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ORIGINAL ARTICLE

Characteristics and Outcomes of Patients Treated with Drotrecogin Alpha and Other Interventions of the "Surviving Sepsis" Campaign in Clinical Practice*

Características e Evolução dos Pacientes Tratados com Drotrecogina Alfa e Outras Intervenções da Campanha "Sobrevivendo à Sepse" na Prática Clínica

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SUMMARY

BACKGROUND AND OBJECTIVES: To face the high mortality of sepsis, interventions grouped as "Surviving Sepsis Campaign" have been suggested. The aim of the study was to describe the application of glycemic control, corticoid use in septic shock, inotropics and drotrecogin-alpha in sepsis.
METHODS: We studied 110 patients with sepsis from Recife/Brazil, who received drotrecogin-alpha between 2003/2006. Data on management of sepsis considering Surviving Sepsis Campaign, drotrecogin-alpha, mortality at 28 days and severe bleeding were recorded.
RESULTS: Mean APACHE II was 25.6 and mean SOFA was 9.2. Around 95% of the patients presented two or more organ dysfunctions and 98% presented septic shock. The majority (56%) were under 65 years. Abdominal (48%) and respiratory (28%) focus of infection were the most prevalent. Hydrocortisone was used in 61% of the patients, and 29 (48.3%) died. Of the 38 patients with prolonged shock that did not receive it, 28 (73.7%) died. Of the 97 patients who presented uncontrolled glycemia only 65% achieved strict glycemic control and the mortality was 51.6%. Fluid gain ranged from 600 ml to 9,400 ml in the first 24h. In only 30 patients was myocardial dysfunction detected. The infusion of drotrecogin alpha started within 24h in 45%, between 24 and 48h in 35% and after 48h in 20%. Death occurred in 57% and severe bleeding in 9%.
CONCLUSIONS: Discrepancy between the recommendations of Surviving Sepsis Campaign and clinical practice was observed. Death rate was 57%, similar to that found in the literature for septic shock irrespective of the use of drotrecogin-alpha.
Key Words: drotrecogin alpha, sepsis, septic shock, treatment

RESUMO

JUSTIFICATIVA E OBJETIVOS: Para reduzir a mortalidade da sepse, foram sugeridas intervenções agrupadas na campanha "Sobrevivendo à Sepse". O objetivo do estudo foi descrever a aplicação destas intervenções: controle glicêmico, corticóide no choque séptico, inotrópicos e drotrecogina-alfa na sepse.
MÉTODO: Foram estudados 110 pacientes com sepse de sete hospitais do Recife/Brasil, que receberam drotrecogina alfa entre 2003/2006. Foram obtidos dados no manuseio da sepse conforme a campanha "Sobrevivendo a Sepse", uso da drotrecogina alfa, mortalidade aos 28 dias e sangramentos intensos.
RESULTADOS: O APACHE II médio foi 25,6 e o SOFA médio foi 9,2; 95% dos pacientes apresentaram duas ou mais disfunções orgânicas e 98% apresentavam choque séptico; 56% tinham menos de 65 anos. O foco de infecção mais comum foi abdominal (48%) e respi-

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ratório (28%). Utilizou-se hidrocortisona em 61% dos pacientes, e 29 (48,3%) morreram. Dos 38 pacientes com choque séptico prolongado que não o receberam, 28 (73,7%) faleceram. Cerca de 97 pacientes apresentaram glicemia não controlada, destes, 65% atingiram controle glicêmico estrito e a mortalidade foi 51,6%. O ganho de fluídos variou de 600 mL a 9.400 mL nas primeiras 24h. Disfunção miocárdica foi detectada em 30 pacientes. A infusão da drotrecogina-alfa foi iniciada em 24h em 45%, entre 24 e 48h em 35% e após 48h em 20%. Morte ocorreu em 57% e sangramento intenso em 9%.

CONCLUSÕES: Observou-se divergências entre as recomendações da campanha "Sobrevivendo à Sepse" e a prática clínica. A mortalidade foi 57%, similar à encontrada na literatura para pacientes com choque séptico, independente do uso da drotrecogina-alfa.

Unitermos: Choque séptico, drotrecogina alfa, sepse, tratamento

INTRODUCTION

Severe sepsis is a clinical syndrome triggered by the presence of infectious agents in sterilized tissue. It is characterized by intense inflammatory activity, especially in its earlier stages, and by activation of the coagulation system[1-4]. In view of this, clinical studies have tested the hypothesis that the use of endogenous anticoagulants with anti-inflammatory properties might be effective for treating sepsis, balancing the inflammatory response and recovering homeostasis[5]. Following on from this, three factors were studied: antithrombin III, tissue factor pathway inhibitor and protein C[2,5]. The first two of these produced frustrating results in phase III studies[6,7] and only activated protein C was shown to be effective in reducing the relative risk of death by 20%[8]. The use of activated drotrecogin alpha was approved for clinical practice in 2001 by the supervisory agencies in the United States (Food and Drug Administration, FDA) and in Europe (European Agency for the Evaluation of Medicinal Products, EMEA). In 2004, the "Surviving Sepsis" campaign[9] included the use of activated protein C among its recommendations. This campaign aimed at standardizing the management of cases of severe sepsis and septic shock in order to reduce mortality. However, more recently, criticism of the use of activated drotrecogin alpha and of the "Surviving Sepsis" campaign itself was published in prestigious medical journals[10-12], in which the real efficacy of activated protein C was questioned. Since a new clinical study comparing activated protein C with placebo might not be feasible on ethical grounds, one way of obtaining data on activated drotrecogin alpha would be by means of studies using information from daily clinical practice. It is also important to have regional data available to enable critical comparison with worldwide practices and with other regions presenting different socioeconomic, cultural and genetic conditions.

The aim of the present study was to describe the clinical characteristics of patients who received activated drotrecogin alpha, including indications; time elapsed between organ dysfunction and the start of medication, mortality at 28 days and the complications associated with the medication. A secondary objective was to describe the practical application of therapeutic methods such as glycemic control, corticoid use in patients with septic shock, use of positive inotropics in sepsis-induced myocardial dysfunction and vigorous volemic resuscitation in patients with severe sepsis who were given activated drotrecogin alpha.

METHODS

The present study was approved by the Medical Research Ethics Committee of Hospital Agamenon Magalhães, State of Pernambuco Health Department, and was registered with the National Research Ethics Commission of the National Health Council of the Ministry of Health under number FR 93597.

This was a case series study. The data was obtained by consulting patients' clinical records by means of a specific form for patients hospitalized in the metropolitan region of the city of Recife receiving activated drotrecogin alpha between January 2003 and October 2006.

According to information from the manufacturer, 119 courses of treatment with activated drotrecogin alpha were acquired in the metropolitan region of Recife over this period. The medical records of 110 of these patients were analyzed. Of these, three patients did not start infusion of activated drotrecogin alpha, three medical files were not in a good enough state to meet the minimum requirements for information, two patients had their infusions of the drug withdrawn on the orders of the attending doctor and two were receiving the drug for the second time during the same hospital stay and therefore only the first utilization was taken into account. Thus, data on 100 patients was used for the analysis. The patients were from seven hospitals in the metropolitan region of Recife, of whom 99 were from six private tertiary-level hospitals and one was from a

public tertiary-level hospital.

All the patients were given activated drotrecogin alpha in a dose of 24 µg/kg/h, with the intention of completing 96h of infusion in an intensive care unit. The treatment was indicated by the medical team of the unit and/or the attending doctor.

Data on demographic factors, clinical factors, diagnosis on admission and comorbidities (diabetes mellitus, cardiopathy, obesity, malignant neoplasia, chronic renal insufficiency, chronic liver disease, chronic obstructive pulmonary disease, Acquired Immunodeficiency Syndrome and thrombophilia) were collected. In addition, the patients were classified as clinical or surgical cases. The latter were defined as those undergoing any surgical procedure during the study period. Data on foci of infection (pulmonary, urinary, abdominal, skin and subcutaneous tissue, or in the bloodstream), etiological agent, whether the infection was nosocomial (i.e. starting more than 48h after hospitalization), presence of septic shock (with the use of vasoactive drugs), acute myocardial dysfunction (documented by echocardiogram or pulmonary artery catheter), lactate assaying (mmol/L) at the start and end of drug infusion and coagulation disorders (low platelet count, i.e. < 100,000/µL; INR elevation to twice baseline in the absence of any drug explaining this; or a PTT rise to twice baseline in the absence of concomitant use of any measure that would explain this change) were also collected.

The APACHE II[13] and SOFA[14] scores were measured, taking the baseline of the 24h preceding the start of infusion. In calculating the APACHE II and SOFA scores for variables that were not measured on the specific day, the value for the preceding 24h was taken. All laboratory and clinical data that were not available were recorded as normal. To assess the neurological state on the Glasgow scale for sedated patients, the patient's state prior to sedation was defined.

Data relating to the therapy were collected, such as time elapsed between documentation of the first organ failure (by means of SOFA) and the start of drug infusion; continuous insulin use in cases of uncontrolled glycemia (when more than two blood glucose tests yielded results greater than 150 mg% within 24h), with the aim of maintaining glycemia levels between 80 and 150 mg%; use of endovenous hydrocortisone (100 mg every 8h or 50 mg every 6h) to treat shock; difference between fluid gain and loss over the first 24h after the septic shock; whether there was any temporary interruption of activated drotrecogin alpha administration; and whether 96h of infusion were completed.

Information on any severe bleeding was recorded. This was defined as intracranial hemorrhage, a need for three or more units of packed red blood cells per day for two consecutive days, or life-threatening bleeding that was defined as such by the attending doctor or the intensive care unit team. The observation period for bleeding was from the start of infusion of activated drotrecogin alpha until 24h after its definitive discontinuation. Finally, mortality was recorded at 28 days after infusion of the drug.

The definitions for infection were based on the criteria of the NNISS (National Nosocomial Infection Surveillance System) and on the diagnosis made by the attending physician. Cases were considered to present severe sepsis if the sepsis was associated with organ dysfunction, hypoperfusion or hypotension. The main signs for hypoperfusion were lactic acidosis, oliguria and acute abnormalities in mental state. Septic shock was defined as the presence of sepsis that induced hypotension that was unresponsive to adequate fluid resuscitation, with signs of hypoperfusion or the use of vasopressor drugs[15].

The statistical analysis was performed on the basis of whether the patient was dead or alive at 28 days. The patients were divided into two groups, with the aim of identifying potential prognostic factors. The means of the continuous variables were evaluated for their relationship with the outcome by means of Student's t test. The chi-squared or Fisher test was used for categorical variables. Possible risk factors influencing the outcome were identified by means of a three-stage process. In the first stage, the possible associations between each factor alone and the outcome were evaluated before the continuous variables were categorized. In the second stage, the initial logistic regression model was chosen. This was composed of all the factors that, in the first stage, presented an observed significance level (p value) of less than 0.20, as recommended by Hosmer and Lemeshow. In the third stage, the stepwise method was used to identify the final regression model, i.e. to identify the risk factors that presented collective and individual associations with the outcome. In the data analysis, the Stata 9.2 SE software was used.

RESULTS

Fifty-three percent of the patients were female and 56% were under 65 years of age. The abdomen was the most common site of infection, accounting for 48% of foci, followed by the respiratory tract with 28%, the

urinary tract with 11% and skin and subcutaneous tissue with 9%. Thirty-three percent of the infections were of nosocomial origin. Fifty-two percent of the patients were surgical cases. Prominent among the comorbidities were cardiopathy (27%), diabetes mellitus (24%), obesity (13%), malignant neoplasia (9%), "uncontrolled" malignant neoplasia (6%) and chronic renal insufficiency (6%) (Table 1).

Table 1 – Epidemiological and Clinical Characteristics of the Patients

Variables	Mean ± SD	n = 100 (%)
Gender		
Female		53 (53)
Male		47 (47)
Age (years)	60 ± 18,2	
Age < 65 years		56 (56)
Male ≥ 65 years		44 (44)
Condition of the patient		
Clinical		48 (48)
Surgical		52 (52)
Site of infection		
Lung		28 (28)
Urinary tract		11 (11)
Intra-abdominal		48 (48)
Skin and subcutaneous tissue		09 (9)
Blood stream		02 (2)
Other		02 (2)
Nosocomial infection		33 (33)
Comorbities and other special conditions		
Cardiopathy		27 (27)
Diabetes mellitus		24 (24)
Obesity		13 (13)
Neoplasia		09 (9)
Chronic renal failure		06 (6)
Chronic liver disease		05 (5)
Acquired immunodeficiency syndrome		01 (1)
Chronic obstructive pulmonary disease		04 (4)
V-Leiden factor		01 (1)
Pregnancy		01 (1)
Total		100(100)

The mean APACHE II score was 25.6 ± 4.7 and the mean SOFA score was 9.2 ± 2.5. Around 95% of the patients presented two or more organ dysfunctions at the time the infusion was initiated. Septic shock with the use of vasoactive drugs occurred in 98% of the patients and respiratory insufficiency with the use of mechanical ventilation in 97%. Coagulation disorders occurred in 56% of the patients (Table 2).

Table 2 – Severity Scores and Therapeutic Interventions

	Mean ± SD	n (%)
Baseline APACHE II score	25.63 ± 4.68	
Baseline APACHE II		
Score <25		29 (29)
Score ≥25		71 (71)
Baseline APACHE II (quartiles)		
0 to 16		04 (4)
17 to 21		14 (14)
22 to 26		29 (29)
≥ 27		53 (53)
Baseline SOFA score	9.2 ± 2.53	
Baseline SOFA (quartiles)		
0 to 7		21 (21)
8 to 9		36 (36)
10 to 12		37 (37)
>12		06 (6)
Number of organ dysfunctions at the beginning of infusion		
1		01 (1)
2		15 (15)
3		21 (21)
4		34 (34)
5		21 (21)
6		08 (8)
Baseline lactate (mmol/L)	4.13 ± 1.94	
Final lactate (mmol/L)	3.5 ± 3.94	
Coagulation disorder		56 (56)
Mechanical ventilation		97 (97)
Vasopressor support		98 (98)
Cardiovascular dysfunction		30 (30)
Use of corticosteroids		60 (61)
Intravenous insulin		62 (63.9)
Temporary interruption of infusion		32 (32)
Δ T from the first dysfunction to starting drotrecogin *		
< 24h		45(45)
24 to 48h		35 (35)
> 48h		20 (20)
Δ hydric in the first 24h of shock	+4320 ± 2035 mL	100 (100)
Total **		100 (100)

*Δ T = time in hours
** Δ hydric = difference between gain and loss of fluids

Table 3 – Biological and Clinic Characteristics in the Group of Patients who Died Compared to those Alive at 28 Days

	Dead N (%)	Alive N (%)	p Value
Total	57 (57)	43(43)	
Gender			0.259
Female	24 (51.1)	23 (48.9)	
Male	33 (62.3)	20 (37.7)	
Age (years) Mean ± SD	61.72 ± 17.34	57.77 ± 19.23	
< 65 years	32 (57.1)	24 (42.9)	0.974
≥ 65 years	25 (56.8)	19 (43.2)	
Condition			
Clinical	31 (64.6)	17 (35.4)	0.141
Surgical	26 (50)	26 (50)	
Site of infection			0.084
Intra-abdominal	29 (60.4)	19 (39.6)	
Lung	17 (60.7)	11 (39.3)	
Urinary tract	02 (18.2)	09 (81.8)	
Skin and subcutaneous tissue	06 (66.7)	03 (33.3)	
Bloodstream and others	03 (75)	01 (25)	
Comorbities and special conditions			
Cardiopathy	14 (51.9)	13 (48.1)	0.527
Diabetes mellitus	16 (66.7)	08 (33.3)	0.251
Obesity	07 (53.8)	06 (46.2)	0.805
Neoplasia	05 (55.6)	04 (44.4)	0.927
Chronic renal failure	04 (66.7)	02 (33.3)	0.697
Chronic liver disease	01 (20)	04 (80)	0.162
Acquired immunodeficiency syndrome	01 (100)	00 (0)	
Chronic pulmonary disease	03 (75)	01 (25)	0.631
V-Leiden factor	00 (0)	01 (100)	
Pregnancy	00 (0)	01 (100)	

In 38 patients, the causative agent of the sepsis was identified; of these 52.6% were Gram-negative bacteria, 36.8% were Gram-positive bacteria and 10.5% were fungi.

All thirty patients who had acute myocardial dysfunction that was attributed to sepsis used dobutamine as their positive inotropic drug. Of the 98 patients with septic shock who were using vasoactive drugs, only 60 (61%) used hydrocortisone, at doses of 200 or 300 mg per day, divided into three or four doses. Of these, 29 (48.3%) died. Of the 38 patients with an indication for hydrocortisone but who did not receive it, 28 (73.7%) died.

Ninety-seven patients presented uncontrolled glycemia. Of these, only 62 (63.9%) achieved strict glycemic control through the use of endovenous insulin. In this group, 32 (51.6%) died. Of the 35 patients with an indication for strict glycemic control but not submitted to it, 22 (62.9%) died.

The difference between fluid gain and loss (delta H) over the first 24h after the septic shock was positive: 4320 ± 2035 ml, ranging from 600 ml to 9400 ml over 24h. There were no statistical differences in mean delta H between survivors and non-survivors (Table 4).

Table 4 – Severity Scores and Therapeutic Interventions in the Group of Patients who Died Compared to those Alive at 28 Days

	Dead N (%)	Alive N (%)	p Value
Baseline APACHE II (Mean ± SD)	26.88 ± 4.32	23.98 ± 4.6	0.002#
Baseline APACHE II			0.260
Score < 25	14 (48.3)	15 (51.7)	
Score ≥ 25	43 (60.6)	28 (39.4)	
Baseline APACHE II quartiles			< 0.001
0 to 21*	09 (50)	09 (50)	
22 to 26	09 (31)	20 (69)	
≥ 27	39 (73.6)	14 (26.4)	
Baseline SOFA (Mean ± SD)	10.07 ± 2.53	8.05 ± 2.05	0.224#
Baseline SOFA quartiles			< 0.001
0 to 7**	05 (23.8)	16 (76.2)	
8 to 9	20 (55.6)	16 (44.4)	
10 to > 12	32 (76.2)	14 (26.4)	
No. of organ dysfunctions at the beginning of infusion			0.048
≤ 2	09 (50)	09 (50)	
>2 to ≤ 4	32 (58.2)	23 (41.8)	
>4 to ≤ 6	20 (69)	09 (31)	
Baseline lactate > 2.5 (mmol/L)	34 (60.7)	22 (39.3)	0.023
Final lactate > 2.5 mmol/L	24 (70.6)	10 (29.4)	< 0.001
Coagulation disorder	37 (66.1)	19 (33.9)	0.039
Mechanical ventilation	57 (58.8)	40 (41.2)	0.200
Vasopressor support	56 (57.1)	42 (42.9)	1
Cardiovascular dysfunction	20 (66.7)	10 (33.3)	0.201
Use of corticosteroids	29 (48.3)	31 (51.7)	0.032
Glycemic control	32 (51.6)	30 (48.4)	0.284
Temporary interruption of infusion	17 (53.1)	15 (469)	0.591
Δ hydric in the first 24h of shock&	4169 ± 1884	4530 ± 2263	0.410#
Δ T from the first dysfunction to starting drotrecogin§			0.146
< 24h	22 (48.9)	23 (51.1)	
24 to 48h	20 (57.1)	15 (42.9)	
> 48h	15 (75)	05 (25)	
Completed 96h of infusion	23	39	
Total	57(57%)	43 (43%)	

* First and second quartiles were accumulated
** Third and forth quartiles were accumulated
# Student *t* test
&Δ hydric = difference between gain and loss of fluids
§Δ T = time in hours

The time elapsed between the first organ failure and the start of infusion of activated drotrecogin alpha was less than or equal to 24h in 45% of the cases, greater than 24h and less than or equal to 48h in 35% and greater than 48h in 20%. The mean time elapsed between the first organ failure and the start of infusion of activated drotrecogin alpha was greater in the group of patients that progressed to death (Table 4). Only 62% of the patients completed the recommended total of 96h of infusion of activated drotrecogin alpha (Table 4). Among the 38 patients who did not complete it, the great majority (34 patients) did not do so because they died during the infusion, while only four patients had the drug withdrawn for other reasons (two due to coagulation disorders and two due to bleeding).

Bleeding classified as severe occurred in nine patients (9%). Five of these patients were surgical cases. Two deaths related to bleeding occurred, both in the surgical group (Table 5).

Table 5 – Severe Bleeding Events during Infusion of Drotrecogin Alpha (activated) in 100 Patients

	Total	Dead N (%)	Alive N (%)	p Value
Severe bleeding events	09 (9)	07 (7)	02 (2)	0.293
Severe bleeding events in surgical patients	05 (5)	03 (3)	02 (2)	-
Site of bleeding				
Intra-abdominal	02 (2)	01 (1)	01 (1)	
Intrathoracic	02 (2)	02 (2)	00 (0)	
Urinary tract	01 (1)	01 (1)	00 (0)	
Skin and subcutaneous tissue	02 (2)	01 (1)	01 (1)	
Intracranial	01 (1)	01 (1)	00 (0)	
Unknown	01 (1)	01 (1)	00 (0)	

The outcome was death in 57% of the patients. When the 20 patients who started on activated drotrecogin alpha more than 48h after the first organ failure were disregarded, the mortality rate became 52.5%. Of the 57 deaths, 55 were directly related to sepsis. The other two patients died from bleeding.

Statistical analysis of the individual variables in relation to the risk of death showed significant differences with regard to the following: the mean and fourth quartile of APACHE II; the second, third and fourth quartiles of SOFA; the greatest number of organ failures; initial and final lactate levels greater than 2.5 mmol/L; nonuse of corticoids for treating septic shock; and presence of coagulation disorders (Table 4).

In the multivariate analysis, it was observed that a final lactate level (at the end of the infusion of activated drotrecogin alpha) greater than 2.5 mmol/L was related to the unfavorable outcome with an adjusted OR of 11.5 (95% CI from 2.6 to 51.6; p = 0.001). A greater risk of death was also observed among the clinical patients, with an adjusted OR of 4.8 (95% CI from 1.1 to 21.3; p = 0.04). None of the other variables presented a statistically significant difference.

DISCUSSION

The first conclusion from the present study is the dissociation between the recommendations of the "Surviving Sepsis" campaign and their use in clinical practice. For example, it was seen that simple practices that are known to reduce mortality, such as early fluid replacement, are not implemented. The second conclusion is that the mortality of the patients with severe sepsis submitted to activate drotrecogin-alpha under the usual conditions of clinical practice is high, as death occurred in 57% of the patients submitted to the drug. The death rate identified in the present study was similar to that found for septic shock in Brazil by Silva et al. (52.2%)[16] and by Sales Jr. (65.3%)[17], in the United States by Alberti et al. (60%)[18] and in Europe by Vincent et al. in 2006[19], irrespective of whether activated drotrecogin alpha was used.

It could be argued that the poor results from using activated drotrecogin alpha stemmed from the fact that the patients in the present study presented conditions of great severity, exemplified by the high frequency of septic shock and ventilatory insufficiency. It was also due to the use of exclusion criteria that differed from those used in the PROWESS and ENHANCE studies[8,20,21]. Furthermore, a considerable proportion of the patients started their treatment later than the recommended limit of no more than 48 hours after the onset of sepsis. It could also be argued that many of the patients were surgical cases, which may have delayed the indication of therapy. Finally, not all the recommendations of the "Surviving Sepsis" campaign[9] had been implemented. However, strong arguments against these criticisms include the following: it has been recommended that this medication would be even more beneficial for patients in a more severe condition; mortality remained at a high level (52.5%) even after excluding the patients who started to use the medication more than 48 hours after the onset of sepsis; the use of the drug by surgical patients did not delay its utilization; and the frequency of bleeding in this group was not greater than in clinical patients. The greater frequency

of an abdominal focus identified in this study will have contributed to a better therapeutic response, given that the highest mortality was observed in respiratory infections. From an evaluation of the exclusion criteria in the PROWESS[8] and ENHANCE[20] studies, it was noted that around 14% of the patients in our study would have been excluded from these major studies, such as liver transplant patients, cases of "uncontrolled" malignant neoplasia, pregnant women, cases of chronic renal insufficiency undergoing dialysis treatment and patients at a high risk for bleeding (traumatic brain injury). The difference between the populations in the samples of major studies and those encountered in daily practice has already been pointed out by a number of authors[22]. Finally, failure to adopt the measures recommended in the "Surviving Sepsis" campaign is not exclusive to the present study, having already been described by other authors[23].

The results from using activated drotrecogin alpha in the present study are in line with what was found in two studies that evaluated its efficacy in daily practice in Italy[24] and Canada[25], which showed death rates of 46.4% and 45%, respectively. These two studies also showed higher death rates than those found in the PROWESS[8] and ADRESS[21] studies.

Our study also demonstrated a greater occurrence of severe bleeding (9%) than that reported in the PROWESS (3.5%)[8], ENHANCES (3.6%)[20] and ADRESS (2.4%)[21] studies and was very similar to the Italian (10.9%)[24] and Canadian (10%)[25] ones. The reason for this difference does not seem to result from the proportionally greater number of surgical patients in our study, although such patients are recognized as being more prone to bleeding[26]. We found that the proportion of bleeding among surgical patients (9.6%) was similar to that of clinical patients (8.3%).

With regard to the implementation of other practices that are recommended for sepsis treatment, the "Surviving Sepsis" campaign[9] recommends the continuous use of insulin to keep the glycemic levels lower than 150 mg%, with frequent monitoring in order to prevent hypoglycemia. The severity of our patients' conditions indicated that they would stay in intensive care units for more than three to five days, and thus would constitute a group that would benefit more from using a schema for rigidly controlling glycemic levels[27]. It should be noted that only 63.9% of the patients with an indication were actually using insulin. The lack of association between insulin use and favorable outcomes may be related to the small number of cases evaluated and/or to not having fully implemented the protocol (use of low insulin doses, leading to a greater time required for achieving glycemic control) or to the lack of real benefit of this intervention in septic patients. This last point recently arose in the VISEP study[28], which concluded that the use of intensive insulin therapy in critically ill patients with sepsis increased the risk for serious adverse events related to hypoglycemia.

Several studies have shown that low doses of hydrocortisone in septic shock patients who had been using vasoactive drugs caused a significant improvement in their hemodynamics, and a beneficial effect on survival[29-31], based on the concept of relative adrenal insufficiency during septic shock. Thus, the "Surviving Sepsis" campaign of 2004[9] recommended the use of 200 to 300 mg of hydrocortisone per day for septic shock patients. The conflicting data from the CORTICUS[32] study, which evidenced no benefits from using corticoids in septic shock, resulted in changes introduced in the new edition of the Surving Sepsis Campains of 2008[32], suggesting the consideration (instead of the clear indication) of intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors. Among our 98 septic shock patients who had been using vasoactive drugs, only 60 (61%) used hydrocortisone at the recommended doses. Among those who used this corticoid, mortality was 48.3%, while among those who did not use it, it was 70%. In evaluating possible associations between each factor alone and the outcome of death, nonuse of corticoid was significantly associated with death, although this difference was not confirmed in multivariate analysis. This result was very likely due to the small number of patients in our sample. Another important finding was the relatively low frequency (61%) of hydrocortisone use for septic shock among our patients, which may have been due to the doubts that still exist regarding its effectiveness and risks.

Around 40% to 50% of the patients with severe sepsis had some form of acute dysfunction of the left ventricle[34-36]. There is a consensus that myocardial dysfunction is related to a lower survival among patients with severe sepsis or septic shock[37] and dobutamine use is recommended for improving ventricular performance[9]. In the present study, around 30% of the patients (all with septic shock) presented myocardial dysfunction that was documented by echocardiograms or pulmonary artery catheters, as a result of which they made use of dobutamine. The relatively small percentage of myocardial dysfunction might be questioned in relation

to its severity among our group and the high death rate. We believe that this may have resulted from the low number of pulmonary artery catheters used, and the fact that echocardiograms were not routinely taken in septic shock patients.

The study by Rivers et al.[38] demonstrated the importance of fluid replacement for patients with severe sepsis, based on the objectives of central venous pressure of 8 to 12 mmHg; mean arterial pressure ≥ 65 mmHg, urine flow rate ≥ 0.5 mL/kg/h and central venous saturation ≥ 70%. It also showed the importance of early replacement (within the first six hours). The present study only evaluated the total fluid difference for the first 24 hours after the septic shock, which makes it difficult to make comparisons with the strategy of aggressive early fluid replacement recommended by Rivers et al. in 2001 and by the "Surviving Sepsis" campaign in 2004[9]. What can be clearly seen is the wide variation, with fluid gains over 24 hours that ranged from 600 to 9400 mL. This range of variation may be related either to the heterogeneity of the patients in the sample or to a lack of standardization in the management of fluid replacement.

The design of the present study contained intrinsic selection and confounding biases, since it involved small, highly selected groups. Because of the retrospective nature of this study, it is of little value for studying prognoses and cause-effect relationships. Obtaining data from medical files involves the use of impressions and data recorded by third parties at different times in the past, without any commitment to following protocols, thereby carrying the risks of losses and interpretation bias. The lack of any control group for comparisons makes conclusions difficult. Finally, the absence of statistically significant results may have resulted from the small number of cases evaluated. On the other hand, despite these biases, the present study was able to bring together a considerable number of patients with severe sepsis who were treated with activated drotrecogin alpha in the usual treatment conditions in an intensive care unit, in other words, in "real life" conditions.

The results from the present study, together with those of other recent studies, raise important questions regarding the use of activated drotrecogin-alpha and the risks of its use in daily clinical practice. They also raise the question of the extent to which patients are benefiting from relatively new and low-cost therapeutic strategies that indicate benefits such as treatment of myocardial dysfunction due to sepsis, and vigorous fluid replacement.

REFERENCES

01. Vervloet MG, Thijs LG, Hack CE - Derangements of coagulation and fibrinolysis in critically ill patients with sepsis and septic shock. Semin Thromb Hemost, 1998;24:33-44.
02. Esmon CT, Gu JM, Xu J, et al. Regulation and functions of the protein C anticoagulant pathway. Haematologica, 1999;84:363-368.
03. Esmon CT - The protein C pathway. Chest, 2003;124:(Suppl3):26S-32S.
04. Esmon CT - The interactions between inflammation and coagulation. Br J Haematol, 2005;131:417-430.
05. Esmon CT - Role of coagulation inhibitors in inflammation. Thromb Haemost, 2001;86:51-56.
06. Eisele B, Lamy M, Thijs LG, et al. Antithrombin III in patients with severe sepsis. A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Intensive Care Med, 1998;24:663-672.
07. Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA, 2003;290:238-247.
08. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med, 2001;344:699-709 (PROWESS).
09. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med, 2004;32:858-873.
10. Farmer JC - Drotrecogin alfa (activated) treatment in severe sepsis: a "journal club" review of the global ENHANCE trial. Crit Care Med, 2005;33:2428-2431.
11. Eichacker PQ, Danner RL, Suffredini AF, et al. Reassessing recombinant human activated protein C for sepsis: time for a new randomized controlled trial. Crit Care Med, 2005;33:2426-2428.
12. Eichacker PQ, Natanson C, Danner RL - Surviving sepsis-practice guidelines, marketing campaigns, and Eli Lilly. N Engl J Med, 2006;355:1640-1642.
13. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med, 1985;13:818-829.
14. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med, 1998;26:1793-1800.
15. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med, 2003;31:1250-1256.
16. Liaw PC - Endogenous protein C activation in patients with severe sepsis. Crit Care Med, 2004;32:(Suppl5):S214-S218.
17. Silva E, Pedro Mde A, Sogayar AC, et al. Brazilian Sepsis Epidemiological Study (BASES study). Crit Care, 2004;8:251-260.
18. Sales Jr JA, David CM, Hatum R, et al. An epidemiological study of sepsis in intensive care units. Sepsis Brazil study. Rev Bras Ter Intensiva, 2006;18:9-17.
19. Alberti C, Brun-Buisson C, Goodman SV, et al. Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. Am J Respir Crit Care Med, 2003;168:77-84.
20. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med, 2006;34:344-353.
21. Vincent JL, Bernard GR, Beale R, et al. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. Crit Care Med, 2005;33:2266-2277.
22. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med, 2005;353:1332-1341.
23. Warren HS, Suffredini AF, Eichacker PQ, et al. Risks and benefits of activated protein C treatment for severe sepsis. N Engl J Med, 2002;347:1027-1030.
24. De Miguel-Yanes JM, Andueza-Lillo JA, Gonzalez-Ramallo VJ, et al. Failure to implement evidence-based clinical guidelines for sepsis at the ED. Am J Emerg Med, 2006;24:553-559.
25. Bertolini G, Rossi C, Anghileri A, et al. Use of Drotrecogin alfa (activated) in Italian intensive care units: the results of a nationwide survey. Intensive

Care Med, 2007;33:426-434.
26. Kanji S, Perreault MM, Chant C, et al. Evaluating the use of Drotrecogin alfa (activated) in adult severe sepsis: a Canadian multicenter observational study. Intensive Care Med, 2007;33:517-523.
27. Barie PS, Hydo LJ, Shou J, et al. Efficacy and safety of drotrecogin alfa (activated) for the therapy of surgical patients with severe sepsis. Surg Infect (Larchmt), 2006;7:(Suppl2):S77-S80.
28. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med, 2001;345:1359-1367.
1. 28.. Brunkhorst FM, Engel C, Bloos F, et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. N Engl J Med, 2008;358:125-139
29. Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med, 1998;26:645-650.
30. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA, 2002;288:862-871.
31. Prigent H, Maxime V, Annane D, et al. Science review: mechanisms of impaired adrenal function in sepsis and molecular actions of glucocorticoids. Crit Care, 2004;8:243-252.
32. Sprung CL, Annane D, Keh D, Moreno R, et al. Hydrocortisone Therapy for Patients with Septic Shock. N Engl J Med, 2008;358:111-124.
33. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med, 2008;36:296-327.
34. Kumar A, Haery C, Parrillo JE - Myocardial dysfunction in septic shock. Crit Care Clin, 2000;16:251-287.
35. Kumar A, Haery C, Parrillo JE - Myocardial dysfunction in septic shock: Part I. Clinical manifestation of cardiovascular dysfunction. J Cardiothorac Vasc Anesth, 2001;15:364-376.
36. Kumar A, Krieger A, Symeoneides S, et al. Myocardial dysfunction in septic shock: Part II. Role of cytokines and nitric oxide. J Cardiothorac Vasc Anesth, 2001;15:485-511.
37. Maeder M, Fehr T, Rickli H, et al. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. Chest, 2006;129:1349-1366.
38. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med, 2001;345:1368-1377.