ARTIGO ORIGINAL

Delayed hemodynamic monitoring with pulmonary artery catheter is a non-essential care in severe sepsis and septic shock.

Monitorização tardia com cateter de artéria pulmonar é um cuidado desnecessário em pacientes com sepse grave ou choque séptico.

Suzana M. Lobo[1], Márcio Queiroz[2], Patrícia Serrano[2], Carlos A. Polachini[2], Ligia M. Contrin[2], Sergio M. Guimarães[2], Marco A. Spergiorin[2], Susana P. Orrico[2], Carlos A. Mendes[2], Antonio C. Christiano Jr[2], Silvia P. Teixeira[2], Neymar E. Oliveira[2], Helder S. Sanches[2], Gilberto Friedman[3]

[1] Intensive Care Unit, Medical School – FAMERP São José do Rio Preto-SP, [2] Medical School, São José do Rio Preto-SP, [3] UFRGS, Department of Internal Medicine - Hospital de Clínicas de Porto Alegre-RS

Abstract

Objective: Prompt adequate antibiotic therapy, eradication of infection, fluids and vasoactive drugs are the main strategies for initial resuscitation of septic shock. Once initial resuscitative efforts are not effective, invasive hemodynamic monitoring (HM) with pulmonary artery catheter (PAC) has been frequently used to guide filling pressures and optimal doses of vasoactive agents. However, the evidence of benefit from PAC use in septic shock is still a matter of debate. We aimed to determine whether early compared to delay placement of PAC could have influenced outcome.

Methods: Retrospective analysis in a 24-bed general ICU tertiary care university hospital. From January 1999 to December 2000, patients admitted with severe sepsis and septic shock and having a PAC inserted were studied. Early invasive HM was defined whenever a PAC was placed in the first 48 hours, and delayed invasive HM was placed more than 48 hours after the diagnosis of severe sepsis or septic shock. Organ failure was defined as a SOFA score of ≥ 3 points.

Results. Among 104 patients submitted to invasive monitoring with PAC, 56 patients had sepsis. Fifty-two patients with severe sepsis (5, 9.6%) and septic shock (47, 90.4%) were enrolled. Thirty-six patients (69%) had early HM and 16 (21%) delayed HM. Overall in-hospital mortality was 69%. The groups had similar APACHE II score (18.6 ± 8.0, early HM; 18.5 ± 3.8, delayed HM), SOFA score (9.4 ± 3.2, early HM; 9.9 ± 4.4, delayed HM) and number of organs failure (1.6 ± 0.9, early HM; 1.8 ± 1.4, delayed HM) at the onset of severe sepsis/septic shock. The in-hospital mortality rate was significantly higher in delayed HM group (87.5%) compared with early HM (61.3%) (RR: 0.70, CI 95% 0.50-0.96, $p < 0.05$). Compared with delayed HM, early HM patients received significantly higher amount of fluids (10.3 ± 3.6 L vs 6.8 ± 3.5 L, $p = 0.002$) within 48 hours from onset of severe sepsis/septic shock.

Conclusion. Delayed monitoring with PAC patients with severe sepsis/septic shock is associated with a very high risk of death and might be considered a non-essential care.

Keywords severe sepsis, septic shock, mortality, hemodynamic monitoring, pulmonary artery catheter.

Resumo

Objetivo: As principais estratégias para a reanimação inicial após choque séptico são: a terapia antibiótica adequada imediata, líquidos e drogas vasoativas. Usa-se com freqüência a monitorização hemodinâmica invasiva (MH) com cateter de artéria pulmonar (CAP), quando os esforços de reanimação inicial não são eficientes, para guiar as pressões de enchimento e as doses mais adequadas de agentes vasoativos. Contudo, o indício do benefício proveniente do uso do CAP no choque séptico ainda é assunto de debate. Objetivamos determinar se a colocação precoce do CAP comparada com a colocação tardia poderia ter influenciado o resultado. **Métodos.** Análise retrospectiva realizada em um hospital universitário de cuidados terciários com 24 leitos na UTI geral. Estudamos no período de janeiro de 1999 a dezembro de 2000, pacientes internados com sepse grave, choque séptico e com CAP. Definiu-se como monitorização hemodinâmica invasiva precoce a colocação do CAP nas primeiras 48 horas e, como monitorização hemodinâmica invasiva tardia, a colocação do CAP mais de 48 horas após o diagnóstico de sepse grave e choque séptico. Definiu-se a falência orgânica por meio de um escore SOFA $\geq$ a 3. **Resultados.** Dentre os 104 pacientes submetidos à monitorização invasiva com CAP, 56 pacientes tinham sepse. Admitiu-se cinqüenta e dois pacientes com sepse grave (5; 9,6%) e

Recebido em 16.11.2004
Aceito em 18.03.2005

quarenta e sete (47; 90,4%) com choque séptico. Trinta e seis pacientes (69%) submeteram-se à monitorização hemodinâmica precoce e 16 (21%) à tardia. A mortalidade hospitalar global foi de 69%. Os grupos obtiveram escore APACHE II (18,6 ± 8,0; monitorização hemodinâmica precoce; 18,5 ± 3,8; monitorização hemodinâmica tardia), escore SOFA (9,4 ± 3,2; monitorização hemodinâmica precoce; 9,9 ± 4,4; monitorização hemodinâmica tardia) e número de falências orgânicas (1,6 ± 0,9; monitorização hemodinâmica precoce; 1,8 ± 1,4; monitorização hemodinâmica tardia) semelhantes no início da sepse grave/choque séptico. A taxa de mortalidade hospitalar foi significativamente maior no grupo submetido à monitorização hemodinâmica tardia (87,5%) comparada com o grupo submetido à monitorização hemodinâmica precoce (61,3%) (RR: 0,70, IC 95% 0,50-0,96, p < 0,05). Os pacientes submetidos à monitorização hemodinâmica precoce, comparados com os submetidos à monitorização hemodinâmica tardia, receberam quantidades significativamente maiores de líquidos (10,3 ± 3,6 L vs 6,8 ± 3,5 L, p = 0,002) nas 48 horas a partir do início da sepse grave/choque séptico. **Conclusão.** A monitorização tardia em pacientes com CAP, com sepse grave/choque séptico está associada a um risco muito alto de morte e poderia ser considerada uma assistência sem importância.

Palavras-chave sepse grave, choque séptico, mortalidade, monitorização hemodinâmica, cateter de artéria pulmonar.

Introduction

Despite major advances have been recently realized in the understanding of septic shock, mortality remains extremely high[1]. Cardiopulmonary physiology can be assessed with pulmonary artery catheter (PAC) allowing early assessment of the complex physiologic interactions occurring in these patients[2]. In fact, invasive hemodynamic monitoring (HM) is frequently delayed due to different reasons. Probably, the uncertainty about the precise impact of PAC use is one of the reasons[3].

There is an urgent need to better perform and use information obtained with PAC in septic shock patients once the impact of right heart catheterization remains controversial in special due to misinterpretation of the data derived from PAC [4, 5]. Studies on the use of PACs to achieve supranormal therapy show conflicting results and PAC-guided hemodynamic intervention to augment oxygen delivery to supranormal values in patients with SIRS-related organ dysfunction from sepsis is not recommended at this time [3-6]. *Connors et al* reported in a retrospective study that PAC placed in the first 24 hours of ICU admission was associated with a greater mortality in critically ill patients[7]. A recent published multicenter randomized controlled study reported that clinical management involving the early use of PAC in patients with shock, acute respiratory distress syndrome (ARDS) or both is a safe procedure but not associated with significant changes in mortality. However in this multicenter study no standardized protocols for managing patients were proposed intentionally what could lead to different data interpretations and consequently different therapies[8].

Timing has been shown to be relevant during resuscitation. *Rivers et al*[9] showed in a randomized controlled trial a significantly decreased in in-hospital mortality (30.5%) of patients with severe sepsis and septic shock receiving a 6-hour early goal directed therapy (EGDT) in the emergency room compared to a standard therapy (46.5%). EGDT patients received more intravenous fluids and inotropic support. *Shoemaker et al*[10] performed early invasive and non-invasive monitoring in a similar group of patients in the emergency department and reported that invasive hemodynamic variables were able to provide early warning of outcome. Besides, *Mimoz et al*[11] suggested that outcome might be better in patients with septic shock if PAC guides changes in therapy.

Insufficient evidence exists to determine if invasive hemodynamic monitoring with PAC improves outcome and if timing is relevant in patients with severe sepsis/septic shock. We therefore conducted this study to evaluate if a delayed invasive HM to guide resuscitation is comparable to an early approach. We also sought to determine differences in the early as compared to delayed patterns of central hemodynamics and peripheral tissue perfusion/oxygenation as well as differences in associated organ dysfunction.

Methods

This study is a retrospective analysis of a prospectively maintained database of patients who had invasive monitoring with a thermo-dilution PAC, without continuous cardiac output (CCO) and SvO_2, for more than 48 hours in our ICU. Each patient had a 7.5-Fr PAC (Balloon Thermodilution Catheter, Arrow International Laboratories, USA). Hemodynamic and oxygen transport variables were obtained according to standard methods and formulas[10]. Infection was considered according to usual clinical, laboratory and microbiological parameters[12]. Diagnosis of sepsis was based in the presence of three or four signs of SIRS associated with documented infection. Severe sepsis was considered when sepsis was associated with at least one organ failure and septic shock for those requiring administration of vasopressors (dopamine > 5 µg/kg/h or norepinephrine at any dose) to maintain mean arterial pressure higher than 70 mmHg for more than 4 hours[13]. Organ functions were evaluated on admission and daily during invasive HM with a set of clinical and laboratory parameters retrieved from the medical records and the most abnormal value for each of 6 organ systems (respiratory, renal, cardiovascular, hepatic, coagulation and neurological) were scored according to the sequential organ failure assessment (SOFA) score[14]. Organ failure was defined by a score of 3 or 4.

From the diagnosis of severe sepsis/septic shock, early HM was defined whenever a PAC was placed in the first 48 hours and delayed HM after 48 hours. According to the results the procedures carried out were as follow: fluid infusion, increase or decrease of vasoactive drugs and inotropic drugs. In our institution during the period of the study in patients with a PAC, hemodynamic measurements were carried out at each 8 hours or more frequently if necessary according to the data obtained, and fluid administration was guided by measurements of pulmo-

nary artery balloon-occluded pressure (PAOP), which was maintained between 12-16 mmHg. Therapy was titrated to our standard endpoints as oxygen delivery (DO_2) > 520 mL/min.m^2, oxygen consumption (DO_2) > 110 mL/min.m^2, a mean arterial pressure (MAP) > 65 mmHg, urine output of at least 0.5 mL/kg/hour and a serum lactate lower than 3.0 mEq/L. In patients without a PAC therapy was titrated to a central venous pressure (CVP) of 8-18 mmHg, and the same values for MAP, urine output and a serum lactate concentrations.

The cardio-respiratory and tissue oxygenation variables obtained in the first 48 hours were analyzed. The lowest values from each day for MAP, CI, DO2, PAOP and mixed venous oxygen saturation (SvO2) and the highest value of serum lactate concentrations were registered. Acute Physiologic and Chronic Health Evaluation II score (APACHE II) was calculated on admission[15]. Information regarding daily amount of fluids including colloids, crystalloids, blood derivates and vasoactive drugs were obtained from the medical records.

Results are expressed as mean ± SD. Continuous variables were compared with analysis of variance for repeated measurements (ANOVA). The mortality rates in both groups were evaluated with the relative risk (RR) and 95% confidence interval (CI) were calculated. A p value of < 0.05 was considered statistically significant.

Table 1. Demographic and outcome data.

	Early HM	Delayed HM
N° of patients	36	16
Sex, female/male	(16/20)	(5/11)
Medical/Surgical	(21/15)	(11/5)
Age, years	49 ± 18	56 ± 19
APACHE II	18.7 ± 8.0	18.5 ± 3.8
SOFA	9.4 ± 3.2	9.9 ± 4.4
MV, days	12.9 ± 12.3	18.5 ± 3.8
ICU stay, days	11.0 ± 2.4	10.5 ± 17.8
Patients with MOF	20 (55.0%)	6 (37.5%)
2 organs	13 (36.0%)	3 (18.7%)
3 organs	6 (16.6%)	2 (12.5%)
4 or more organs	1 (2.7%)	1(6.2%)
ICU mortality, %	61.0%	87.5%*

SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiologic and Chronic Health Evaluation II score , MV: mechanical ventilation, ICU: Intensive Care Unit, MOF: Multiple organ failure.
No (%), mean ± SD are given. * p<0.05, vs early HM.

Table 2. Volume (in Liters) administered within 48h from onset of severe sepsis/ septic shock for early and delayed HM groups.

	Crystalloids	Colloids	Blood derivates	Total volume
Early HM	6.86 / 8.42/ 9.87	0.22 / 1.00 / 1.62	0 / 0 / 0.68	7.50 /10.03/ 11.97
Delayed HM	4.65 / 5.22 / 6.61*	0 / 0.45 / 1.66	0 / 0 / 0.28	5.0 / 6.1 / 8.86*

Results are expressed as 25% / median / 75%. *:p<0.05 vs early HM group.

Results

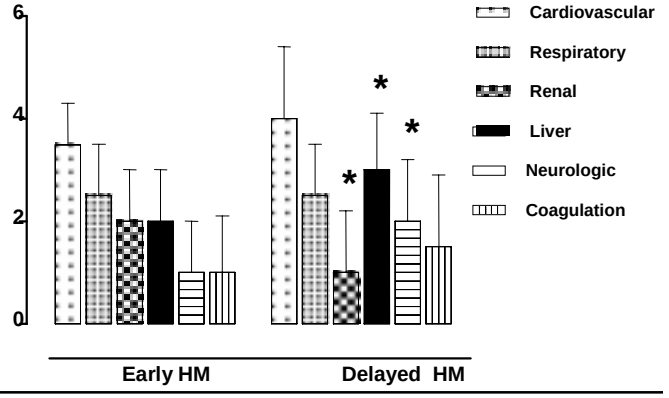
Over a 17-month period (1999-2000) 104 patients had a PAC placed in our ICU. Fifty-six patients had HM due to an initial diagnosis of sepsis. Forty-seven patients (90.4%) with septic shock and 5 with severe sepsis (9.6%) were included. Four patients with sepsis were excluded. Three patients recovered from shock after fluid replacement and vasoactive drugs were interrupted in less than four hours and one had right heart catheterization for less than 48 hours. All patients were in the ICU at the time of diagnosis of severe sepsis or septic shock. Thirty-six patients had early invasive HM (69%) and 16 had delayed invasive HM (31%). The overall hospital mortality was 69%. Demographic and outcome data are shown in Table 1. Patients with early HM and delayed HM patients had similar APACHE II score (16.5 ± 8.0, early HM; 17.0 ± 5.9, delayed HM), SOFA scores (9.5 ± 3.2, early HM; 9.0 ± 3.4, delayed HM) and number of organs failures within 48 hours from the onset of severe sepsis/ septic shock (1.6 ± 0.9, early HM; 1.8 ± 1.4, delayed HM) (Table 1). However, mortality was significantly higher in delayed HM group (87.5%) compared with early HM (61.3%) (RR: 0.70, CI 95% 0.50-0.96, p < 0.05). Early HM group received significantly

Table 3. Cardio-respiratory variables and indices of tissue perfusion at day 0 and day 1 of HM.

	Day	Early HM	Delayed HM
MAP (mm Hg)	0	79 ±14	69 ± 14*
	1	76 ± 16	65 ± 22*
CI (l/min.m^2)	0	5.9 ± 2.0	5.2 ± 1.6
	1	5.8 ± 1.8	4.7 ± 1.1*
PAOP (mm Hg)	0	14.0 ± 3.4	13.9 ± 3.7
	1	14.4± 3.6	18.2 ± 5.6*
DO_2 (ml/ min.m^2)	0	836 ± 227	862 ± 123
	1	845 ± 209	709 ± 122*
$ScvO_2$ (%)	0	80.0 ± 7.8	78.2 ± 8.0
	1	82.1 ± 6.9	76.3 ± 13.2*
Serum lactate (mEq/l)	0	1.6 ± 1.2	3.9 ± 6.0*
	1	2.4 ± 2.5	4.2 ± 4.6

MAP: mean arterial pressure, CI: cardiac index, PAOP: pulmonary artery balloon-occluded pressure, DO_2: Oxygen delivery; $ScvO_2$: central venous oxygen saturation. *: p<0.05 vs early HM.

Figure 1. SOFA scores for early HM and delayed HM groups at the first day of PAC.



higher amount of crystalloids and total fluids than delayed HM group within 48 hours from the onset of severe sepsis/septic shock (Table 2).

Patients with delayed HM had a significantly higher sofa score for liver and neurologic dysfunction but a lower score for renal dysfunction than patients with early HM (Figure1). PAC derived variables and indices of tissue perfusion at day 0 and day 1 of invasive HM are shown in Table 3.

Discussion

Invasive hemodynamic monitoring of severe sepsis and septic shock patients is still an important tool to guide resuscitation although doubts remain as to their benefits. In our study, mortality rate in patients with severe sepsis/septic shock was 87.5% when invasive monitoring with PAC was delayed for some reason for more than 48 hours after diagnosis of severe sepsis/septic shock.

A recent study reported that the total in-hospital mortality rate for sepsis fell from 27.8% during the period from 1979 through 1984 to 17.9% during the period from 1995 through 2000, yet the total number of deaths continued to increase[16]. The mortality rate in patients in the early HM group was 61% in agreement with other studies reporting very high mortality rates in patients with severe sepsis/septic shock treated with cathecolamines or having associated multiple organ dysfunction syndrome (MODS)[17]. *Hugonnet et al.*[18] reported similar mortality rates for septic shock of 69% and 68% for periods from 1984-1988 and 1994-1997, respectively. Brazilian ICUS most recent data (BASES study) showed a mortality of 47.3% for severe sepsis and 52.2% for septic shock[19]. Nevertheless, the systematic review by *Friedman et al.* [20] reported mortality rates ranging from 40-80% associated with a decrease in mortality overtime. In particular, abdominal sepsis exhibits the highest mortality rate with 72%[21].

In the present investigation, delayed HM carried a very high mortality rate of 87.5% suggesting that patients in this group were inappropriately treated or managed. In septic shock, treatment consists of vigorous fluid therapy combined with vasoactive drugs and inotropics. It seems from the current data that patients in the first 48 hours of septic shock and receiving therapy titrated to standard endpoints of CVP, MAP, urine output and laboratory studies as arterial blood gases and lactic acid level did not receive adequate amount of fluids. Probably confidence about fluid status using PAOP has permitted a more generous resuscitation. Both groups had similar APACHE II score, SOFA score and number of organs failure at the onset of severe sepsis/septic shock. However when invasive HM was performed patients with delayed HM presented a more severe hypotension associated with lower indices for cardiac output, DO_2 and SvO_2 and higher PAOP suggesting a worsening cardiac function and a pattern less likely to be reverted. Whether an earlier goal oriented intervention by CAP would prevent organ failure is difficult to say but if delayed for more than 48 hours invasive monitoring showed to be less effective.

The reason why the patients in the delayed invasive HM group were not invasively monitored with a PAC in the first 48 hours from the diagnosis of severe sepsis/septic shock was not evaluated, but lack of a protocol guiding a standard care for invasive monitoring during resuscitation of septic shock was probably the main one. Furthermore, a temporary recovery of the cardiovascular and metabolic functions after non-invasive guided therapy was seen in some patients leading to a delay in the use of the PAC that was than placed with the worsening of the patients' status. Another possibility is that there were totally different patients with much more severely ill patients in the delayed group. However the presence of similar APACHE and SOFA scores at admission on protocol do not support this view.

The definition of early invasive HM as opposed to delayed invasive HM in severe sepsis or septic shock was arbitrarily chosen based in the real daily care of many ICUs. Considering the circulatory problems obtained in middle or late stage shock when MOF is often associated with, and the outcome reported here, PAC are not useful anymore. Even in early invasive HM group, evaluation was not actually physiologically early. The hypotensive episode represents failure of protective circulatory mechanisms, not the beginning of circulatory dysfunction[2, 9]. When monitoring is started after hypotension, the first half of the problem is missed[2]. *Rivers et al*[9] reported severe sepsis and septic shock patients in the first 6 hours in the emergency department presented a cardiovascular pattern characterized by normal to increased blood pressures in addition to hypovolemia and decreased cardiac output (decreased SvO_2). As we noted in the present study, patients in the ICU have high SvO_2, hypotension requiring vasoactive drugs and elevated CI, a completely different pattern from the one observed in the emergency room. In a recent meta-analysis, *Kern et al*[22] have reported that the early treatment with optimal therapeutic goals in critically ill patients before the development of organ failure may significantly reduced mortality. However, the therapeutic optimization when established after the development of organ failure has proved to be useless. It is therefore, appropriate to focus on the earliest period of circulatory dysfunction with noninvasive methods to evaluate pathophysiology, to predict outcome, and to propose therapeutic protocols to improve outcome. SvO2 has been shown to be very useful to detect cardiovascular dysfunction before hypotension is present[10].

Nevertheless, by the time these therapies are applied to septic shock in the ICU, invasive HM is still an important tool to guide fluid therapy. What we called early intervention was actually late in the process of septic shock and carried a high mortality rate. What we called delayed HM was done at the time of an irreversible process of MODS and by this time such intervention may have been too late and futile. Hence, the focus of therapy has to shift towards an "as early as possible" hemodynamic optimization as well as searching for biomarkers capable of detecting such alterations occurring before hypotension and able to drive therapy.

Impaired tissue perfusion due to hypovolemia, disturbed vasoregulation and myocardial dysfunction contribute to multiple organ dysfunctions. At the first day of PAC renal system was significantly less compromised in delayed HM group compared to early HM group. This could be due to the high frequency of renal dysfunction occurring in the setting of severe dehydration and hypovolemia usually rapidly reverted after adequate fluid. Liver and neurologic failures are usually reported to be temporally a late event in the process of MODS and significantly higher SOFA scores for liver and neurologic system were observed in delayed HM group at the first day of PAC[14]. Strategies to protect patients from developing MODS must control the reperfusion injury cascade and normalize gastrointestinal blood flow very early in the process of sepsis[23].

Survival in severe sepsis depends not only of "adequate" invasive homodynamic monitoring. Individual practice variations have to come to an end and new proven strategies have to be implemented as intensive glucose control, low-dose corti-

costeroids, and recombinant human activate protein C (rhAPC)

PAC is able to provide important data such as CI, SVR, PAOP and ScvO2. Although the present study suffers from some limitation because of its retrospective, nonrandomized, open-label design, this data suggest benefits with the use of PAC in severe sepsis/septic shock patients once when its use was delayed for whatever reason, the outcome was worse. The mechanism underlying might be earlier correction of hypoxia and the possibility of preventing the inflammatory aspects of global tissue hypoxia that accompany the inflammation or infection. A randomized clinical trial with early goal-oriented therapy is needed to clearly establish whether PAC use reduces morbidity and mortality rates. Until such evidence becomes available severe sepsis and septic shock patients should receive early aggressive therapy using fluids and inotropic agents to restore and maintain oxygen availability to the cells. Therapy must be given promptly within appropriate limits after diagnosis of severe sepsis or septic shock. PAC must be considered to guide therapy but with higher restraining limitations not after 48 hours of cardiovascular dysfunction.

References

1. Vincent JL, Abraham E, Annane D, Bernard G, Rivers E, Van den Berghe G. Reducing mortality in sepsis: new directions. Crit Care 2002;6 Suppl 3:S1-18.
2. Shoemaker WC. Temporal physiologic patterns of shock and circulatory dysfunction based on early descriptions by invasive and noninvasive monitoring. New Horiz. 1996;4(2):300-18.
3. Parker MM, Peruzzi W. Pulmonary artery catheters in sepsis/septic shock. New Horiz. 1997;5(3):228-32.
4. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 1995;333(16):1025-32.
5. Iberti TJ, Fischer EP, Leibowitz AB, Panacek EA, Silverstein JH, Albertson TE. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. JAMA 1990;264(22):2928-32.
6. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330(24):1717-22.
7. Connors Jr AF, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 1996;276(11):889-97.
8. Richard C, Warszawski J, Anguel N, Deye N, Combes A, Barnoud D, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2003;290(20):2713-20.
9. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368-77.
10. Shoemaker WC, Wo CC, Yu S, Farjam F, Thangathurai D. Invasive and noninvasive haemodynamic monitoring of acutely ill sepsis and septic shock patients in the emergency department. Eur J Emerg Med 2000;7(3):169-75.
11. Mimoz O, Rauss A, Rekik N, Brun-Buisson C, Lemaire F, Brochard L. Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy. Crit Care Med 1994; 22(4):573-9.
12. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16(3):128-40.
13. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864-74.
14. Vincent JL, Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, 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. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998; 26(11):1793-800.
15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29.
16. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348(16):1546-54.
17. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. Crit Care Med 2000;28(8):2758-65.
18. Hugonnet S, Harbarth S, Ferriere K, Ricou B, Suter P, Pittet D. Bacteremic sepsis in intensive care: temporal trends in incidence, organ dysfunction, and prognosis. Crit Care Med 2003;31(2):390-4.
19. Silva E, Pedro MA, Sogayar ACB, Mohovic T, Silva CLO, Janiszewski M, et al. Brazilian sepsis epidemiological study (BASES study). Crit Care 2004;8(4):R251–60. 20. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. Crit Care Med. 1998; 26(12): 2078-86.
20. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. Crit Care Med 1998;26(12):2078-86.
21. Schoenberg MH, Weiss M, Radermacher P. Outcome of patients with sepsis and septic shock after ICU treatment. Langenbecks Arch Surg 1998;383(1):44-8.
22. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care med 2002;30(8):1686-92.
23. FitzGerald JF, Fox SH, Civetta JM, Kirton OC, Hudson-Civetta JA. Strategies to prevent organ failure. Curr Opin Anaesthesiol 1999;12(2):115-9.

Correspondência:
Suzana Margareth Ajeje Lobo
Av Brigadeiro Faria Lima, 5544 – 7º andar
15090-000 – São José do Rio Preto – SP
Tel.: (17)210-5083
e-mail: cepemi.hbase@famerp.br