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Guidelines for treatment of severe sepsis/septic shock – tissue perfusion assessment

Diretrizes para tratamento da sepse grave/choque séptico - avaliação da perfusão tecidual

ABSTRACT

Sepsis is a very frequent condition and causes high mortality rates and healthcare costs; it is the main cause of death in intensive care units. Clear, improved prognosis was shown for early diagnosed and treated patients. Treatment guidelines

are fundamental for appropriate therapy. It is clear that hypoperfusion patients should be hemodynamically optimized; therefore, recognition of hypoperfusion signs is one of the main therapeutic steps. This guideline discusses the current literature and available data regarding the evaluation of hemodynamic parameters.

INTRODUCTION

The impairment of the oxygen intake versus consumption balance is one of the main mechanisms involved in sepsis-related organ dysfunctions. Therefore, the identification of early hypoperfusion signs in patients is very important for their appropriate care. For this, mixed (SvO₂) or central (SvcO₂) venous oxygen saturation levels in addition to lactate levels are currently the most widely used parameters assessed. These variables provide for macro-hemodynamic evaluation; however, they fail to provide regional perfusion or even microcirculation assessments. The questions below address appropriately based responses to fundamental topics related to perfusion assessment in severe sepsis and septic shock patients.

OBJECTIVE

This guideline aims to provide minimal guidance on the use of tissue perfusion markers during hemodynamic resuscitation of severe sepsis patients that is suitable for the Brazilian setting.

Description of evidence collection methods

The primary search was conducted using the MEDLINE database via the PubMed medical bibliography search service. Using the MeSH (Medical Subject Headings) interface, the following key words were used: (severe sepsis OR septic shock AND central venous oxygen saturation OR venous oximetry AND outcome), (severe sepsis OR septic shock AND lactate OR lactic acid AND outcome) and (severe sepsis OR septic shock OR circulatory failure OR shock AND central venous oxygen saturation AND mixed venous oxygen saturation). Secondarily searched sources were

Cochrane, Ovid and the Trip Database. The searches were directed to deal with P.I.C.O. (Population, Intervention, Comparison and Outcome) methodology structured questions.

Degree of recommendation and evidence strength

A: More consistent experimental or observational studies

B: Less consistent experimental or observational studies

C: Case reports (non-controlled studies)

D: Opinion without a critical evaluation, based on consensus, physiological or animal model studies

1. Can systemic perfusion assessment based on lactate evaluation provide a better prognosis for severe sepsis and septic shock patients?

Global tissue hypoxia occurring in severe sepsis and septic shock comes from an association between heterogeneous microvascular blood flow distribution, low systemic flow (ischemic hypoxia) and cell metabolism failure (cytopathic hypoxia). Consequently, anaerobiosis and increased serum lactate develop; this last symptom arises from several factors. Lactate increase is very fast and is proportional to the metabolic oxidative defect and shock severity (**D**).⁽¹⁾ The prognostic value of serial lactate measurements is well-established (**D**)⁽¹⁾(**B**).⁽²⁻⁵⁾ Lactate levels are a better metric for prognosis evaluation than oxygen-derived variables (**B**)⁽⁶⁾ and the 'lactime' – the time that lactate persists above 2 mmol/liter – was shown to be predictive of death due to organ dysfunction in sepsis patients (**B**).⁽⁷⁾

Septic patients who participated in the Early Goal-Directed Therapy group showed serum lactate levels significantly below those of the control group patients at 6 hours (4.9 ± 4.7 mmol/L vs. 4.3 ± 4.2 mmol/L; $p \leq 0.01$) and 72 hours (3.0 ± 4.4 mmol/L vs. 3.9 ± 4.4 mmol/L; $p \leq 0.02$) from the start of therapy (**A**).⁽⁸⁾

In addition to the observation of higher serum lactate in non-survivors than in survivor patients (8.8 mmol/L vs. 6 mmol/L; $p = 0.01$), lactate clearance was lower in non-survivor patients (12% vs. 38%; $p = 0.005$). When low lactate clearance (< 10%) patients were compared to high lactate clearance (> 15%) patients, increased risk of lower platelet counts, partial thromboplastin time, use of vasopressor drugs and Acute Physiologic Chronic Health Evaluation II (APACHE II) levels were observed after 12, 24 and 36 hours (**B**).⁽⁹⁾ In addition, the risk of death

dropped by 11% for each incremental 10% lactate clearance. After 6 hours of resuscitation, <10% lactate clearance had a 44.7% sensitivity and 84.4% specificity to predict hospital mortality (**B**).⁽⁹⁾ These findings are supported by the observation that failing to achieve >10% lactate clearance results in a poorer prognosis (**B**).⁽¹⁰⁾

More recently, a randomized clinical trial compared two early severe sepsis patients' resuscitation (first 6 hours) protocols (**B**).⁽¹¹⁾ The 'ScvO₂ group' (n = 150) was treated, targeting CVP, MBP and ScvO₂ normalization. The 'lactate clearance group' (n = 150) targeted CVP and MBP normalization in addition to a >10% clearance of lactate. The overall therapeutic measures were the same for both groups. The in-hospital mortality for the 'ScvO₂ group' was 23% (95% CI 17%-30%), while that for the 'lactate clearance group' was 17% (95% CI 11%-24%); the difference did not reach the pre-defined boundary of -10% in the intent-to-treat analysis (95% CI for a 6% difference -3% to 15%). These results show that lactate as a therapeutic goal is not inferior to ScvO₂. However, this was a clinical trial in which a significant portion of the patients had normal lactate and ScvO₂ levels; therefore, it was difficult to externally validate the findings.

In another randomized trial published in 2010, lactate group patients were treated with a target lactate clearance of $\geq 20\%$ for two hours during their first 8 hours following ICU admission (**B**).⁽¹²⁾ These patients were given more fluids and vasodilators than the control group patients; additionally, they were discontinued earlier from inotropes and mechanical ventilation and remained in the ICU for a shorter time period. In the intent-to-treat analysis, the hospital mortality rate of the control group was 43.5% (77/177) as compared to 33.9% (58/171) for the lactate group ($p = 0.067$). Adjusting for pre-defined risk factors, hospital mortality was significantly lower in the lactate clearance group (hazard ratio 0.61; 95%CI 0.43-0.87; $p = 0.006$). However, this study also evaluated other types of shocks in addition to septic patients, again making an external validation difficult.

Recommendations

- Initial lactate assessment has evident prognostic implications, and lactate should always be measured when sepsis is suspected (**B**).^(6,7)

- Lactate clearance of > 10% during the first 6 hours of hemodynamic resuscitation is related to a

better prognosis. Serial lactate measurements during hemodynamic resuscitation are more relevant for prognosis than eventual measurements (B).^(9,10)

2. May the evaluation of systemic perfusion using a venous oxygen saturation assessment provide a better prognosis in severe sepsis and septic shock patients?

Venous oxygen saturation (SvO₂) or central venous oxygen saturation (ScvO₂) reflect the oxygen intake versus demand ratio and have been used as global tissue oxygenation indicators in the treatment of severely ill patients (B).⁽¹³⁾ Low ScvO₂ values indicate low cardiac output (CO) after myocardial infarction (C),⁽¹⁴⁾ and are associated with increased post-operative complications (B).⁽¹⁵⁾ Additionally, when diagnosed by the ICU admission staff, low ScvO₂ values result in increased mortality (B).⁽¹⁶⁾

In the beginning of sepsis, the low CO secondary to hypovolemia and/or myocardial dysfunction (ischemic hypoxia) results in decreased ScvO₂ (D).⁽¹⁷⁾ ScvO₂ may remain low, and lactate may remain increased. However, mean blood pressure (MBP) is stabilized at normal levels, showing that macrodynamic normalization does not mean restored cell oxygen metabolism (B).⁽¹⁸⁾

In severe sepsis and septic shock patients with twice the normal lactate levels or who are hypotensive, it was shown that in addition to normalized central venous pressure (CVP, maintained between 8 and 12 mm Hg), MBP (> 65 mm Hg) and urinary output (> 0.5 mL/kg/hour), the achievement of ScvO₂ > 70% within the first 6 hours of hemodynamic resuscitation results in a 15% absolute mortality reduction. This emphasizes the relevance of early tissue oxygenation restoration (A).⁽⁸⁾

Recommendation

- In hyperlactemic patients (lactate > twice the normal level), ScvO₂ normalization-focused therapy results in significant mortality reduction (A).⁽⁸⁾

3. Can central venous oxygen saturation (ScvO₂) replace mixed venous oxygen saturation (SvO₂)?

SvO₂ changes reflect the overall oxygen intake (DO₂) versus use (VO₂) balance, configuring a tissue oxygenation index even without cardiac output (CO) or DO₂ and VO₂ determination (D).⁽¹⁹⁾ DO₂ and VO₂ values from CO monitoring are similar to those from ScvO₂-guided therapy (A).⁽²⁰⁾ SvO₂ measurement

has diagnostic, prognostic and therapeutic values in myocardial infarction patients (B),⁽²¹⁾ in major surgeries (B),⁽¹⁵⁾ in clinical intensive care units (ICUs) (C),⁽²²⁾ after heart surgery (A)⁽²³⁾ and in vascular (B),⁽²⁴⁾ lung transplantation (C),⁽²⁵⁾ trauma (B)⁽²⁶⁾ (C)⁽²⁷⁾ (D),⁽²⁸⁾ cardiogenic shock (B)^(29,30) and septic shock (B)^(31,32) patients.

However, pulmonary artery catheters (PAC) are not free of complications. Conversely, central venous catheters (superior vena cava) are associated with lower costs and fewer complications and are used as routine care.

Therefore, ScvO₂ is currently seen as a simple alternative for global tissue hypoxia detection and therapeutic guidance. As with SvO₂, ScvO₂ also reflects the DO₂ versus VO₂ balance and may be used as a sequential DO₂ indicator and to guide the hemodynamic therapy (B).⁽¹¹⁾

However, some trials have clearly shown no numerical equivalence between SvO₂ and ScvO₂ levels (D)⁽¹⁷⁾ (B).⁽³³⁻³⁵⁾ Absolute ScvO₂ levels were not sufficiently similar to SvO₂ values for tissue oxygen extraction calculations (A).⁽²⁰⁾ Also, ScvO₂ values were observed to be (on average) 5% above SvO₂ values, likely due to less oxygenated blood from the coronary sinus (B).⁽³³⁾ More recently, absolute SvO₂ and ScvO₂ values were shown to have no numerical equivalence (B).⁽³⁴⁻³⁶⁾

Although isolated SvO₂ and ScvO₂ values are not interchangeable, sequential analyses (trends) have shown consistent parallelism between SvO₂ and ScvO₂ levels in different clinical conditions (D).⁽¹⁹⁾ Equally, for therapeutic decision making, SvO₂ trend analysis may be replaced by ScvO₂ trend evaluation (B).⁽³⁴⁾

Recommendations

- Absolute numerical ScvO₂ and SvO₂ values are not equivalent (B).⁽³³⁻³⁶⁾

- The analysis of SvO₂ trends may be replaced by ScvO₂ trends during hemodynamic resuscitation (B).⁽³⁴⁾ SvO₂ ≥ 65% or ScvO₂ ≥ 70% are recommended for the first 6 hours of severe sepsis or septic shock patients' resuscitation (D).⁽³⁷⁾

4. Is continued SvO₂ evaluation better than intermittent evaluation?

It is reasonable to wonder whether SvO₂ variations may reflect the real-time oxygen intake versus use ratio. SvO₂ changes may reflect cardiac output changes and allow immediate therapeutic measures. Continued ScvO₂ monitoring was used targeting ≥ 70% values

during the first 6 hours of severe sepsis or septic shock patients' treatment, with significant mortality reduction (A).⁽⁸⁾ In children and adolescent patients with septic shock, continued SvcO₂ monitoring was a determinant for improved prognosis (A).⁽³⁸⁾ No information is available on prognostic implications of the therapeutic use of continued versus intermittent SvO₂ or SvcO₂ assessment. Therefore, it is not possible to state whether intermittent assessment is either equivalent or inferior to continued evaluation.

Recommendations

- SvcO₂ assessment during the first 6 hours of severe sepsis or septic shock patients' care may guide the therapy and result in significantly reduced mortality (A).⁽⁸⁾
- There are no data to conclude that continued assessment is better than intermittent assessment, although the first allows easier therapeutic target (optimization within 6 hours) achievement.

5. Do regular intervals of lactate measurements have a prognostic implication in severe sepsis patients? How frequently should it be tested?

Increased plasma lactate is clearly associated with a poorer prognosis in septic shock patients; the duration of increased plasma lactate is associated to poorer prognosis as well (B).^(2,7) Lactatemia was assessed at admission (baseline) and after 6 hours of clinical management, and the survivors' group was shown to have $38.1 \pm 34.6\%$ lactate clearance versus only $12.0 \pm 51.6\%$ for the non-survivors group ($p = 0.005$) (B).⁽¹⁰⁾ Also, after 6 hours, patients surviving severe sepsis or septic shock had more reduced lactatemia as did those in the Early Goal-Directed Therapy patients' group (A).⁽⁸⁾

Recommendations

- Serial lactate assessment at baseline and after 6 hours of hemodynamic resuscitation has prognostic relevance and should be used (A).⁽⁸⁾
- Subsequent lactate measurements at 6-hour intervals may be required for eventual therapeutic refinement.

6. Do regional perfusion assessment devices, such as gastric tonometry, have a prognostic implication?

The concept of fluids inside hollow viscera having O₂ and CO₂ tensions close to these viscera tissues is

well-established (D).⁽³⁹⁾ In tissue dysoxia conditions, CO₂ builds up in tissues due to two main mechanisms: blood flow stagnation (failing to 'wash' peripheral CO₂) and buffering of [H⁺] ions from anaerobic ATP with tissue-abundant bicarbonate. In this context, gastric tonometry - a technique using gastric probes with distal CO₂-permeable balloons - provides intraluminal CO₂ values that may be directly compared to arterial CO₂ levels (CO₂ gap) or used to calculate the intra-mucosal pH (pHi) using the Henderson-Hasselbalch equation. This distal balloon, usually made of silicon, may be filled with either saline or air; in this last case, CO₂ can be automatically measured with a specific device, sparing laboratory testing of the saline solution.

Two hundred sixty patients admitted to the ICU with an APACHE II score between 15 and 20 were evaluated (A)⁽⁴⁰⁾ - all of them with gastric tonometers - and the usual hemodynamic management (control group) was compared to a pHi drops-guided protocol (protocol group). In the protocol group's patients with over 0.10 unit drops or pHi < 7.35, measures for increased tissue oxygen intake were used, such as saline fluid infusion and/or dobutamine. The survival of patients admitted with pHi < 7.35 was similar for both protocol and control groups (37% vs. 36%, respectively), while for patients admitted with normal pHi, the survival was significantly higher in the protocol patients relative to the control group (58% vs. 42%; $p < 0.01$).

However, when 210 patients with a mean APACHE II score of 24 were compared, once pHi < 7.35 was reached, usual or colloid and dobutamine infusion therapy patients had a similar 30-day mortality (43.7% for usual therapy versus 40.2% for intervention groups) (A).⁽⁴¹⁾

Intra-mucosal acidosis (reduced pHi) and intra-mucosal hypercarbia (widened CO₂ gap) are gastric mucosa dysoxia markers and are morbidity and mortality predictors in critically ill patients (B).⁽⁴²⁻⁴⁵⁾ Gastric PCO₂ was measured with an air tonometer in 95 patients on admission and 24 hours later, and pHi was significantly higher both on admission and after 24 hours in survivor versus non-survivor patients (B).⁽⁴⁵⁾

Recommendation

- Gastric tonometry is not recommended as a therapeutic guidance. Patients with no pHi or CO₂ gap normalization have a poor prognosis.

7. Do devices for microcirculation perfusion assessment have a prognostic implication?

Marked capillary blood flow changes are part of severe sepsis and associated organ dysfunction pathophysiology. Using an orthogonal polarized spectral (OPS) imaging technique for assessment of sublingual microcirculation, 50 severe sepsis patients and a healthy volunteers/non-infected ICU patients cohort were analyzed (B).⁽⁴⁶⁾ Using a semi-quantitative microcirculation assessment, a significantly reduced vascular density and perfused small vessels (< 20 µm) ratio (from 90% to 48%) was identified, in volunteers and non-septic patients versus severe sepsis patients. These perfusion changes were more marked in the non-survivor patients.

With this same technique, 49 septic shock patients were evaluated, in whom assessments were conducted every 24 hours until shock resolution. Microcirculatory changes improved quickly in the survivors but persisted in those who eventually died from multiple organ dysfunction (B).⁽⁴⁷⁾

Recommendation

- Severe sepsis patients' prognosis is worse when microcirculation changes persist. Currently, no specific therapeutic protocol is available for these changes.

RESUMO

A sepse tem alta incidência, alta letalidade e custos elevados, sendo a principal causa de mortalidade em unidades de terapia intensiva. Está claramente demonstrado que pacientes reconhecidos e tratados precocemente tem melhor prognóstico. A formulação de diretrizes de tratamento é fundamental para a adequação desse tratamento. Pacientes com claros sinais de hipoperfusão devem ser submetidos a otimização hemodinâmica. Assim, o reconhecimento dos sinais de hipoperfusão é um dos principais passos do tratamento. A presente diretriz aborda as evidências disponíveis na literatura em relação aos principais parâmetros hemodinâmicos utilizados atualmente.

REFERENCES

1. Mizock BA, Falk JL. Lactic acidosis in critical illness. *Crit Care Med*. 1992;20(1):80-93.
2. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA*. 1993;270(14):1724-30.
3. Jansen TC, van Bommel J, Mulder PG, Rommes JH, Schievelde SJ, Bakker J. The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study. *Crit Care*. 2008;12(6):R160.
4. Rivers EP, Kruse JA, Jacobsen G, Shah K, Loomba M, Otero R, Childs EW. The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Crit Care Med*. 2007;35(9):2016-24.
5. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37(5):1670-7.
6. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;99(4):956-62.
7. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg*. 1996;171(2):221-6.
8. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-77.
9. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32(8):1637-42.
10. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, Parrillo JE, Dellinger RP, Trzeciak S; on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multi-Center Study of Early Lactate Clearance as a Determinant of Survival in Patients with Presumed Sepsis. *Shock*. 2008 Dec 22. [Epub ahead of print].
11. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-46.
12. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-

- label, randomized controlled trial. *Am J Respir Crit Care Med.* 2010;182(6):752-61.
13. Yazigi A, Abou-Zeid H, Madi-Jebari S, Haddad F, Hayek G, Jabbour K. Correlation between central venous oxygen saturation and oxygen delivery changes following fluid therapy. *Acta Anaesthesiol Scand.* 2008;52(9):1213-7.
 14. Goldman RH, Klughaupt M, Metcalf T, Spivack AP, Harrison DC. Measurement of central venous oxygen saturation in patients with myocardial infarction. *Circulation.* 1968;38(5):941-6.
 15. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Changes in central venous saturation after major surgery, and association with outcome. *Crit Care.* 2005;9(6):R694-9.
 16. Bracht H, Hänggi M, Jeker B, Wegmüller N, Porta F, Tüller D, et al. Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: an observational study. *Critical Care.* 2007;11(1):R2.
 17. Vincent JL, Gerlach H. Fluid resuscitation in severe sepsis and septic shock: an evidence based review. *Crit Care Med.* 2004;32(11 Suppl):S451-4.
 18. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. *Am J Emerg Med.* 1996;14(2):218-25.
 19. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. *Chest.* 1989;95(6):1216-21.
 20. 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.
 21. Muir AL, Kirby BJ, King AJ, Miller HC. Mixed venous oxygen saturation in relation to cardiac output in myocardial infarction. *Br Med J.* 1970;4(5730):276-8.
 22. Birman H, Haq A, Hew E, Aberman A. Continuous monitoring of mixed venous oxygen saturation in hemodynamically unstable patients. *Chest.* 1984;86(5):753-6.
 23. Pölonen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg.* 2000;90(5):1052-9.
 24. Powelson JA, Maini BS, Bishop RL, Sottile FD. Continuous monitoring of mixed venous oxygen saturation during aortic operations. *Crit Care Med.* 1992;20(3):332-6.
 25. Conacher ID, Paes ML. Mixed venous oxygen saturation during lung transplantation. *J Cardiothorac Vasc Anesth.* 1994;8(6):671-4.
 26. Kremzar B, Spec-Marn A, Kompan L, Cerović O. Normal values of SvO₂ as therapeutic goal in patients with multiple injuries. *Intensive Care Med.* 1997;23(1):65-70.
 27. Kazarian KK, Del Guercio LR. The use of mixed venous blood gas determinations in traumatic shock. *Ann Emerg Med.* 1980;9(4):179-82.
 28. Rady MY. Patterns of oxygen transport in trauma and their relationship to outcome. *Am J Emerg Med.* 1994;12(1):107-12.
 29. Edwards JD. Oxygen transport in cardiogenic and septic shock. *Crit Care Med.* 1991;19(5):658-63.
 30. Creamer JE, Edwards JD, Nightingale P. Hemodynamic and oxygen transport variables in cardiogenic shock secondary to acute myocardial infarction, and response to treatment. *Am J Cardiol.* 1990;65(20):1297-300.
 31. Heiselman D, Jones J, Cannon L. Continuous monitoring of mixed venous oxygen saturation in septic shock. *J Clin Monit.* 1986;2(4):237-45.
 32. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest.* 1993;103(3):900-6.
 33. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation. *Chest.* 2004;126(6):1891-6.
 34. Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U. Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology.* 2005;103(2):249-57.
 35. Varpula M, Karlson S, Ruokonen E, Petillä V. Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Med.* 2006;32(9):1336-43.
 36. Ho KM, Harding R, Chamberlain J. The impact of arterial oxygen tension on venous oxygen saturation in circulatory failure. *Shock.* 2008;29(1):3-6.
 37. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327. Erratum in: *Crit Care*

- Med. 2008;36(4):1394-6.
38. de Oliveira CF, de Oliveira DS, Gottschald AF, Moura JD, Costa GA, Ventura AC, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med.* 2008;34(6):1065-75.
 39. Dawson AM, Trenchard D, Guz A. Small bowel tonometry: assessment of small gut mucosal oxygen tension in dog and man. *Nature.* 1965;206(987):943-4.
 40. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet.* 1992;339(8787):195-9.
 41. Gomersall CD, Joynt GM, Freebairn RC, Hung V, Buckley TA, Oh TE. Resuscitation of critically ill patients based on the results of gastric tonometry: a prospective, randomized, controlled trial. *Crit Care Med.* 2000;28(3):607-14.
 42. Marik PE. Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest.* 1993;104(1):225-9.
 43. Schlichtig R, Mehta N, Gayowski TJ. Tissue-arterial PCO₂ difference is a better marker of ischemia than intramucosal pH (pHi) or arterial pH-pHi difference. *J Crit Care.* 1996;11(2):51-6.
 44. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *JAMA.* 1993;270(10):1203-10.
 45. Levy B, Gawalkiewicz P, Vallet B, Briancon S, Nace L, Bollaert PE. Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. *Crit Care Med.* 2003;31(2):474-80.
 46. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med.* 2002;166(1):98-104.
 47. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med.* 2004;32(9):1825-31.