconsistencies. The steering committee was easily accessible to all participating investigators by phone or e-mail to answer all queries during the study.

Each case report form has 237 items. The assessment of the compliance with sepsis care bundles was done by all or no technique. Data collection included demographic data and comorbid diseases. Clinical and laboratory data at the time of hospital admission, as well as the time till ICU admission were recorded. The Simplified Acute Physiology Score (SAPS) II (17) was calculated from the worst values within 24 hours after ICU admission. Microbiological and clinical infectious data were reported, along with the antibiotics prescribed, their changes, and the duration of therapy. Organ dysfunction was evaluated at hospital admission and during the first 5 days of ICU stay based on a set of clinical and laboratory variables according to the Sequential Organ Failure Assessment (SOFA) score (18). The vasopressor support during the first 5 days of ICU stay, namely, the use of dopamine, norepinephrine, and dobutamine, was closely scrutinized. In addition, the prescription of low-dose steroids in patients with septic shock was also assessed.

Statistical Analysis. Continuous variables were expressed as median and interquartile range unless stated otherwise. Comparisons between groups were performed with two-tailed unpaired Student's t test, one-way analysis of variance, Mann-Whitney U test, or Kruskal-Wallis H test for continuous variables according to data distribution. *Post hoc* multiple comparisons were performed with the Bonferroni test. Fisher's exact test and chi-square test were used to carry out comparisons between categorical variables as appropriate.

We performed a multivariate, forward stepwise, logistic regression analysis with ICU mortality as the dependent variable in patients with community-acquired septic shock. To assess the impact of the adrenergic support on mortality during the first 5 days of ICU stay, variables considered for the multivariate analysis included age, sex, admission diagnoses, SAPS II, SOFA score, the choice of vasopressor support, specifically vasopressor agents (norepinephrine or dopamine), and the need of inotropic support (dobutamine). Variables were introduced in the multivariate model if significantly associated with a higher risk of ICU mortality on a univariate basis at $p < 0.1$. Multicolinearity between all these discrete variables was checked by computing pairwise correlation coefficient (r) between variables taken two by two. An $r < .4$ was considered low enough to exclude correlation between the predictors. After adjustment for demographic variables, admission diagnoses, and severity scores, the need of each adrenergic agent (norepinephrine, dopamine, and dobutamine) was injected in the model in a stepwise fashion. The use of each catecholamine was introduced in the last step as a categorical variable. Furthermore, a multivariate, forward stepwise, logistic regression analysis was performed to assess the impact on mortality of the compliance with the variables from the resuscitation 6-hour bundle and management 24-hour bundle related to septic shock handling, namely, the use of vasopressors after fluids if MAP <65 mm Hg and use of inotropes from the 6-hour bundle and low-dose steroids from the 24-hour bundle. The variables age, sex, admission diagnoses, SAPS II, and SOFA scores were also introduced in the model. A Hosmer and Lemeshow goodness-of-fit test was performed; Nagelkerke pseudo R^2, classification tables, and odds ratios with 95% confidence interval (CI) were computed.

Kaplan-Meier survival curves were plotted for patients with septic shock in whom a vasoactive agent (dopamine, norepinephrine, and dobutamine) was prescribed vs. those who never received that agent and compared the curves using a signed log-rank test. To minimize the effect of censored data in the survival analysis, we considered 28-day survival as a target. The Cox proportional hazards model was used to evaluate the impact of administration or not of dopamine, norepinephrine, and dobutamine on mortality rate of septic shock patients. We calculated both univariate and SAPS II-adjusted hazards ratios. Data were analyzed using SPSS v. 15.0 for Windows (SPSS, Chicago, IL). All statistics were two-tailed, and significance was accepted for $p < 0.05$.

RESULTS

The participating ICUs (n = 17) represent 41% (150 of 362) of the Portu-

Table 1. Baseline characteristics of patients with community-acquired sepsis (n = 897)

Age, mean ± SD	60 ± 17
Sex, n (%)	
Female	320 (36)
Male	577 (64)
Simplified Acute Physiology Score II, mean ± SD	50 ± 19
Primary admission diagnoses, n (%)	
Medical noncoronary	699 (78)
Medical coronary	10 (1)
Trauma	38 (4)
Scheduled surgery	4 (0)
Emergency surgery	146 (16)
Intensive care unit length of stay, days, median (interquartile range)	9 (4.2–18.0)
Hospital length of stay, days, median (interquartile range)	18 (9.8–34.2)
Intensive care unit outcome, n (%)	
Nonsurvivors	265 (30)
Survivors	631 (70)
Hospital outcome, n (%)	
Nonsurvivors	337 (38)
Survivors	560 (62)

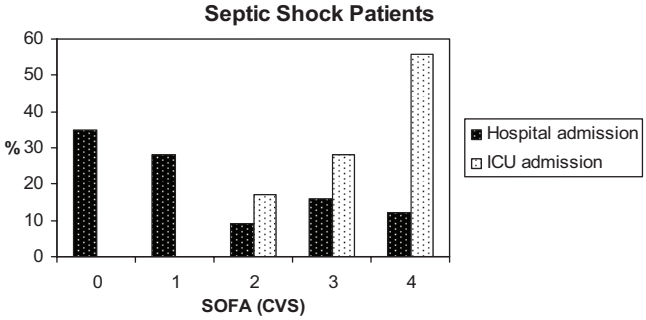

Figure 1. Cardiovascular Sequential Organ Failure Assessment (*SOFA*) score course of patients with septic shock from hospital to intensive care unit admission. The median time span between hospital and intensive care unit admission was 2 days. At hospital admission, 35% of the patients admitted in the intensive care unit in septic shock presented a cardiovascular SOFA score of 0 (zero), that is, without any cardiovascular dysfunction. Besides, at intensive care unit admission, cardiovascular failure, SOFA ≥3, occurred in 81% of the patients, whereas at hospital admission, only 28% presented such organ failure severity ($p < 0.001$). *ICU*, intensive care unit; *CVS*, cardiovascular.

guese ICU beds according to the 2001 Registry of the National Health Service. During the study period, a total of 4202 patients were admitted to the participating ICUs, of which 60 were excluded (53 were <18 years of age and 7 for incomplete data), resulting in 4142 patients to be analyzed. The median patient age was 64 years (mean ± SD, 60 ± 18 years), and 61% were men. Medical noncoronary admissions account for 54% of admissions, medical coronary 4%, trauma 13%, scheduled surgery 15%, and emergency surgery 14%. A total of 897 patients (22%) with community-acquired sepsis were included in the final analysis (Table 1). Almost two thirds of the patients with sepsis were admitted from the emergency room of the hospital of the participating ICU, and the remaining came from emergency departments of other hospitals.

Patients with community-acquired sepsis (n = 897) had a median age of 63 years (mean ± SD, 60 ± 17 years) and 64% were men and had a median SAPS II of 47 (mean ± SD, 50 ± 19). The median length of ICU stay was 9 days (interquartile range, 4.2–18 days; mean ± SD, 12 ± 11 days). The lung was by far the most common site of infection (61%), followed by the abdomen (18%) and urinary tract (7%). Cultures were positive in 40% of the patients, with *Streptococcus pneumoniae* (21%), *Escherichia coli* (18%), and methicillin-sensitive *Staphylococcus aureus* (12%) being the three most common isolated microorganisms. At ICU admission, 9% of patients with community-acquired sepsis presented with sepsis, 40% severe sepsis, and 51% septic shock.

The overall ICU and hospital mortality rate of community-acquired sepsis was 30% and 38%, respectively. The ICU mortality rate in patients with community-acquired sepsis was higher than in those without community-acquired sepsis at ICU admission (30% vs. 23%, $p < 0.001$). The ICU mortality rate of patients with community-acquired sepsis admitted with sepsis, severe sepsis, and septic shock was significantly different, 11%, 16%, and 44%, respectively ($p < 0.001$).

The median time span between hospital and ICU admission was 2 days (mean ± SD, 2 ± 2 days). Overall, the time interval was similar between survivors and nonsurvivors ($p = 0.897$) and between patients with sepsis, severe sepsis, and septic shock ($p = 0.201$). However, significantly more patients with septic shock were admitted to the ICU during the first day of hospitalization than with severe sepsis, 67% vs. 60% ($p = 0.026$). Mortality of patients admitted in the ICU in the first 6 hours of hospital admission was similar to those admitted in the first 12 hours and to those admitted very late, >48 hours after hospital admission, 32%, 31%, and 29%, respectively ($p = 0.624$).

Cardiovascular failure (cardiovascular SOFA ≥3) occurred in 77 patients (8.6%) with community-acquired sepsis at hospital admission. However, at ICU admission, this figure increased more than five times, to 51% ($p < 0.001$), consequence of a marked cardiovascular deterioration. At hospital admission (Fig. 1), 35% of the patients admitted in the ICU with septic shock presented no cardiovascular dysfunction.

The course of cardiovascular dysfunction was assessed during the first 5 days of ICU stay. In survivors, a marked cardiovascular improvement was observed, from 61% of patients with a cardiovascular SOFA score ≤2 at day 1 to 80% at day 5, whereas in nonsurvivors, the presence of cardiovascular failure (cardiovascular SOFA ≥3) on the fifth day was still elevated, 60% ($p < 0.001$). The resolution of cardiovascular dysfunction was faster in patients admitted to the ICU with sepsis than in those with severe sepsis and septic shock, in whom 47% persist in septic shock at day 5.

Vasopressor Agent and Septic Shock Mortality. In patients with septic shock (n = 458), norepinephrine was the most frequently administered vasopressor agent (73%), and it was used as a single drug in 31.6% of patients. Dopamine was used in 50.5% of patients with septic shock, as a single agent in 14.4% and

combined most commonly with norepinephrine in 20%. Dobutamine was combined with other vasopressor agents in 26.1% of patients, more often with norepinephrine (17.1%). All three catecholamines were given simultaneously in 7.2% of patients with septic shock.

Patients with septic shock treated with norepinephrine showed a significantly higher mortality rate than those treated with dopamine, 52% and 38.5%, respectively ($p = 0.002$). This difference in mortality rate was also observed among patients treated with norepinephrine and dopamine as the single vasopressor agent, 46.7% and 20.3%, respectively ($p < 0.001$). Patients who were treated with dobutamine associated either with norepinephrine or dopamine had a higher mortality rate than those treated only with vasopressor agents; however, they did not reach statistical significance, 52.2% and 41.1%, respectively ($p = 0.057$). Patients who received all three cathecolamines simultaneously, norepinephrine, dopamine plus dobutamine, were excluded from this analysis.

In a multivariate, logistic forward stepwise regression analysis with ICU mortality as the dependent factor, SAPS II and norepinephrine administration were found to be independently associated with a higher risk of death in patients with septic shock (Table 2).

The Kaplan-Meier survival curves of patients with septic shock are shown in Figure 2. Similarly, we found that the 28-day survival was significantly de-

Table 2. Summary of a multivariate forward stepwise logistic regression analysis with intensive care unit mortality as the dependent factor in patients with community-acquired septic shock

Septic Shock (n = 425)[a]	Odds Ratio	95% Confidence Interval	*p*
Simplified Acute Physiology Score II (per point)	1.051	1.035–1.067	<0.001
Norepinephrine	3.821	1.837–7.948	<0.001

[a]Hosmer and Lemeshow chi-square = 11.587 ($p = 0.171$), Nagelkerke $R^2 = .281$. This model has 72.2% correct classification (81.1% in survivors and 60% in nonsurvivors).

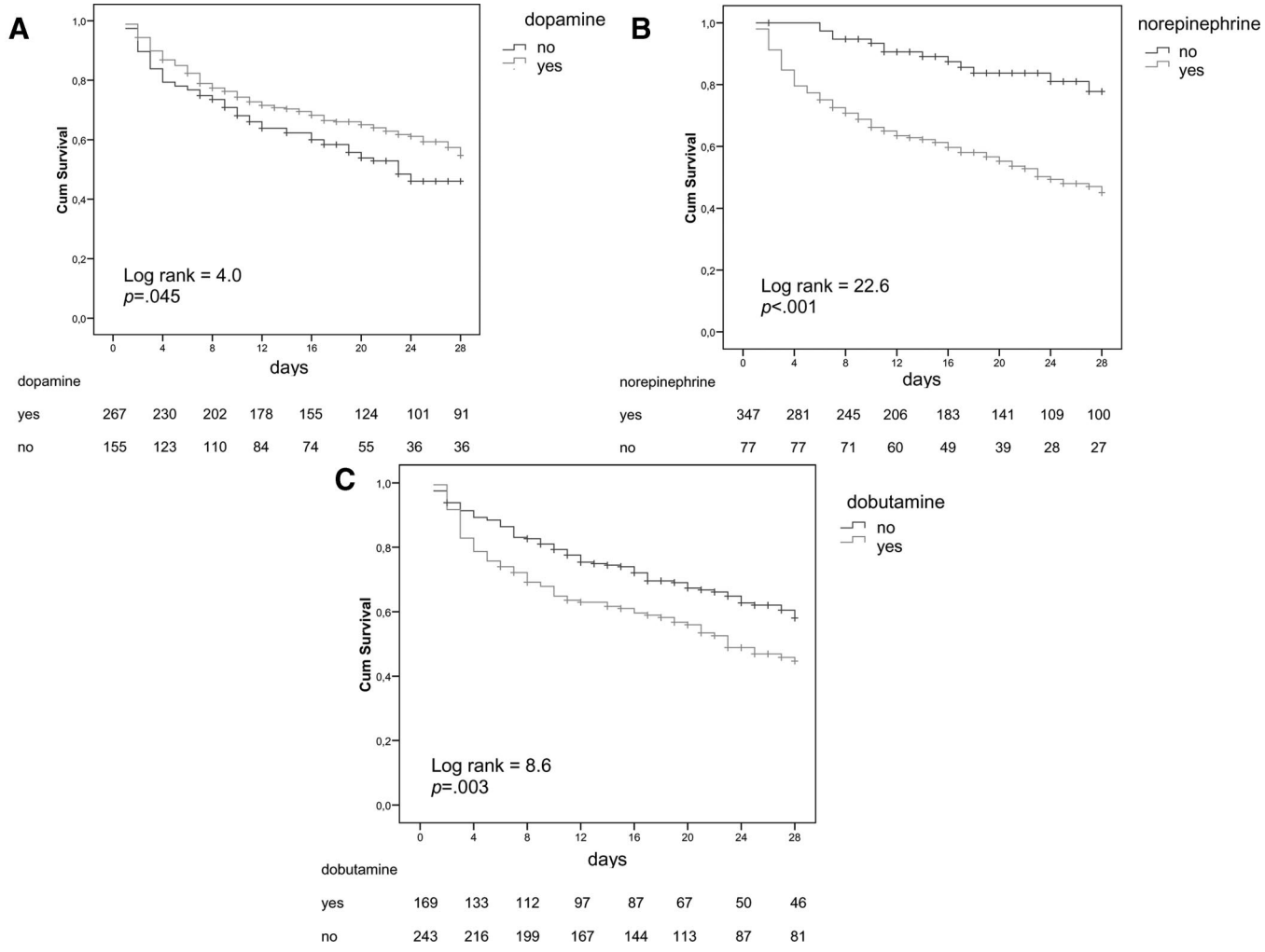

Figure 2. Kaplan-Meier survival curves at 28 days of intensive care unit admission in patients with septic shock according to the administration of dopamine (*upper*), norepinephrine (*middle*), and dobutamine (*lower*). Each graph represents the survival experience according to the prescription or not of each adrenergic agent (dopamine, norepinephrine, and dobutamine). Survival was decreased in patients who received norepinephrine and dobutamine in comparison with those who did not, whereas the use of dopamine improves survival.

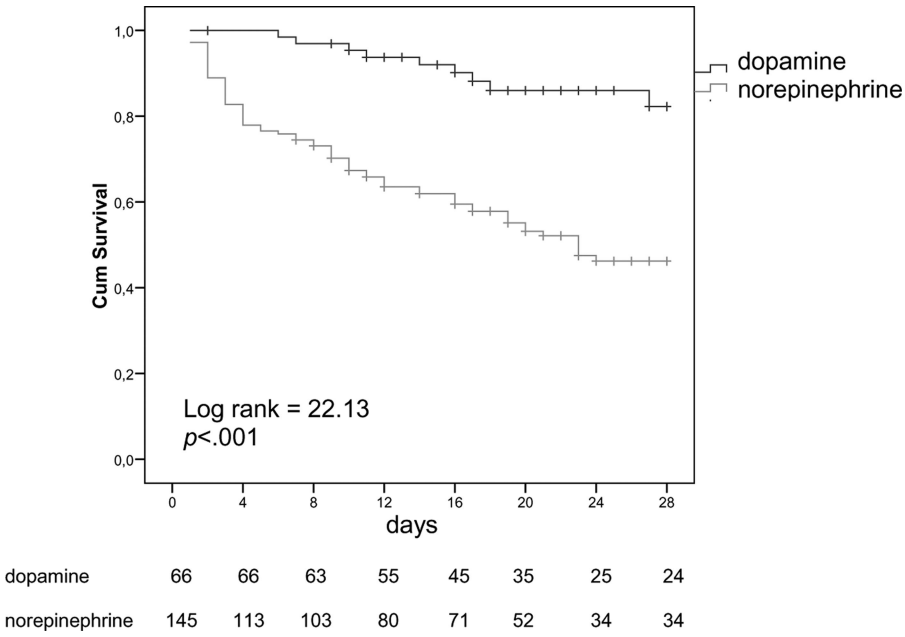

Figure 3. Kaplan-Meier survival curves at 28 days of intensive care unit admission in patients with septic shock treated only with norepinephrine or only with dopamine. Survival was significantly decreased in patients who received norepinephrine in comparison with those whose septic shock was treated with only dopamine.

creased in the norepinephrine group (log-rank = 22.6; $p < 0.001$), whereas in the dopamine group, there was a tendency toward a higher 28-day survival (log-rank = 4.0; $p = 0.045$). In addition, in patients treated with norepinephrine or dopamine as the single vasopressor agent, we found that the 28-day survival was significantly decreased in the norepinephrine group in comparison with dopamine (log-rank = 22.13; $p < 0.001$) (Fig. 3). Dobutamine administration was also associated with a significant decrease in 28-day survival (log-rank = 8.6; $p = 0.003$). Furthermore, we performed a Cox regression analysis to assess the hazard ratios (HRs) of the administration of each of the studied agent, dopamine, norepinephrine, and dobutamine, to define its independent effect on mortality. The dopamine group showed a decrease mortality risk, with a, HR = 0.742 (95% CI 0.552–0.999; $p = 0.049$). On the contrary, the norepinephrine and dobutamine groups were associated with an increase risk of death, with a, HR of 3.532 (95% CI 2.01–6.204; $p < 0.001$) and 1.548 (95% CI 1.148–2.088; $p = 0.004$), respectively. After adjustment of the regression model to the clinical severity assessed with the SAPS II, Cox proportional hazard analysis revealed that the administration of norepinephrine still remained significantly associated with an increase risk of death, with an adjusted HR of 2.501 (95% CI 1.413–4.425; $p = 0.002$).

Hemodynamic-Related Interventions of Sepsis Care Bundles and Mortality. The ICU mortality of patients with septic shock in whom vasopressors, either dopamine or norepinephrine, were used after fluids if MAP <65 mm Hg (from the resuscitation 6-hour bundle) was lower, although not statistically different from those in whom vasopressor agents were not initially prescribed, 42.3% and 55.9%, respectively ($p = 0.182$).

The use of inotropes, dobutamine, was limited (50%), partially reflecting the low implementation rate of the superior vena cava oxygen saturation measurements recommendation, just 13%. In our group of patients with septic shock, the ICU mortality was not influenced by the administration or dobutamine, 52.5% and 51.1%, respectively ($p = 1.0$).

Among patients with septic shock, low-dose steroids were administered as part of the management bundle in the first 24 hours of ICU admission in 51% of patients. The ICU mortality rate was higher in those treated with low-dose steroids, although not reaching significance, 54.5% and 41.7%, respectively ($p = 0.064$).

In a multivariate, logistic forward stepwise regression analysis with ICU outcome as the dependent factor designed to assess the impact on mortality of compliance with the variables of the resuscitation 6-hour bundle and management 24-hour bundle previously mentioned, only SAPS II (per point; adjusted odds ratio, 1.044; 95% CI, 1.022–1.067; $p < 0.001$) was found to be independently associated with a higher risk of death in patients with septic shock. However, in bivariate analysis with ICU mortality as the dependent factor, compliance with the variable use of vasopressors after fluids if MAP <65 mm Hg improves survival (odds ratio 0.522; 95% CI 0.287–0.950; $p = 0.033$).

DISCUSSION

We found among patients with community-acquired sepsis a marked cardiovascular deterioration between hospital and ICU admission. However, we were unable to demonstrate that this time delay influenced outcome. Our data also suggest that in patients with septic shock, norepinephrine administration may be associated with worse outcome, either used as a single agent or in combination, whereas dopamine administration seemed to have a beneficial effect. The use of dobutamine was associated with a higher mortality, although not reaching significance. Among the analyzed elements of sepsis bundles, we found a good compliance with the use of vasopressors-provided fluids have been given if MAP <65 mm Hg in the first 6 hours of diagnosis. On the contrary, the use of inotropic support was very restricted, just 50%. Concerning the use of low-dose steroids in patients with septic shock, the compliance was also quite low.

The time between hospital and ICU admission has not been previously investigated. The study of Rivers et al (19) clearly demonstrated that the time span between hospital and ICU admission was not the sole and crucial factor. Indeed, patients treated in the standard therapy arm stayed significantly lesser time in the emergency department than did the patients in the early goal-directed therapy arm, 6.3 ± 3.2 vs. 8.0 ± 2.1 hours, respectively ($p < 0.001$), and their hospital mortality was significantly higher, 46.5% vs. 30.5% ($p = 0.009$), respectively. We could hypothesize that the sooner patients are admitted to the ICU, the better because it is theoretically the place where these patients could receive the best supportive care. However, we were unable to find any influence on mortality of the time between hospital and ICU admission. This unexpected finding could be explained, at least in part, by the fact that

patients with septic shock were those who were admitted earlier in the ICU than those with severe sepsis, biasing the results.

One striking, but expected, result in our group of patients was the marked cardiovascular deterioration before the ICU admission. A systematic analysis of the potential causes of this finding was not performed, but several factors could have contributed: overcrowded emergency departments, shortage of medical staff, inability to correctly assess the severity of sepsis and to recognize the early signs of clinical deterioration, shortage of ICU beds, and lack of specific training. Besides, we were unable to determine whether the cardiovascular deterioration took place gradually or, on the contrary, suddenly just before ICU admission. These problems could have resulted in an inadequate identification of patients with community-acquired sepsis at risk and in an insufficient treatment and support before ICU admission, as others have already pointed out (20).

The discussion concerning the best vasopressor agent in patients with septic shock is not yet concluded. Data from the SOAP study suggested that the use of dopamine as a vasopressor agent in patients with shock, from which only 14.7% was of septic origin, was associated with higher mortality when compared with norepinephrine (10). We were unable to reproduce these findings. However, our patient population is markedly different because our patients with shock were solely of septic origin. Our data suggest that norepinephrine administration in patients with septic shock could be associated with a worse outcome, with a 3.5 increase in the 28-day mortality risk. This finding could not be explained by differences in clinical severity because after adjusting for SAPS II, norepinephrine administration remained significantly associated with an increase risk of death. The use of dopamine showed a trend toward a lower mortality in our group of patients, with septic shock reaching a marginal significance (HR = 0.742; 95% CI 0.552–0.999; $p = 0.049$). However, this tendency resulted, at least in part, from differences in clinical severity in the two groups because after adjusting for SAPS II, this difference became lighter. The administration of dobutamine seems to be associated with a higher mortality rate; however, in the multivariate regression analysis, dobutamine was excluded from the final model. Our study has the same limitations as the SOAP study because it was not designed to assess the efficiency and safety of vasopressor agents. The future publication of the results from three trials in patients with septic shock (12, 13) could finally bring some light to this controversy.

Previous studies (21, 22) have shown that prompt therapeutic intervention, namely, the implementation of the elements of the 6- and 24-hour sepsis bundles, seems to favorably influence outcome (23, 24). A preliminary evaluation of the SACiUCI database showed that total compliance with the resuscitation 6-hour and with the management 24-hour sepsis bundles had a favorable impact on outcome even after adjustments for sex, age, and SAPS II, adjusted odds ratio of 0.6 (95% CI 0.396–0.910) and 0.34 (95% CI 0.124–0.929), respectively (25). In our study, we analyzed just three isolated elements from the sepsis bundles, mainly associated with hemodynamic support. In patients with septic shock, the use of vasopressors after fluids if MAP <65 mm Hg from the 6-hour sepsis bundle has a positive impact on mortality. The use of inotropic support and low-dose steroids showed no beneficial effect in our group of patients with septic shock.

Our study has several important strengths. To date, this is the first large multiple-center Portuguese epidemiologic study on community-acquired sepsis. We prospectively evaluated patients admitted with community-acquired sepsis for a 12-month period, eliminating possible effects related from seasonal variation. An external audit performed a revision of randomly selected patients' protocols, ensuring data quality. Besides, we recognize that the study also has some limitations. The nonrandomized, observational design of our study may have induced some unknown bias that may have caused differences in vasopressor choice because sicker patients could have received more norepinephrine than dopamine, as well as in the rate of compliance of the sepsis bundles elements. Besides, the results of the impact of vasopressor administration in patients with septic shock must be cautiously taken because a relationship between a therapeutic intervention and outcome obtained from a cohort study should be carefully read, and additionally, the dose of a particular vasopressor agent was not collected in the database. Furthermore, we have no data concerning severe sepsis not admitted to ICU that represent an important problem in the process of care. Participation in the study was voluntary, and we could not evaluate whether the contributions of academic and nonacademic ICU reflect the reality and are truly representative of Portuguese ICUs as a whole.

CONCLUSIONS

In conclusion, the results of this analysis provide valuable information about the Portuguese ICU community-acquired sepsis patient population, in particular, the aspects of hemodynamic evaluation and support. In addition, our investigation identified important problems in the process of care of these patients, namely, the time delay between hospital and ICU admission. Finally, our data suggest that in patients with septic shock, norepinephrine administration could be associated with worse outcome. This last observation needs further evaluation with a prospective, randomized controlled trial.

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APPENDIX

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Hemodynamic support of shock state: Are we asking the right questions?*

Septic shock is one of the most challenging problems in the critical care. Its mortality toll in the United States ranges between 200,000 and 250,000, a number comparable with myocardial infraction. Diagnosing and treating a septic shock is like looking the stars at night: from single bright spots, you have to reconstitute the constellations to have the complete picture.

For the last 40 years, catecholamines have been used routinely in shock state, trying to restore normal or near-normal hemodynamic parameters. The rationale is to maintain a minimal level of blood pressure in septic shock patients (1). From a quasi-empirical use, more and more knowledge has emerged on the mechanisms and effect of these drugs. Our understanding of shock state improves, including myocardial depression in septic shock, the links between inflammation and coagulation, and microcirculation and cellular energetics. Our pharmacologic tool set expanded and include vasopressin and analogs, phosphodiesterase inhibitors, and calcium sensitizers. As knowledge expand, the picture gets more complex and the clinicians more confused.

The Quest for the Magic Bullet

In this issue of *Critical Care Medicine*, Povoa et al (2) adds to the comparison of different catecholamine in shock states. They observed a large multicentered population of septic shock patients, the various catecholamines used, and the patient's outcome. They show that dopamine, norepinephrine, and dobutamine increase mortality. Should we ban these drugs from our pharmacopoeia? Certainly not. First, the natural catecholamines are part of the acute-phase response to physiologic stress and are essential for human species. These molecules are part of our survival kit (3). Second, using a similar strategy, others (4) observed that that dopamine decreases mortality in septic shock patients and that norepinephrine and dobutamine have no effect. This is contrary to the conclusion in the present study. Other cohorts have investigated this question with variable results (Table 1). One can argue that these are not randomized control trials, but most randomized control studies also failed to point out a consistent effect. Third, most of the studies do not start with patients on no adrenergic support: when a certain level of dopamine or norepinephrine is reached randomize into replace by or add "A" vs. "B." First, the picture is blurred. Catecholamines at a usual pharmacologic range yield to concentrations 100 times above the physiologic concentrations. Second, there is a significant interindividual variability in catecholamine kinetics: a fixed dose of dopamine can yield to plasma concentrations in a 20-fold range. Third, dopamine is the natural direct precursor of norepinephrine through beta-hydroxylase. During dopamine infusion (3 μg/kg/min), plasma norepinephrine concentration increases (5).

Should We Change Our Approach to Shock States

Until recently, hemodynamic support of shock state was focused on restoring normal or near-normal physiologic parameters. In the 1980s, there was even a tendency toward supranormal physiologic goals. To easily achieve target hemodynamic parameters, having one single magical drug would make the clinician's life easier. There is a quest toward the magic bullet applicable in all patients: Is dopamine better than norepinephrine? Is vasopressin better than norepinephrine? What is the optimal target for mean arterial blood pressure? What is the optimal cardiac output/mixed venous saturation? Consensus panel supported the use of catecholamines in septic shock with a grade E evidence (6). Clinical investigations suggest that increasing the target mean arterial pressure (MAP) from 65 to 85 mm Hg does not change oxygen-

*See also p. 410.

Key Words: septic shock; catecholamines; outcome; sepsis bundle; quality control

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Table 1. Some studies investigating the effect of vasopressors in vasodilatory shock in adults

Study	Patients	Methods	Main Conclusions	Comments
Cohort studies				
Goncalves, et al (26)	406 patients requiring NE	Observational prospective cohort	NE does not facilitate development of MODS	
Martin, et al (27)	97 septic shock patients	Observational prospective cohort	NE lower mortality when compared to Dopa	
Hall, et al (28)	150 patients receiving either Dopa NE or AVP	Observational prospective cohort	Fixed dose AVP is comparable with titrated doses of NE or Dopa	
Sakr, et al (4)	462 septic shock patients	Observational multicenter study	Dopa tends to worsen mortality NE and Dobu has no effect	Significant international variation in catecholamine use
Micek, et al (29)	137 septic shock patients all receiving NE, some with AVP	Observational prospective cohort	Patients receiving AVP plus NE have a worse mortality than patients receiving NE	AVP was used as a rescue therapy in NE resistant patients
Povoa, et al (2)	458 septic shock patients	Observational multi center study	Dopa decreases mortality. NE and Dobu increases mortality	
Randomized control trials				
Martin, et al (30)	32 patients in septic shock	NE vs. Dopa	NE provided a better hemodynamic profile, No difference in outcome	
Ruokonen, et al (31)	10 patients in septic shock	Dopa alone or with NE	Discrepancy between global and regional blood flow. No difference in outcome	
Marik, et al (32)	20 septic shock patients	Dopa vs. NE	NE improve splanchnic perfusion. No difference in outcome	
Levy, et al (33)	30 patients with septic shock	Epi vs. fixed Dobu plus NE	Trend toward less oliguria with NE plus Dobu, No differences in mortality	
Malay, et al (34)	10 trauma patients with vasodilatory shock	AVP vs. placebo plus NE	Trend toward less mortality in the AVP group	Very small n, 24 hr follow-up
Seguin, et al (35)	22 patients in septic shock	Titrated Epi vs. fixed Dobu plus titrated NE	No difference in outcome	
Patel, et al (36)	24 patients in septic shock	AVP vs. NE fixed dose plus open label NE	Better creatinine clearance with AVP, no difference in outcome	4 hr follow-up
Dunser, et al (37)	48 patients with vasodilatory shock	AVP 4 U/hr vs. placebo plus norEpi to MAP >70	Better hemodynamic response with AVP but no difference in outcome	
Albanese, et al (38)	20 septic shock patients	Terlipressin vs. NE	No differences in MAP, renal function and outcome	
Lauzier, et al (39)	23 patients in septic shock	First-line treatment: NE versus AVP alone, rescue by adding the other drug	No difference in outcome	Open label. 85% of AVP patients received additional NE due to MAP <70 mm Hg at 1 hr
Schmoelz, et al (40)	61 patients with septic shock	NE plus dopexamine or plus Dopa	Dopexamine associated with better renal function. No difference in organ failures or mortality	
Annane, et al (41)	330 patients with septic shock	NE plus Dobu vs. Epi	No difference in hemodynamic, organ failure, duration of therapy, and mortality	
Russell, et al (42)	778 patients in septic shock	NE vs. AVP	Better survival with AVP in less sick patients. No overall mortality difference	

NE, norepinephrine; AVP, arginine-vasopressin; Dobu, dobutamine; Dopa, dopamine; Epi, epinephrine; norEpi, norepinephrine; MAP, mean arterial pressure; MODS, Multiple Organs Dysfunction Syndrome.

ation parameter and skin microcirculation (7) no renal function or outcome (8). Our actual concept is that below a certain MAP, blood flow is linearly dependent on organ perfusion (1). This cutoff is probably not the same in the various organs and probably different between different various capillary beds of the same organ. The inlet pressure of physiologic capillaries is 20–25 mm Hg. There are no data to suggest that 50 mm Hg MAP is more deleterious in term of microcirculatory and organ perfusion than 65 with vasopressors. Sepsis induces a state of nutrient and oxygen deficiency at the cellular level. This cellular energetic failure lead to organ dysfunction, myocardial depression, and microcirculatory dysfunction (Fig. 1). The myocardium is energetically exhausted. Increasing the catecholamines level is like whipping an exhausted horse. With worsening cellular dysfunction, the horse will not respond the whip—the shock will became refractory to cat-

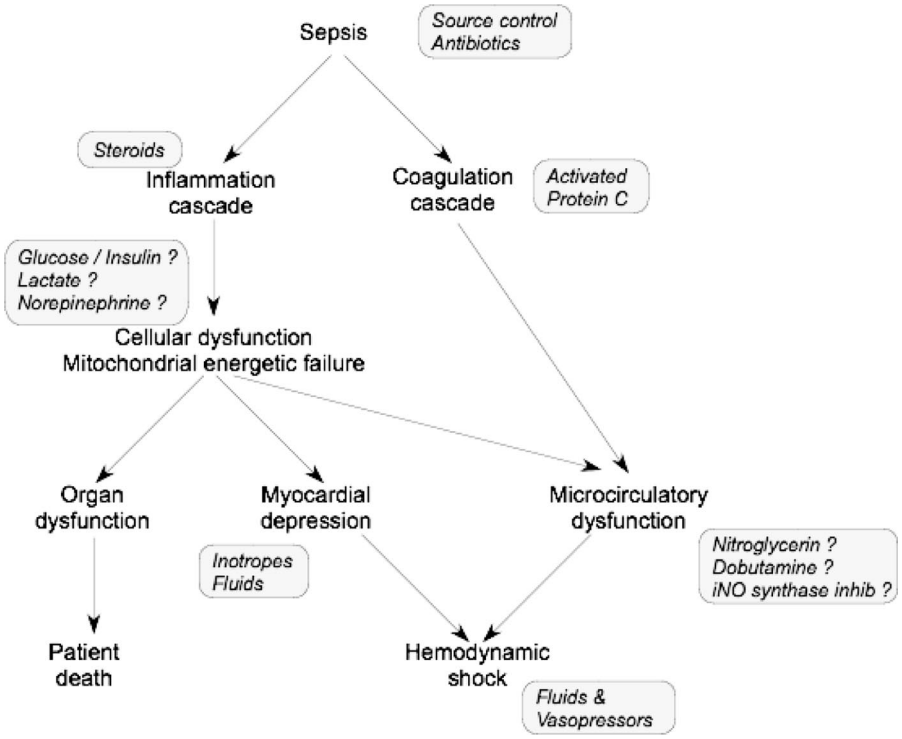

Figure 1. Proposed physiopathology of septic shock. Proposed physiopathologic links between sepsis, mitochondrial energetic failure, and organ dysfunction and death. Therapeutic target is shown in the *gray boxes*. Innovative therapies and new effects of therapies are shown with a *question mark*. *iNO*, inducible nitrous oxide.

echolamines. We can change whip—as by using vasopressin or analogs—but the underlying problem will remain and, if not corrected, shock will worsen and be refractory to vasopressin. This may explain why "dopamine sensitive" patients in septic shock have a better outcome than "dopamine resistant" patients (9): In dopamine-resistant shock, the cellular energetic is failing. This may also explain that in the Vasopressin and Septic Shock Trial, the patients who may benefit from the change of whip—*switch to vasopressin*—are those requiring the lowest doses of norepinephrine—the not too exhausted horses. Researchers have started to explore the link between hemodynamic and microcirculation: Trzeciak et al (10) showed that there is a correlation between survival and microcirculatory disturbances. Sakr et al (11) showed that small vessel perfusion improved over time in septic shock survivors but not in nonsurvivors. Despite similar hemodynamic parameters and amount of support, patients dying after the resolution of shock in multiple organ failure had a lower percentage of perfused small vessels than did survivors. This shows that the cellular dysfunction and microcirculatory disturbances can still be present despite restored hemodynamics. Following these hypothesis, innovative and provocative, strategies have been proposed in septic shock. Spronk et al (12) administered nitroglycerine in septic shock patients and showed an improvement in the microcirculation. De Backer et al (13) demonstrated that dobutamine can improve but not restore microcirculatory perfusion in patients with septic shock, independently of its inotropic effect. Going one step upstream (Fig. 1), Levy et al (14) measured intermediate substrate metabolism in septic shock patients and pointed out a mitochondrial dysfunction. Some have suggested that lactate is not a waste product but a high-octane fuel and an adaptive mechanism during shock states (15). The epinephrine-induced release of glucose and lactate from the muscles during shock may be a survival mechanism aiming to feed a starved horse (16). Recently, Regueira et al (17) showed that norepinephrine was able to increase maximal mitochondrial respiration in the liver during an endotoxin challenge. This suggests that in shock, the so-called cytopathic hypoxia is related to mitochondrial substrate availability (18). Obviously, this view of septic shock is simplistic: There are probably two types of feedback and control systems: First, standard feedback such as improvement of hemodynamic parameter should be associated with improved microcirculation and cell oxygenation. Second, control of hemodynamic parameters may help to avoid vicious circles such as worsening of inflammatory response because of ongoing shock state (19). With this in mind (Fig. 1), hemodynamic support alone has little chances to reverse the complete cascade. It will be hard to find a link between the type of catecholamine and the outcome. This will also require that further randomized trial investigating the effect of hemodynamic support in septic shock patients will have to include a homogeneous patient group and control all these other therapies. Dobutamine and norepinephrine have recently shown unexpected positive side effects in shock state at the microcirculatory and mitochondrial level.

Some intensivists dream about the multicentered international randomized control trial comparing norepinephrine vs. dopamine vs. vasopressin in septic shock patients: The design would be study drug "X" vs. "Y" in a concealed bag titrated to MAP of 70 mm Hg. What is the best in terms of MAP? What is the best in terms of outcome? Maybe we should change from "what is the best in term of MAP?" to "what is the best for the mitochondria?" (20).

Sepsis Bundle Is a Whole Package: Take it as a Whole

Following the fundamental study by Rivers (21), several consensus conferences proposed a structured multisystem approach to patients in septic shock (22). Items of a bundle are inseparable: It is not a flexible contract. The strength of these bundle and outcome improvement come from 1) a standardized approach (23), 2) the check list effect avoiding missed items, and 3) the speed of intervention including time points were goals should be met (6 and 24 hours). Compliance to the surviving sepsis campaign bundle in the SACiUCI study was also published as a preliminary abstract (24). The compliance to selected items of the 6-hour bundle ranges from 30% (antibiotics within 3 hours) to 80% (vasopressors after adequate fluid). Using an all-or-none approach, ≥70% of the patients failed the 6-hour bundle. Failing the 6-hour bundle is associated with an increased mortality in the present cohort (24). There are three strategies to assess

compliance to a set of interventions/markers (25): 1) As Povoa et al presented as item-by-item measurement, 2) as a composite variable i.e., four items of six, or 3) using an all-or-none measurement. The outcome improvement does not come from a specific intervention or a specific catecholamine. It is time to raise the bar and assess the surviving sepsis campaign recommendation as an inseparable package. We should go further than the 6-hour limit: In parallel to data from myocardial infarction regarding door-to-balloon time, we should focus on a door to sepsis bundle time. Despite an excellent worldwide campaign, endorsement by a dozen of critical care societies and organizations, practice has room for improvement. Sepsis is like myocardial infarction: its an emergency!

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Treatment of septic renal injury by alkaline phosphatase: An emperor with new clothes*

In this issue of *Critical Care Medicine*, Heemskerk et al (1) describe a clinical trial on the effect of treatment with purified bovine intestinal alkaline phosphatase (AF) vs. placebo in a small series (n = 36) of patients with severe sepsis or septic shock from Gram-negative and Gram-positive microorganisms and having (impending or manifest) acute kidney injury and failure. Indeed, AF is capable of detoxifying endotoxin, even at physiologic concentrations, by dephosphorylation of the lipid A moiety of lipopolysaccharide (2), and exogenous administration in animals with Gram-negative sepsis and shock appeared beneficial (3, 4). The Heemskerk et al (1) trial was too small to discern a morbidity or survival benefit of AF treatment, but, nevertheless, the authors observed some effect on renal function parameters. In a small substudy (in patients not on renal replacement therapy), in which the effect of AF seemed even more pronounced, protection appeared associated with less inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO) production and release of markers of the (resultant?) injury in the tubular cells and excreted in the urine. These (selected) observations should be regarded as preliminary, and protection by AF of renal function in sepsis and shock should be confirmed in larger studies with stronger end points, such as the need for renal replacement therapy, the speed of recovery of septic renal failure, and alike, which have not been studied by Heemskerk et al (1). In contrast, the authors have focused on acute kidney injury criteria including serum creatinine, even in patients already on renal replacement therapy at the start. We cannot formally exclude that AF affected tubular creatinine excretion rather than glomerular filtration. Furthermore, the mechanisms behind this potentially beneficial and relatively specific effect on the kidney remain to be demonstrated, because, among others, it is unclear how AF would also benefit patients with Gram-positive septic shock.

Endogenous AF is ubiquitous and abundant in epithelial cells and serves, among others, as an ectonucleotidase, to dephosphorylate and degrade extravascular (high energy, monoester) phosphate compounds. There are various isoenzymes for different tissues, which, for instance, play a role in bone turnover, bile excretion, and placental development and function (5). Expressed in the mucosa of the gastrointestinal tract, AF may help to limit translocation of harmful endotoxin from the lumen (5). The function of the enzyme located in the brush border of the proximal tubule is unclear and may only partly relate to resorption of phosphate. It is shed and excreted in the urine in the course of tubular injury and may be upregulated in the kidney during (experimental) sepsis (6, 7).

Extracellular phosphate compounds, released by various cells and tissues particularly on hypoxia or inflammation, may, via nucleotide signaling and purinergic receptors, affect a wide variety of processes, involving innate immunity, epithelial transport, and regulation of blood flow (8–10). This applies to both adenosine triphosphate and its dephosphorylation products adenosine diphosphate, adenosine monophosphate, and adenosine, and the kidney, but effects depend on specific receptor stimulations and conditions (11). For instance, the compounds are vasodilators in normal rats but vasoconstrictors (also in the renal bed) in endotoxin-challenged animals (12). Adenosine triphosphate and adenosine, being mediators of tubuloglomerular feedback, may also decrease renal blood flow by afferent vasoconstriction via A_1-adenosine receptor stimulation (8, 11, 13, 14). The compounds may have proinflammatory actions so that (specific) adenosine (receptor) antagonists are protective, whereas, in contrast, stimulation of some (A_{2A}) adenosine receptors may have anti-inflammatory actions, even in the kidney (15, 16). We also know that inhibitors of phosphodiesterases, degrading phosphate diesters, such as cyclic adenosine monophosphate to adenosine can be protective in experimental acute kidney injury after a wide variety of challenges, including endotoxemia (17). How AF might interfere with these processes is largely unknown. Indeed, the study by Heemskerk et al (1) does not give insight into the specific effect or the routing of AF in the kidney during sepsis. Nevertheless, it suggests that iNOS upregulation is associated, even perhaps in a causative manner, with proximal tubular damage and, thereby, contributes to acute kidney injury, as observed before (18). Oxidative stress, NO-derived peroxynitrite and subsequent mitochondrial and nuclear DNA damage, and protein nitrosylation may be some of the mechanisms underlying iNOS–NO-derived toxicity. This may also explain, at least in part, the often presumed maintenance of renal blood flow and the observed fall in filtration fraction and glomerular filtration in patients with impending acute renal fail-

***See also p. 417.**

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