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Early detection strategy and mortality reduction in severe sepsis

Estratégia de detecção precoce e redução de mortalidade na sepse grave

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ABSTRACT

Objective: To evaluate the impact of implementing an institutional policy for detection of severe sepsis and septic shock.

Methods: Study before (stage I), after (stage II) with prospective data collection in a 195 bed public hospital.. Stage I: Patients with severe sepsis or septic shock were included consecutively over 15 months and treated according to the Surviving Sepsis Campaign guidelines. Stage II: In the 10 subsequent months, patients with severe sepsis or septic shock were enrolled based on an active search for signs suggesting infection (SSI) in hospitalized patients. The two stages were compared for demographic variables, time needed for recognition of at least two signs suggesting infection (SSI-Δt), compliance to the bundles of 6 and 24 hours and mortality.

Results: We identified 124 patients with severe sepsis or septic shock, 68 in stage I and 56 in stage II. The demographic variables were similar in both stages. The Δt-SSI was 34 ± 54 hours in stage I and 7 ± 8.4 hours in stage II (p <0.001). There was no difference in compliance to the bundles. In parallel there was significant reduction of mortality rates at 28 days (54.4% *versus* 30%, p <0.02) and hospital (67.6% *versus* 41%, p <0.003). **Conclusion**: The strategy used helped to identify early risk of sepsis and resulted in decreased mortality associated with severe sepsis and septic shock.

Keywords: Shock, septic /diagnosis; Shock, septic/therapy; Shock, septic/mortality; Sepsis/diagnosis; Sepsis/therapy; Sepsis/mortality

INTRODUCTION

Sepsis is a set of sometimes dramatic and catastrophic reactions of human beings in response to invasion by pathogenic microorganisms. It is a clinical syndrome that presents with different degrees of severity. If not diagnosed and adequately treated it may worsen over time. Usually, the clinical condition begins with nonspecific and subtle changes of the vital signs such as tachycardia and tachypnea.[1-4]

Generally speaking, sepsis often goes unnoticed until advanced stages even in hospital settings[4] because its manifestations are not marked by an *ictus* as in acute myocardium infraction (AMI) or stroke (S).

Diagnosis of the septic syndrome is clinical, based on changes that comprise the systemic inflammatory response syndrome SIRS. It was defined in 1991 by the *American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee* as a set of at least two of the following

manifestations: a) fever or hypothermia; b) tachycardia c|) tachypnea, d) leukocytosis or leukopenia. It is an acute condition caused by systemic release of inflammatory mediators and generalized activation of the endothelium, generating break of the endothelial homeostasis with impairment and dysfunction of organs distant from the primary focus. It reflects the level of organic stress associated to different clinical conditions such as: trauma, burns, acute severe pancreatitis, surgery, transfusion therapy and infection. When SIRS is secondary to infection, the diagnosis is sepsis. Sepsis is considered severe when there is at least one associated organ dysfunction and, if hypotension persists regardless of vigorous administration of water, it is septic shock.[1]

It was proven that adopting the therapeutic strategy proposed by the Serving Sepsis Campaign (SSC) that includes early tissue reperfusion and control of the infection focus,[2,5,6] bring about decreased mortality.[7-14] In our hospital, as well as in other Brazilian institutions, notwithstanding adhesion to SSC, mortality rates continue to be unacceptably high.[15-17] Perhaps this was related to delay in diagnosis of sepsis. Failure to identify sepsis delays onset of adequate treatment, causes progress of multiple organ dysfunction and severely jeopardizes prognosis of patients.[16] Therefore, ongoing search for detection of signs of SIRS and organ dysfunction during routine control of vital signs, might involve identification of patients at risk of sepsis. In this context we proposed a simple institutional procedure to facilitate identification of severe sepsis or septic shock in our hospital.

This study intended to verify if institutional emphasis to identify risk of sepsis may help early recognition of severe sepsis or septic shock and influence its prognosis.

METHODS

This is a before/after study (stage 1/stage II) conducted from August 2005 to September 2007, in the wards of the emergency department and intensive care unit (ICU) of the Hospital Municipal São José (HMSJ), Joinville, Santa Catarina, Brazil. HMS is a general and public hospital with 195 beds for general admission and 2 ICU with 14 beds. Written consent was not given, as it is an institutional program to attend patients. Patients detected in any sector of the hospital with a diagnosis of severe sepsis or septic shock was included. Terminal disease or shock by other etiologies were considered exclusion criteria.

The study encompasses two distinct periods (stage I and stage II) that differ according to the screening strategy of patients with risk of sepsis. In stage I (15 months) were consecutively included patients with severe sepsis or septic shock, managed according to the SSC recommendations. Diagnosis and treatment strategy was divided into three parts, shown in chart 1.[17]

Chart 1 - Strategy for diagnosis and treatment of stage I

Screening - According to the following questions for diagnosis
a. Is there an infectious focus?
b. Are there two or more SSI: temperature > 38ºC or < 36ºC; Chills and shivering; heart rate > 90 bpm; respiratory rate > 20 mpm; systolic arterial pressure < 90 or mean arterial pressure < 65 mmHg.
c. Affirmative reply to two questions results in diagnosis of sepsis
d. Is there organ dysfunction?
(e) Affirmative reply to all previous questions results in diagnosis of severe sepsis
Initial management – Patients with severe sepsis or septic shock must fulfill all of the seven goals below in the first 6 hours after diagnosis, and the sum of these goals is called the "6 hours bundle".
a. Mesurment of serum lactate
b. Collection of at least two samples of hemoculture from different sites
c. Onset of adequate antibiotic therapy in the first hour after diagnosis
d. If there is hypotension or lactate above or equal to 4mmol/l, administer 20 to 30 ml/kg of crystalloid.
e. Initiate vasopressor if MAP of 65 mmHg or more has not been reached after crystalloid infusion.
f. Reach a CVP above 8 mmHg in patients needing this generous infusion of crystalloid
g. Reach a central venous saturation above 70%
24 hours bundle – goals that must be fulfilled in the first 24 hours after onset of treatment
a. administer low dose corticoids according to the ICU policy, if institutional policy is not to use any, record it.
b. administer (according to the policy of each institution) recombinant human activated protein C. HMS policy regarding application of rhPC is not to use the drug.
c. glycemic control with insulin therapy according to institutional protocol
d. Keep inspiratory plateau pressure < 30 cmH_20 in patients under mechanical ventilation.

CVP – central venous pressure; SSI – signs suggesting infection; ICU– intensive care unit; HMSJ – Hospital Municipal São José.

At stage II, (10 months) patients with sepsis or septic shock were identified as from an active search strategy for signs suggesting infection (SSI) in all patients admitted to the hospital. A new form was devised for a record of SSI (Appendix 1), grouping vital signs and eventual clinical signs of organ dysfunction of all patients in each ward. Register of at least two SSI in this form were promptly informed to the responsible nurse by the sector that completed the screening form (Appendix 2). A single nursing technician in each ward was in charge of the task. After initial assessment by the responsible nurse and by the sector, the nursing staff of the Hospital Infection Control Committee (HICC) was advised to evaluate and follow-up the case. The on duty physician (internal medicine resident) was immediately called when suspicion of sepsis was confirmed (Appendix 2). When diagnosis was defined, therapeutic bundles were started from 6 and 24 hours (Appendix 3 and 4) according to SSC guidelines (Figure 1).

Nurses and resident physicians of intensive care and internal medicine of HMS were trained and supervised by intensivists to ascertain that patients were adequately treated in any ward. In our hospital, as well as many others in Brazil, often a bed is not available in the ICU. That is why many training sessions were carried out so that all understood severe sepsis/septic shock, stressing the importance of changes in the vital signs.

The groups of patients of stage I and stage II were compared for: age, gender, provenance (ward, ICU, emergency room), time elapsed since first record (medical chart) of at least two SSI, moment of diagnosis of severe sepsis (Δt-SSI), APACHE, Acute Physiology and Chronic Health Evaluation II score, complete compliance to the bundles of 6 and of 24 hours, ICU and hospital stay, mortality at 28th day and intra-hospital.

For statistical analysis of data, the programs *NCSS: Statistical Software 2000 & PASS 2000: Power Analysisande Sample Size and GraphPad Prism 4* were used. Continuous variables were presented as mean ± standard deviations and compared using the Student's t test. Categorical variables were expressed in absolute and relative values and compared by the Chi-Square test. A p=0.05 value was considered statistically significant.

RESULTS

Three hundred seventy eight patients were consecutively assessed. During stage I, 76 patients were identified with severe sepsis or septic shock, of which 8 were excluded for lack of a therapeutic perspective related to the baseline disease. At stage II, 240 patients had two or more signs suggesting infection. Sixty two patients presented severe sepsis criteria (n=26) or septic shock

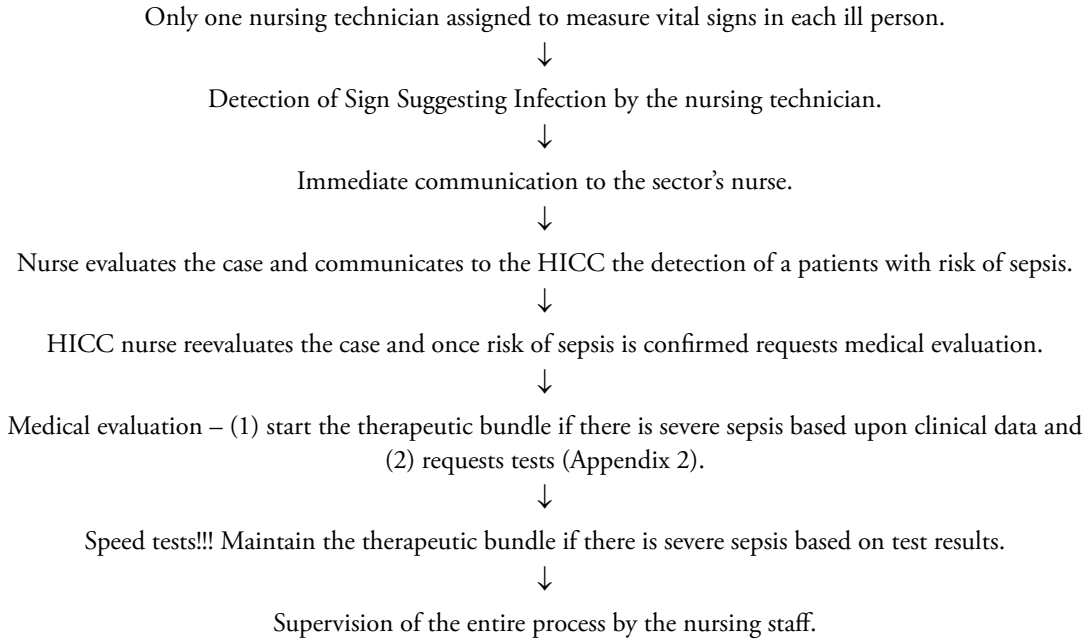

Figure 1- Description of the protocol for early detection of severe sepsis or septic shock at the Hospital Municipal São José during stage II. HICC – Hospital Infection Control Committee.

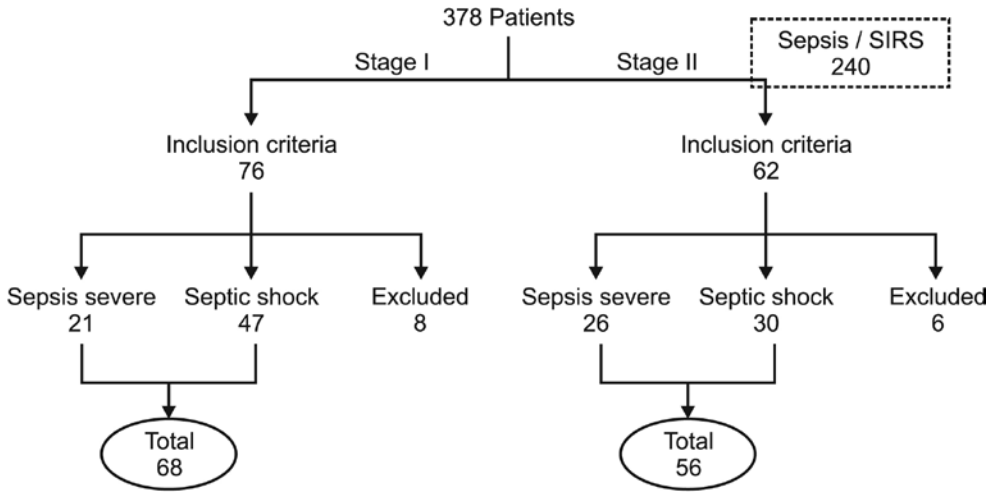

Figure 2 - Flowchart representing distribution of patients enrolled in each stage of the study.

(n=30) and 6 were excluded. That is to say, in the second stage of the study for each 2.7 patients with at least two signs suggesting infection, one patient presented severe sepsis or septic shock (Figure 2).

The groups of patients of stage I and of stage II were similar regarding age, gender and APACHE II at the time of diagnosis. Compliance to the therapeutic bundles of 6 and 24 hours was similar at the two stages, while Δt-SSI was lower at stage II ($p < 0.001$). At this stage, the number of severe sepsis or septic shock detected was significantly higher in the wards ($p < 0.02$). Together with earlier detection, there was a significant drop of mortality at the 28th day ($p < 0.02$) and in hospital ($p < 0.003$). It was further observed that length of stay in the ICU and hospital was not significantly different between stages (Table 1).

It was noted that dosage of lactate ($p < 0.001$) and creatinine ($p < 0.001$), oliguria ($p < 0.001$) and hypotension ($p < 0.008$) were significantly more present in stage I patients.

Table 2 shows comparisons among survivors and not survivors in the 2 stages of this study. When comparing the total of survivors to the total of not survivors it was found that age, APACHE II, number of patients in septic shock, number of patients of male gender and time of detection of severe sepsis were significantly higher among not survivors. Length of hospital stay was significantly shorter among not survivors.

APACHE II score was evidently higher among not survivors when compared to survivors in both stages. At stage II, the Δt-SSI was lower among survivors as well as not survivors. Time of detection of survivors was similar in both stages (Table 2).

Table 1- Comparative summary of data observed during the two stages of the Surviving Sepsis Campaign

Variable	Stage I (N=68)	Stage II (N=56)	p Value
Male gender	49 (72)	31 (55.3)	NS
Age (years)	51.1 ± 19.5	47 ± 21	NS
APACHE II	21.5 ± 7.3	21.9 ± 8.6	NS
Infectious focus			
Pulmonary	33 (48.5)	17 (30.4)*	< 0.05
Urinary	5 (7.3)	2 (3.6)	NS
Abdominal infection	11 (16.2)	11 (19.6)	NS
Meningitis	2 (2.9)	9 (16)**	< 0.02
Soft parts	6 (8.8)	6 (10.7)	NS
Blood flow	2 (2.9)	2 (3.6)	NS
Indeterminate	9 (13.2)	8 (14.2)	NS
Septic shock	47 (69.1)	30 (53.6)	NS
Site of diagnosis			
Emergency room	18 (26.4)	13 (23.2)	NS
Wards	8 (11.7)	21 (37.5)*	< 0.001
ICU	42 (61.7)	22 (39.3)*	< 0.02
Compliance to the 6 h bundle	11 (17)	11 (19.4)	NS
Compliance to the 24 h bundle	20 (30)	17 (31)	NS
ICU length of stay (days)	14.3 ± 13.1	11.3 ± 9.4	NS
Length of hospital stay	32.2 ± 32.8	42.3 ± 35.7	NS
Δt-SSI (hours)	33.8 ± 53.9	6.8 ± 8.4**	< 0.001
Mortality at 28th day	37 (54.4)	18 (30)*	< 0.02
Hospital mortality	46 (67.6)	23 (41)**	< 0.003

APACHE II - Acute Physiology and Chronic Health Evaluation II; ICU – intensive care unit; Δt-SSI – time elapsed between the first record (on medical chart) of at least two signs suggesting infection and time of diagnosis of severe sepsis; NS – not significant. Results expressed in mean ± standard deviation or N (%).

Table 2 – Summary of the comparison between survivors and not survivors encompassed in the two stages of the Surviving Sepsis Campaign

	Survivors			Not survivors			P Value (Compa-riing totals)
	Stage I (N=22)	Stage II (N=33)	Total (N=55)	Stage I (N=46)	Stage II (N=23)	Total (N=69)	
Gender male	11 (50)	19 (57)	30 (54)	39 (85)	12 (52)[b]	51 (74)	< 0.03
Age (years)	45.7 ± 22.5	38.8 ± 17.2	41.1 ± 18.9	53.9 ± 17.9	57.5 ± 20.2[#]	54.8 ± 19.1	< 0.001
APACHE II	17.6 ± 6.7	17.6 ± 6.9	16.7 ± 7.2	23.5 ± 6.9*	26.5 ± 7.4[#]	24.1 ± 7.4	< 0.001
Site of detection							
ICU	12 (54)	14 (42)	26 (47)	30 (65)	8 (35)[a]	38 (55)	NS
ER and wards	10 (45)	19 (57)	29 (53)	16 (35)	15 (65)	31 (45)	NS
Septic shock	11 (50)	13 (39)	24 (44)	36 (78)	17 (74)	53 (77)	< 0.001
Δt-SSI (hours)	19.4 ± 22.0	5.9 ± 8.2[‡]	11.9 ± 16.4	40.3 ± 6.2	5.8 ± 5.3[a]	19.8 ± 35.8	< 0.03
ICU length of stay (days)	30.8 ± 54.7	14.5 ± 9.1	29.7 ± 36.4	11.3 ± 9.8	9.6 ± 8.7	10.8 ± 9.6	0.07
Hospital stay (days)	50.4 ± 42.5	49.5 ± 33.6	50.6 ± 37.3	24.1 ± 23.7*	33.7 ± 36.8	27.9 ± 29.4	< 0.001

APACHE II - Acute Physiology and Chronic Health Evaluation II; ICU – intensive care unit; ER – emergency room; Δt-SSI – time elapsed between the first record (on medical chart) of at least two signs suggesting infection and time of diagnosis of severe sepsis; NS – not significant. Results expressed in mean ± standard deviation or N (%). *$p < 0.01$ for comparison between survivors and not survivors of Stage I. [#]$p < 0.01$ for comparison between survivors and not survivors of Stage II. [‡]$p < 0.05$ for comparison among survivors of Stages I and II. [a]$p < 0.05$ and [b]$p < 0.01$ for comparison among not survivors of Stages I and II.

DISCUSSION

Findings of this study disclosed that the organized search for signs suggesting infection leads to an earlier diagnosis of sepsis and implies decreased mortality related with this disease.

A series of evidences presented in the last decades clearly point that quick and systematic assistance in clinical situations like AMI, stroke and trauma results in an impressive decrease of associated deaths. However, severe sepsis and septic shock related mortality has undergone changes in the last 25 years.[2,18-23] In Brazil it is higher than in other countries, 56% of mortality versus 30% in the developed countries and 45% in other developing countries.[2,24] Possibly these high rates are due to delay in starting therapy which greatly contributes to spreading of the inflammatory response and development of multiple organ dysfunction (MOD). Patients under treatment, even when appropriate, after multiple organ dysfunction have a worse prognosis.[13,14,25-28]

There is evidence that therapeutic intervention with hemodynamic resuscitation and antibiotic therapy are associated to lower mortality rates.[7-12,15] As such, agile and adequate treatment is the "mainstay" for a successful approach to severe sepsis.[18-20]

Goal directed early therapy proposed by Rivers et al.[13], an early hemodynamic resuscitation protocol, provided an evident decrease of mortality in patients with severe sepsis and septic shock. The basis of this strategy is to treat overall tissue hypoxia as fast as possible to revert the unbalance between offer and consumption of oxygen to avoid development of MOD.[13,26-28] Furthermore, control of the infection focus, with broad spectrum antibiotics and/or surgical drainage in the first hours after diagnosis, also has a major impact on prognosis.[9,10]

All patients cared in the first stage of this study were treated according to SSC guidelines. They set forth that management of the patient be grouped in two "bundles" of procedures which should be accomplished until the sixth and 24th hours. Respectively, "6 hours bundle" and 24 hours bundle".[5,6] At the first stage, compliance to these bundles (6 hours = 17%; 24 hours = 30%) was even higher that that observed by SSC worldwide (6 hours= 13%; 24 hours = 15%).[17] Notwithstanding the good performance regarding management of severe sepsis., mortality remained unacceptably high (67,6%). This rate was higher than Brazilian mortality observed in the PROGRESS study (56%), years before implementation of the SSC.[24]

Probably, the high mortality rate of patients was associated to delayed identification of the septic condition. The long time period needed to detect sepsis at stage I, if compared to stage II, was remarkable. It is possible that organizational shortcomings associated to the low specificity of the systemic signs of infection are the main causes of delay in reaching diagnosis of sepsis, as noted in the first stage.

APACHE II score was similar in both stages, regardless of the diagnostic forecast and lower mortality occurred in

stage II. Probably, early detection permitted identification of patients prior to worsening of lactic acidosis and organ dysfunction such as renal failure, and volume-nonresponsive hypotension. Subsequent early intervention brings about more effective reperfusion and interruption of the sepsis "cascade" effect blocking evolution of this dysfunction. Furthermore, am immeasurable aspect must be considered, the motivational factor that resulted in greater collective involvement surrounding the septic patients and better quality of assistance (Hawthorne effect).

It was possible to reproduce findings from other studies showing a decrease in mortality after adoption of the SSC guidelines.[7,8,11-16] At the second stage, even if there had not been a greater compliance to the bundles, mortality decreased considerably, showing that prognosis does not rely on compliance to the therapeutic bundles, but also on the earlier diagnosis.

Unquestionably, subjectivity and subtlety of signs of inflammation delay diagnosis of sepsis in some patients, with no evident focus of infection at the syndrome's early stages.[1,5,6,29-31] At the same time, international consensus that reviewed SIRS criteria, concluded that: "… these criteria are excessively sensitive and not specific".[29,30] This makes identification and dealing with such a common and lethal syndrome even more difficult. In this context, we added to the screening of sepsis protocols besides the most recent leukometry analysis, manifestations that show organ dysfunction and that might be clinically detected. Probably, increase of sensitivity generated by these screening models has facilitated early identification of physiological changes associated to infectious activity.

Although lack of specificity of the discrete diagnostic signs make earlier recognition of sepsis more difficult, implementation of systematic search for signs of SIRS and/or organic dysfunction in all sectors of the hospital redressed operational shortcomings. This correction was based on retrieval of the importance of care with the patient, the role of each professional involved and importance of vital signs as marker for alert.[31] Changes of the vital signs must be promptly reported by the nursing staff and duly registered by the physician. To investigate the cause of these changes and assess the need for an aggressive treatment is crucial.

CONCLUSION

To adopt a multidisciplinary institutional strategy focused on early identification of patients at risk of sepsis, thwarts evolution of the syndrome towards more severe stages and brings about a decreased risk of death associated to severe sepsis and septic shock.

RESUMO

Objetivo: Avaliar o impacto da aplicação de uma política institucional para detecção da sepse grave ou choque séptico.

Métodos: Estudo antes (fase I)/depois (fase II) com coleta prospectiva de dados em hospital público de 195 leitos. Fase I: Pacientes com sepse grave ou choque séptico foram incluídos consecutivamente durante 15 meses e tratados conforme diretrizes da Campanha Sobrevivendo à Sepse. Fase II**:** Nos 10 meses subseqüentes, pacientes com sepse grave ou choque séptico foram arrolados a partir da busca ativa de sinais sugestivos de infecção nos pacientes internados. As duas fases foram comparadas entre si no que diz respeito às variáveis demográficas, tempo necessário para reconhecimento de pelo menos dois sinais sugestivos de infecção (Δt-SSI), aderência aos pacotes de 6 e 24 horas, e mortalidade.

Resultados: Foram identificados 124 pacientes com sepse grave ou choque séptico, 68 na fase I e 56 na fase II. As variáveis demográficas foram semelhantes nas fases. O Δt-SSI foi de 34 ± 54 horas na fase I e 7 ± 8,4 horas na fase II ($p < 0,001$). Não houve diferença na aderência aos pacotes de tratamento. Paralelamente, observou-se redução significativa das taxas de mortalidade ao 28º dia (54,4% na fase I *versus* 30% na fase II; $p < 0,02$) e hospitalar (67,6% na fase I *versus* 41% na fase II; $p < 0,003$).

Conclusão: A estratégia utilizada contribuiu para a identificação antecipada do risco de sepse e resultou em diminuição da mortalidade associada à sepse grave e ao choque séptico.

Descritores: Choque séptico/diagnóstico; Choque séptico/terapia; Choque séptico/mortalidade; Sepse/diagnóstico; Sepse/terapia; Sepse/mortalidade

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Appendix 1 – General form for record of vital signs (one sheet for every time of SSI verification
Scanning of patients for severe sepsis

Data: Time:

Room /bed	AP Hypotension - SBP< 90	HR Tachicardia >90 bpm	RR Tachipnea > 20 bpm	Temperature - Hyperthermia > 38 ºC - Hypotermia < 36 ºC	Oliguria (<0,5 ml/kg/h)	Mental confusion psychosis	Supplementary oxygen
501 – 1							
2							
3							
502							
503 – 1							
2							
504 – 1							
2							
505 – 1							
2							
506 – 1							
2							
507 – 1							
2							
508 – 1							
2							
509 – 1							
2							
510 – 1							
2							
511 – 1							
2							
3							

AP – arterial pressure; SBP – systolic blood pressure; HR- heart rate; RR – respiratory rate

Obs: If two or more items present changes inform the nurse; RECORD IN RED the changed signs.

Appendix 2

Date	Hour	A. Card for detection of septic patients (Screening)
		1. Were two of the items below marked?
		( ) Hyperthermia > 38 °C
		( ) Hypothermia < 36 °C
		( ) Tachipnea > 20 rpm
		( ) Need for oxygen supplementation
		( ) Tachicardia > 90 bpm
		( ) SBP < 90 ou MAP < 65 mmHg
		( ) Acute Headache (drowsiness, confusion, agitation, coma)
		( ) Oliguria (urinary output < 0.5 ml/kg/h)
		2. Is the history suggestive of acute myocardial infarction?
		( ) Pneumonia/Empyema
		( ) Urinary infection
		( ) Intra-abdominal infection
		( ) Meningitis
		( ) Inflammation of soft parts or skin
		( ) Infection of joints or bones
		( ) Wound infection
		( ) Intravascular catheter infection
		( ) Endocarditis
		3. If the reply to question 1 and 2 is Yes: suspect infection
		( ) Request: blood cultures (1 pair) before antibiotic, with a 15 minute interval.
		( ) Request: Blood gas and blood lactate, blood count, glucose, Na, K, Ur, Cr, bilirubin
		According to the clinic: ( ) Urine test ( ) Chest X-ray, ( ) Amylase, ( ) CT scan
		4. Is there some (one is enough) criterion of acute organ dysfunction?
		( ) Acute encephalopathy (drowsiness, confusion, agitation, coma)
		( ) SBP < 90 or MAP < 65 mmHg
		( ) SpO_2 < 90% with or without oxygen supplementation
		( ) Creatinine > 2.0 mg/dl or urinary output < 0,5 ml/kg/h
		( ) Bilirubin > 2 mg/dl
		( ) Platelet count < 100,000
		( ) Lactate > 4 mmol/L (36 mg/dl)
		5. If one item was marked in question 4 – it is severe sepsis
		Urgently start the resuscitation package. Adopt the check-list of Appendix 3

SBP – systolic blood pressure; PAM – pressão arterial média; SpO_2 – peripheral oxygen saturation.

Appendix 3

Date	Hour	B1. Resuscitation bundle (of the 6 hours)
		Lactate and antibiotic therapy (suggestion of ATB – Attachement 4)
		( ) Record date and hour of obtaining lactate result
		( ) Start broad spectrum antibiotic in time < 1 h (ICU and wards) or < 3 hs (ER)
		( ) Drainage or removal (URGENT) of infectious focus if any (abscess, catheter...)
		Procedures
		( ) Arterial catheterization (ATS)
		( ) Central venous catheter (CVP)
		( ) Bladder catheterization (BC)
		( ) After clinical appraisal considered unnecessary ( ) MAP) ( ) CVP ( ) BC
		Intravenous liquid therapy
		( ) Saline solution 0.9% or Ringer lactate IV 20 ml/kg. Give 500 ml every 30 minutes,
		Repeat until CVP between 8 -12 mmHg or 12 -15 mmHg in patients under mechanical ventilation
		( ) Crystalloid 20 ml/kg to 30 ml/Kg without CVP or $ScvO_2$
		Vasopressors
		If MAP remains < 65 mmHg even though reaching a CVP of 8 -15 mmHg, start vasopressor therapyrapia therapy. Early use of vasopressors may be needed as an emergency in patients with septic shock
		( ) Dopamine title dose until MAP ≥ 65 to 90 mmHg (record time of MAP ≥ 65)
		( ) Noradrenaline title dose until MAP ≥ 65 a 90 mmHg (record time of MAP ≥ 65)
		Assessment of tissue perfusion
		( ) Central venous blood gas 60/60 min until $ScvO_2$ ≥ 70 mmHg (record time of $ScvO_2$ ≥ 70)
		( ) blood gases Continuous monitoring of $ScvO_2$ until ≥ 70mmHg (record time of $ScvO_2$ ≥ 70)
		Blood product transfusion
		If $ScvO_2$ ≤ 70mmHg notwithstanding PVC 8-15mmHg and use of vasopressors, patient must receive transfusion of packaged blood cells until reaching hematocrit (Ht) > 30%
		Inotropic therapy
		If CVP, MAP and Ht were optimized and $SvcO_2$ < 70%, consider initropic therapy
		( ) Dobutamine 2.5 μg/kg/min, title every 30 min until $SvcO_2$ ≥ 70% or 20 μg/kg/min
Date	Hour	B2. Bundle for management of the septic patient (of the 24 hourss)
		Corticosteroids
		( ) It is a ICU policy not to administer this drug to septic patients
		( ) Vasopressor-dependent patient – Administer hydrocortisone 50 mg IV every 6/6
		( ) Patient has no indication because is not vasopressor-dependent
		Glycemic control
		( ) Start with catheter obtained capillary or blood glycemias from 2/2 to 4/4 hours
		( ) Start continuous infusion of insulin if glycemia > 150 mg/dl.
		Drotrecogin alfa activated
		( ) It is the policy of the ICU not to administer this drug to septic patients
		( ) APACHE II ≥ 25 and with no contraindications - Administer drotrecogin alfa activated.
		Mechanical ventilation
		( ) Inspiratory plateau pressure < 30 cm H_2O
		( ) Title lowest PEEP needed to prevent lung collapse and warrant SaO_2 > 90%
		Nurse (Sig.):
		Physician (Sig.):

Source: Adapted from Micek et al.[8] ATB – antibiotics; ER – emergency department; $ScvO_2$ – central venous oxygen saturation; ICU – intensive care unit; PEEP – positive end expiratory pressure.

Appendix 4

Empirical antimicrobial therapy (Must be started within 3 hours in the ER and in 1 hour in the ICU and other sectors)	
Community acquired pneumonia (CAP - PORT III, IV and V	
With no risk factors for pseudomonas	( ) Levofloxacin 750mg/d OR ( ) Azyithromicin 500mg 1x + Amoxi/clavulanate 0.5 to 1g IV 3x OR ( ) Azyt + Ampi/sulbactam 1.5 toa 3g IV 4x OR ( ) Azyt + Ceftriaxone 1 to 2g IV 1x
Risk for pseudomonas	( ) Levofloxacin 750mg/d PLUS( ) Pipe/tazobactam 4.5g IV 4x
Bronchiectasis or ICU	( ) Levofloxacin 750mg/d + ( ) Cefepime 1 to 2g IV 2x
Aspiration	( ) Crystalline Penicillin 2 millionUI 6x or ( )Ampi/sulbactam 1.5 to 3g IV 4x
HIV	( ) Bactrim (100mg of sulfamehtoxazole/kg/dose) 4x. Assess associations.
Nosocomial Pneumonia	
< 5 days of admission	( ) Levofloxacin 750mg 1x OR ( ) Ampi/sulbactam 1.5 to 3g IV 4x OR ( ) Ceftriaxone 1 to 2 g 1x (strong resistance inducer)
≥ 5 days of stay (according to local flora)	( ) Pipe/tazobactam 4.5g IV 4x OR ( ) Cefepime 1 to 2g IV 2x OR ( ) Ceftazidime 1 to 2 g IV 3x (only if culture + for Pseudomonas) OR ( ) Imipenem 1gr IV 3x OR Meropenem 2g IV 3x OR ( ) Aztreonam 2 g IV 3x
Risk for Stafilococcus aureus	( ) Vancomycin 1 to 2 g (15 mg/kg) IV 2x OR ( ) Teicoplanin 400 mg (2x in first 24 hs). After 24hs - 1x/day OR ( ) Linezolid 600 mg IV 2x
Sepsis of unknown origin	
Severe communnity sepsis	( ) Ampi/sulbactam 3g IV 4x OR ( ) Cefepime 1 to 2 g 2x OR ( ) Ceftriaxone 1 to 2 g 1x (strong resistance inducer)
Severe nosocomial sepsis (According to local flora)	( ) Pipe/tazobactam 4.5g IV 4x OR ( ) Cefepime 1 to 2g IV 2x OR ( ) Ceftazidime 1 to 2 g IV 3x (only if culture + for Pseudomonas) OR ( ) Imipenem 1 gr IV 3x OR Meropenem 2g IV 3x OR ( ) Aztreonam 2 g IV 3x
Risk for Stafilococcus aureus resistent to meticillin, associate:	( ) Vancomicin 1 to2 g (15 mg/kg) IV 2x OR ( ) Teicoplanin 400 mg (2x in the first 24 hs). After 24hs - 1x/day OR ( ) Linezolid 600 mg IV 2x
Sepsis of abdominal origin	
Spontaneous peritonitis	( ) Ampi/sulbactam 3g IV 4x
Secondary peritonitis with mild-moderate manifestation	( ) Ampi/sulbactam 3g IV 4x OR ( ) Cefepime 1 to 2 g 2x + Metronidazol 500 mg 3x OR ( ) Pip/tazobactam 4.5g IV 4x
Secondary peritonitis with severe manifestation	( ) Imipenem 1 gr IV 3x OR Meropenem 2gr IV 3x PLUS ( ) Vanco OR ( ) Teico OR ( ) Linez if Risk of Enterococcus resistant to vancomyicin or MRSA
Necro-hemorrhagic pancreatitis	( ) Imipenem 1gr IV 3x OR Meropenem 2 gr IV 3x
Urinary tract infection	
Communnity	( ) Ciprofloxacin 400mg IV 2x OR ( ) Ampi/sulbactam 3g IV 4x
Nosocomial	( ) Pipe/tazobactam 4.5g IV 4x OR ( ) Cefepime 1 to 2g IV 2x OR ( ) Imipenem 1gr IV 3x or Meropenem 2gr IV 3x
Catheter related bloodstream infection	
Immunocompetent	( ) Oxacillin 2 g IV 6x (more potent against Stafilococcus aureus sensitive to metacillin) or ( ) Vancomycin 1 to 2 g (15 mg/kg) IV 2x or ( ) Teico or ( ) Linez
Immunocompromized and/or catheter tunneled	( ) Vancomycion 1 to 2 g (15 mg/kg) IV 2x PLUS ( ) Pipe/tazobactam 4.5g IV 4x or ( ) Ceftazidime 1 to IV 3x or ( ) Imipenem 1gr IV 3x or Meropenem 2 gr IV 3x (according to flora)

* all doses adjusted for creatinine clearance > 75 ml/min. Dose adjustments may be needed after 24 h. Always take heed of risk of fungal infection. Desassign ATB after results of culture. Function of ATB is restricted without urgent removal of infection focus.

ICU – intensive care unit; HIV – human immunodeficiency vírus. Source: (Adapted from Micek et al.[8]).