Improving performance and outcome (mortality) after implementation of a change-bundle approach for management of septic patients

Melhoria de desempenho e desfechos (mortalidade) após implementação de um protocolo institucional de atendimento a pacientes sépticos

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ABSTRACT

Objective: Despite the existence of evidence-based guidelines for the management of patients with severe sepsis and septic shock, there is much variation among individual treatments. **Methods:** A before-after study with prospective data collection was performed at the emergency department and intensive care unit of a 485-bed, private, tertiary, general hospital. A total of 160 patients were enrolled (94 in a "pre-protocol phase" and 66 in a "post-protocol phase"). A resuscitation bundle for the first six hours and a management bundle for 24 hours were used. Additional quality indicators were also proposed and evaluated. The outcomes analyzed included hospital mortality, hospital and intensive care unit length of stay, compliance with bundles and performance related to quality indicators. **Results:** From the "pre-protocol" to "post-protocol" phase, the diagnosis moved from the intensive care unit (52.0 to 18.2%) to the emergency department (26.6 to 40.9%) and to the wards (17.0 to 36.4%). Number of blood cultures prior to antibiotics, administration of activated drotrecogin alfa, use of corticosteroids and compliance with six-hour and 24-hour sepsis bundles were significantly higher after protocol implementation. Patients in the "post-protocol" group had a statistically lower risk of in-hospital mortality (56.4 *versus* 36.4%, $p = 0.01$). The greatest decrease in mortality rate occurred among the most critically ill patients (67.7 to 40.7%, $p = 0.004$). **Conclusions:** Adopting an institutional protocol focused on behavioral changes and using quality improvement tools led to reduced hospital mortality and generated changes in healthcare team practice. This result adds to the growing evidence that optimized process-of-care by implementing managed protocols for sepsis patients can reduce mortality. Therefore, similar strategies should be routinely employed.

Keywords: Sepsis/therapy; Shock, septic/therapy; Clinical protocols; Mortality; Intensive care; Quality indicators, health care

RESUMO

Objetivo: Apesar da existência de diretrizes internacionais baseadas em evidência para o tratamento de pacientes com sepse grave e choque séptico, grande variação existe quanto às características do tratamento oferecido no nível individual. **Métodos:** Estudo do tipo "antes e depois" foi realizado na unidade de pronto atendimento e no centro de terapia intensiva de um hospital geral, terciário, privado, de 485 leitos. Foram incluídos 160 pacientes (94 na fase "pré-protocolo" e 66 na "pós-protocolo"). Um pacote de intervenções para as seis horas (pacote de ressuscitação) e para as 24 horas do início das disfunções orgânicas (pacote de manutenção) foi utilizado. Indicadores locais foram propostos e avaliados. Desfechos analisados: mortalidade hospitalar, permanência hospitalar e no centro de terapia intensiva, aderência aos pacotes e desempenho em relação aos indicadores. **Resultados:** Da "fase pré-protocolo" para a "fase pós-protocolo", o local do diagnóstico mudou do centro de terapia intensiva (52 para 18,2%) para o departamento de emergência (26,6 para 40,9%) e alas (17,0 para 36,4%). O número de hemoculturas colhidas antes do início dos antibióticos, o uso de drotrecogina alfa (ativada), o uso de corticóides e a aderência aos pacotes de seis e

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24 horas foram significativamente maiores. Houve redução da taxa de mortalidade hospitalar (56,4 *versus* 36,4, p = 0,01). Reduções ainda maiores ocorreram entre os pacientes mais graves (67,7 para 40,7%). **Conclusões:** A adoção de um protocolo institucional focado na mudança de comportamento, usando ferramentas de melhoria da qualidade, foi capaz de reduzir a mortalidade hospitalar e gerar mudanças de prática na equipe assistencial. Existe crescente evidência de que a otimização dos processos de atendimento por meio da implementação de protocolos gerenciados direcionados à população com sepse pode reduzir a mortalidade. Por esses motivos, estratégias semelhantes deveriam ser empregadas rotineiramente.

Descritores: Sepse/terapia; Choque séptico/terapia; Protocolos clínicos; Mortalidade; Cuidados intensivos; Indicadores de qualidade em assistência à saúde

INTRODUCTION

Researchers, healthcare providers, managers and government authorities are increasingly drawing attention to sepsis given its evident growing incidence[1-2], high late mortality rate and widespread distribution. In addition, it accounts for financial costs that exceed US$ 16 billion each year in the United States[3].

In the second phase of the Surviving Sepsis Campaign (SSC), a group of critical care and infectious disease experts, representing several international institutions, met to develop guidelines that the bedside clinician could employ in order to improve the outcome of patients with severe sepsis and septic shock. A concise peer review was prepared based on the committee deliberations and was published in two international journals[4-5]. This document was recently revised in light of recently concluded clinical trials (manuscript in preparation).

Even though guidelines are statements based on the best evidences, systematically developed to assist practitioners in the decision-making process under specific clinical circumstances, they are in general not sufficient to generate changes on their own. Physician compliance to guidelines may be hindered by a variety of barriers[6]. There are many recently published papers highlighting several aspects related to this problem and concluding that the development of a plan or strategy directed towards the implementation of guidelines are as important as the guidelines themselves[7-10]. The Institute for Healthcare Improvement (IHI, www.ihi.org) has emerged as an international leader for modifying healthcare professional conduct, in compliance with the clinical evidence-based recommendations, developing procedures that ensure quality of care for the critically ill, standard data-collection tools and educational programs designed to help hospitals attain best practice[9].

Acknowledging these problems and anticipating solutions, the SSC committee, in association with the IHI, did not limit their work to just establishing guidelines. They developed a worldwide campaign aiming to achieve a 25% reduction in mortality due to sepsis within five years by achieving changes in standard of care. Strategies undertaken to optimize guidelines usage included proper and specific methodology used in expert meetings, newer and easier concepts in evidence classification, setting a training period before protocol implementation, data collection to feedback the process implementation and description of the recommendations as "bundles" (term used to name a selected set of interventions extracted from evidence-based practical guidelines that, when implemented as a group, over a defined period of time, are likely to improve outcome when compared to implementing the individual elements alone)[9].

OBJECTIVE

The objective of the present study was to evaluate the compliance of professionals to the program and the impact on mortality rate following implementation of a standard operating procedure (SOP), based on the sepsis bundle-approach, at a tertiary private hospital, comparing the results before and after protocol implementation.

METHODS

Setting and general features

The study was conducted at Hospital Israelita Albert Einstein, a 450-bed private hospital in the city of São Paulo, Brazil. The 40-bed intensive care unit (ICU) and the emergency room (ER) were included. It was analyzed the prospectively collected data from the proposed institutional protocol, in collaboration with the Latin American Sepsis Institute (ILAS). It is here presented the preliminary data from the first 93 patients monitored by the investigators from July 24, 2005 to October 29, 2006. Given its implementation as an institutional protocol, informed consent and institutional review board approval were waived.

Inclusion and exclusion criteria

All patients diagnosed with severe sepsis or septic shock were followed up from clinical presentation to hospital discharge. Severe sepsis was defined by sepsis-induced organ dysfunction. Organ dysfunction was defined as follows: a) cardiovascular: systolic blood pressure less than 90 mmHg or mean arterial pressure ≤ 70 mmHg or decrease in systolic arterial pressure ≥ 40 mmHg; b) respiratory: PaO_2/FiO_2 ratio less than 300; c) renal: diuresis less than 0.5 ml/Kg/h for at least two hours, or creatinine > 2.0 mg/dl after fluid resuscitation; d) coagulation: platelet count less than 100,000/mm^3 or

INR > 1.5 or aPTT > 60 s; e) hepatic: total bilirubin > 2.0 mg/dl or 35 mmol/l; f) metabolic: lactate > 2 mmol/l. There were no exclusion criteria.

Institutional protocol (SOP)

After a planning period, the "SSC Project" was started in May, 2005 with an official opening ceremony inviting all ICU and ER professionals. During this event, the Surviving Sepsis guidelines were discussed and the campaign goals explained. A few weeks later, a multidisciplinary team was created, including physicians, nurses, respiratory therapists, clinical pharmacists, laboratory and imaging professionals. This team was responsible for developing the implementation strategies and tools directed to identify patients that should be included in the sepsis bundle protocols as early as possible, in accordance with the "Changes for improvement" program from the IHI.

In the first six hours, the sepsis resuscitation bundle was implemented for all patients included in the protocol with the following changes for improvement: serum lactate measured; blood cultures obtained prior to antibiotic administration; improving time to broad-spectrum antibiotics within three hours for ER admissions and one hour for non-ER ICU admissions; treat hypotension and/or elevated lactate with fluids at a minimum of 20 ml/Kg of crystalloids or equivalent colloid; apply vasopressors for ongoing hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure > 65 mmHg. Only for hypotensive patients, despite initial volume replacement, or those with serum lactate higher than twice the upper limit: central venous pressure (CVP) ≥ 8 mmHg; and central venous oxygen saturation ($ScvO_2$) ≥ 70%. In the following hours, the sepsis management bundle was implemented and completed within a 24-hour period with low-dose steroids administered for septic shock, in accordance with a standardized ICU policy; drotrecogin alfa (activated), administered in accordance with a standardized ICU policy; maintain adequate glycemic control with values between 80 and 150 mg/dl and maintain inspiratory plateau pressure below 30 cm H_2O for mechanically ventilated patients.

Finally, compliance with six and 24-hour bundles was also evaluated. Furthermore, quality indicators were created for a posterior process evaluation, in order to upgrade and detail some goals with focus on local features. Additional indicators were also created by the local team in parallel: lactate results obtained in 30 minutes; lactate goal (< 36 mg/dl) achieved within the first six hours; antibiotics initiated within two hours from admission. The group also implemented a six-priority strategy which included:

- the development of summarized flow-charts for the ER and ICU describing the criteria for the diagnosis of sepsis, severe sepsis, septic shock, and organ dysfunction and with a list of laboratory exams to be ordered;
- other summarized flow-charts outlining the six and 24-hour bundles with clear definitions of goals to be achieved within the established periods and of selected quality indicators;
- a 'sepsis code' to be activated by ER nurses at identification of suspected sepsis cases, with critical care physicians, ICU respiratory therapists, case managers, clinical and microbiological laboratories summoned by pager;
- a standardized electronic set of lab tests including those determined by the Early Goal Directed Therapy (EGDT);
- a standardized sepsis kit with fluids and hemodynamic monitoring devices including continuous central venous saturation and arterial catheters;
- a case-manager nurse responsible for patient admissions, data collection, optimization of processes and proposal of course adjustments.

An intensive period of training was concurrently started involving several meetings, banners and e-learning tools to disseminate the recommendations and to reinforce the goals of the six and 24-hour bundles. All physicians and nurses were trained by senior medical leaders; laboratory technicians and by the case manager nurse.

Study design and data collection

From July 24, 2005 to April 10, 2006 all patient data were collected by a case manager in a "pre-protocol phase". After this period, when professionals were trained and all tools and strategies were available and implemented, the intervention or "post-protocol phase" was started comprising the period from April 10, 2006 to October 29, 2006. The following variables were prospectively collected: demography; time for diagnosis; APACHE II score; lactate measurement times; blood cultures; antibiotics; amount of fluids administered; use of vasopressors; use of continuous central venous catheter; CVP and central ($ScvO_2$) or mixed (SvO_2) venous oxygen saturation measurements; use of low-dose steroids and drotrecogin alfa (activated); glycemic control; mechanical ventilation and plateau pressures; hospital and ICU length of stay; and status at hospital discharge.

A before-after study was designed to compare data from "pre-protocol phase" to the "post-protocol phase". The primary objective was to evaluate the impact of

protocol implementation on hospital mortality rate. The secondary objectives were to compare hospital and ICU length of stay; measure compliance with six and 24-hour bundles; measure performance related to time intervals and to selected quality indicators created before and after protocol implementation.

Statistical analysis

Categorical variables were described as absolute and relative frequency and compared with the χ^2 test, Fisher's exact test or maximum-likelihood ratio test, when appropriate. Continuous variables were described as mean, standard deviation and interquartile range and compared with the Wilcoxon rank-sum or Kruskal-Wallis tests. A two-tailed p value < 0.05 was considered statistically significant. Statistical analysis was conducted using the SAS System 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Training period

Staff participation during the training period was high among nurses (78/102 = 76.5%) and residents (6/6 = 100%), but not as high among respiratory therapists (20/42 = 48%) and ER / ICU attending physicians (52/113 = 46%).

Patient data

A total of 160 consecutive patients were analyzed: 94 in the "pre-protocol phase" and 66 in the "post-protocol phase". Baseline characteristics were similar between groups. However, the post-protocol sample presented with greater incidence of septic shock (p = 0.03) and multiple organ dysfunctions (p = 0.0004). Moreover, there was a difference in the service in which the diagnosis of severe sepsis was performed when comparing pre and post-protocol phases (Table 1). In the post-protocol phase, the diagnosis of severe sepsis was less common in the ICU (from 52 to 18.2%), moving towards the wards (17 to 36.4%) and the ER (26.6% to 40.9%).

Bundle-related goals

Performance via process of care variables is described in Table 2. After protocol implementation, significant changes in the six-hour sepsis bundle indicators were noted. Number of CVP and $ScvO_2$ measurements were higher than in the "pre-protocol" group because of an increase in number of central venous catheterizations performed (8.5 pre-protocol *versus* 72.7% post-protocol, p < 0.0001). Blood cultures improved, with samples being collected before antibiotic administration in a significantly larger number of cases in the "post-protocol" phase (68.1 *versus* 92.4%, p < 0.0001). Timing of antibiotic administration, before 120 minutes, also improved (61.7 *versus* 81.8%, p = 0.008). No significant changes were detected in the following indicators: lactate sampling time (up to 30 minutes from admission), lactate measurements (< 36 mg/dl in the first six hours), CVP (≥ 8 cm H_2O in the first six hours) and $ScvO_2$ (≥ 70% in the first six hours).

Improvements were also noted in the 24-hour sepsis bundle. Drotrecogin alfa (activated) was administered to only 1.1% of patients in the "pre-protocol" phase in contrast to 13.6% (one *versus* nine patients, p = 0.0016)

Table 1. Baseline characteristics

	Pre-protocol	Post-protocol	p value
Male sex, n (%)	57 (60.6)	36 (54.5)	0.51
Age*	66 ± 19	64 ± 21	0.55
APACHE II score > 25, n (%)	42 (44.7)	25 (38.5)	0.51
Septic shock, n (%)	62 (65.7)	54 (81.8)	0.03
Site of diagnosis, n (%)			0.0001
Emergency room	25 (26.6)	27 (40.9)	
Wards	16 (17.0)	24 (36.4)	
Step-down unit	4 (4.3)	3 (4.5)	
Intensive care unit	49 (52.1)	12 (18.2)	
Mechanical ventilation	66 (70.2)	46 (69.7)	1.00
Hypotension and/or high lactate levels	90 (95.7)	62 (93.9)	0.71
≥ 2 organ dysfunctions	73 (77.7)	64 (97.0)	0.0004

* Age values are expressed as means ± SD

Table 2. Process-of-care variables, quality indicators and compliance rates before and after intervention

	Pre-protocol phase	Post-protocol phase	p value
6-hour bundle			
Lactate sampling time (up to 30 min. from admission), n (%)	28 (30.1)	22 (33.3)	0.72
Blood cultures before antibiotic administration, n (%)	64 (68.1)	61 (92.4)	< 0.0001
Antibiotics started before 2 hours from admission, n (%)	58 (61.7)	54 (81.8)	0.008
CVP goal (higher than 8 cm H_2O, in the first 6 hours), n (%)	26 (49.6)	28 (52.8)	0.84
Lactate measurements (> 36 mg/dl, in the first 6 hours), n (%)	25 (92.6)	17 (89.5)	1.0
$ScvO_2$ goal (higher than 70%, in the first 6 hours), n (%)	34 (51.5)	21 (46.7)	0.7
24-hour bundle			
Drotrecogin alfa (activated), n (%)	1 (1.1)	9 (13.6)	0.001
Corticosteroids, n (%)	53 (56.4)	54 (81.8)	0.001
Glycemic control*	47 (51.1%)	30 (45.5%)	0.5
Plateau pressure, n (%)**	50 (75.7%)	35 (76.1%)	1.0
Compliance rates			
6-hour bundle	0 (0)	4 (6.1)	0.02
24-hour bundle	14 (14.9)	21 (31.8)	0.01

*Glucose levels are expressed as mean of each patient's medians; ** plateau pressure is expressed as means

in the "post-protocol" phase. Corticosteroid use was 25.4% higher after implementation (56.4 to 81.8%, p = 0.001). No significant changes occurred in glycemic control and airway plateau pressure endpoints.

Compliance with the six and 24-hour sepsis bundles was also significantly enhanced after protocol implementation (Table 2).

Outcome

Patients in the "post-protocol" group presented a statistically significant lower mortality rate in the ICU (56.4 *versus* 36.4%, p = 0.01). Greater reduction in mortality was noted among the most severely-ill patients, which were those in septic shock: 67.7 to 40.7% (p = 0.004). Patients with severe sepsis had the mortality rate reduced from 34.4 to 16.7% (p = 0.4) (Figure 1).

Median hospital and ICU length of stay were not statistically different between groups before and after protocol implementation (Table 3).

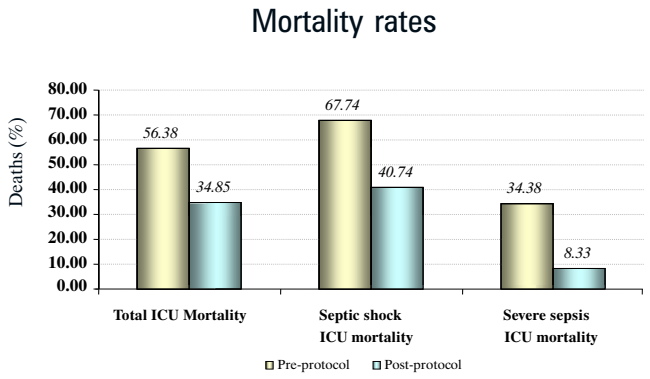

Figure 1 – ICU mortality before and after intervention

Table 3. Hospital and ICU length of stay before and after protocol implementation

	Pre-protocol	Post-protocol	p value
Hospital length of stay*	20.5 (11-45)	20 (11-37)	0.7
ICU length-of-stay*	7.4 (4.0-16.4)	8.8 (2.8-18.9)	0.8

* Data expressed as median (interquartile range)

DISCUSSION

This study reinforces the idea that updated guidelines and reports are not enough to promote behavioral changes in medical practices. Using the same body of evidence (i.e. with no new evidence) it was possible to demonstrate that the creation of an actively working team responsible for standardizing and optimizing diagnosis for the treatment of patients with severe sepsis and septic shock can improve the quality of care and reduce mortality.

Similar results have been demonstrated in other disorders including myocardial infarction[11-12] and severe infections[13-17]. Also, benefits on rationalizing resources allocation and costs reduction may be achieved[18]. For instance, Micek et al. showed that a standardized set of instructions for the management of septic shock in the emergency department was associated with more rigorous fluid resuscitation, greater administration of appropriate initial antibiotic treatment and a lower 28-day mortality rate. This suggests that these standardizations should become routine in the management of patients with septic shock. In Micek's study, the intervention was limited to the implementation of a standardized order set, mainly including fluid resuscitation and antibiotic therapy[17]. Focusing on sepsis bundle adherence, Gao et. al demonstrated a reduced mortality wherever all six-hour care bundle items of the SSC were complied with[13]. Nevertheless, in the same study, compliance with the 24-hour bundle did not show any reduction in mortality. Recently, in a before-after study, Jones et al.[19] published data on the implementation of a routine protocol based on EGDT in the ER. They reported a lower mortality rate after the protocol implementation with a 9% absolute and 33% relative mortality reductions.

In this study, it was demonstrated that by creating a working team and optimizing processes and interventions, mortality of severe sepsis and septic shock could be dramatically reduced. In contrast to previous reports, this intervention aimed at planning, implementing, evaluating and providing feedback to the program, using a SOP (a set of local quality of care indicators, based on the interventions published in six and 24-hour bundles from the SSC guidelines). Some key factors and actions were directly responsible for the favorable results found in terms of changing behavior and mortality reduction in our institution.

First of all, this study was aimed to promote a change in behavior as to how severe sepsis patients should be managed. As demonstrated by Cabana et al.[6] there are some barriers, which could hinder the process. They can be grouped into three different categories: knowledge, attitudes and behavior. A lack of familiarity, inertia of previous practice, self-efficacy, difficult format and environment factors such as insufficient time, resources and institutional barriers are some examples which impair guidelines incorporation into practice. Cinel e Dellinger described strategies to promote behavior changes[7]. The creation of a multidiscipline working team for the daily documentation, communication, education and evaluation of activities is a recommended starting point. A leadership group, with the institutional perspective

and authority, is also essential. Providers must always be kept up-to-date through feedback mechanisms. Express evidence as bundles, standardizations and improved team communication are important details. Finally, identification and investment in early adopters of the innovation will accelerate the rate of diffusion of the whole process.

In our institution, professionals with recognized leadership skills in sepsis management conducted the training programs. As a result, the multidisciplinary team felt more confident in the implementation of new policies and procedures. The same professional was responsible for negotiations with administrative managers in order to have the resources needed. Creation of an active and multidisciplinary working team, representative of all professional categories involved in critical care, was another important factor. This team also worked on the feedback processes, guideline simplification and adaptation. Creating their own quality indicators and specific tools targeted at enhancing data utility, they made the implementation process easier and assured local features to the protocol.

Earlier interventions were believed to be the keystone for the mortality reduction. Higher compliance with six hour-bundle, earlier antibiotic administration and more aggressive fluid resuscitation (data not shown), were the most important interventions. More frequently, drotrecogin alfa (activated) administration also contributed to better survival rates.

Some obstacles were also hit. The apparent low rate of staff involvement in the training period may be explained by the fact that all team leaders in the ICU and the ER were submitted for training. These leaders were responsible for the propagation of the newly instituted process measures. Moreover, all cases were checked by the case manager on ER admission and followed during the treatment bundles. Although no statistical test was performed regarding time of diagnosis, it is strongly believed that the tendency for diagnosis to be increasingly made at the ER and access units, instead of at the ICU, was a consequence of the processes implemented and not of difference in populations. With reference to compliance with bundles, despite an evident statistically significant increase in rates observed with both the six and the 24-hour bundles, the overall compliance rates remain at low levels. Like an institutional protocol, these and all data analyzed are being used by the institution (and will continue to be) to implement changes directed at the correct course of action to improve the standard of care.

There is a greater number of central venous catheterizations in the post-protocol group. However, the number of catheter-associated bloodstream infections did not increase (10.6% or 10/94 patients in the "pre-protocol" phase *versus* 6% or 4/66 patients in the "post-protocol" phase). This finding reinforces the need to monitor CVP and oxygen saturation, as it did no harm.

Extrapolating collected data, to assess the magnitude of results, considering the absolute mortality reduction 35.5%, it was possible to calculate an "estimated number needed to treat" (NNT) as low as five.

Similar strategy was recently tested by Ferrer et al., in the first study to prospectively evaluate the impact of an educational program on guideline compliance and mortality in patients with severe sepsis. In 59 medical-surgical ICUs in Spain, patients were followed before and after implementation of a multicenter educational program and the post intervention cohort had a lower risk of hospital mortality (44 *versus* 39.7%; $p = 0.04$)[20]. Here, a higher rate of mortality reduction was reached (56.4 *versus* 36.4%, $p = 0.01$)

The present study has some limitations. It was performed in a single general, tertiary, private hospital with a small sample population. The patients were not randomized to one group or another and there were only historical controls. However, based on current evidence and on ethical issues, it is acceptable to say that, nowadays, perhaps only studies with this design can be executed evaluating management of sepsis.

CONCLUSIONS

In conclusion, this study demonstrates that an approach to sepsis based on change-bundles was able to reduce ICU mortality in a tertiary Brazilian hospital, generating changes in practice as well as improving performance, as revealed by the measured quality indicators. There is growing evidence that a standardized process of care in the management of severe sepsis and septic shock can reduce mortality and, based on these findings, they should be routinely employed.

Because it was possible to show mortality reduction with this relatively low-cost intervention, other experiences with managed protocols, SOP and active working teams, directed to specific areas (for example, in other highly prevalent and lethal conditions) should be successful. These experiences should take part in the planning process of healthcare actions in these institutions.

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