Monitoring resuscitation in severe sepsis and septic shock (MORESS)
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1. - BACKGROUND

The incidence of severe sepsis is increasing in the last times, with high mortality rates especially in those patients requiring admission in intensive care units (ICU). In Spain, the estimated accumulated incidence for the population was 25 cases of severe sepsis attended in ICUs per 100,000 inhabitants per year with mortality rates ranging from 33 to 48% (1, 2).

The imbalance between the supply and demand of oxygen in patients with septic shock leads to inadequate tissue perfusion. The early detection and correction of this imbalance is essential to improve the prognosis of these patients.

Fluid loading is one of the first steps in the management of septic patients to improve their hemodynamic status. According to Frank-Starling law, the expected effect of the volume expansion is the increase in end-diastolic right ventricle volume, left ventricle, stroke volume and consequently in cardiac output. This increase is also related to ventricular function, therefore a decrease in contractility decreases the slope between end-diastolic volume and systolic volume (3). In all studies that evaluated fluid responsiveness, only 50 % of the patients were fluid responders (4, 5).

Ideally, in the management of an hemodynamic unstable patient we should assess fluid responsiveness before starting volume expansion, in order to avoid excessive fluid that can result in interstitial edema and respiratory insufficiency (6). Static measures of preload like central venous pressure (CVP) or pulmonary arterial occlusion pressure (PAOP) have proved to be poor predictors of fluid responsiveness (7). In the last years, dynamic parameters of fluid responsiveness (pulse pressure variation -PPV-, and stroke volume variation -SVV-) have been described on the basis of the variation of stroke volume induced by cyclic changes in mechanical ventilated patients, detecting preload dependence. These parameters have been found to be better predictors than static indicators (8, 9) and they have been successfully used in several resuscitation protocols (10-12).

In a septic population, Rivers et al. (13) showed a greater than 10% reduction in mortality using a protocol based on clinical signs (CVP, mean arterial pressure –MAP- and urine output) and a balance between delivery and consumption of
oxygen using central venous oxygen saturation (ScvO2). In this protocol, fluid loading was guided only by CVP, and vasopressors were started when CVP > 12 mmHg and MAP < 65 mmHg.

The aim of the present study is to compare two hemodynamic resuscitation protocols in septic patients that are commonly used in critical care units in Spain. One protocol uses static parameters (CVP, PAOP) to guide fluid administration, and the other one uses dynamic parameters (PPV, SVV). Both strategies use authorized sanitary monitoring devices (arterial and venous catheters) with the conformance mark in the European Economic area (CE mark).

The principal objective of this study is to demonstrate a decrease in mortality in septic patients resuscitated using a dynamic-parameter-based fluid administration protocol.
2. **OBJECTIVES**

Our hypothesis is that hemodynamic fluid resuscitation guided by dynamic parameters will improve outcome in patients with severe sepsis and septic shock, by limiting the deleterious effects of fluid overload.

To evaluate the efficacy of dynamic parameters versus static measures to guide fluid resuscitation we pretend to detect a 10% relative reduction in mortality. In addition, we pretend to observe an improvement on the length of resuscitation time, mechanical ventilation and vasopressor supprot-free days, ICU and hospital length of stay, organ failure and renal function.

**Primary outcome:** Mortality at 28 days

**Secondary outcomes:**

- Length of resuscitation:
  - Vasopressor use and fluid load between 0h to 6h
  - Vasopressor use and fluid load between 7h to 72h
- Ventilator-free days (from 1 to 28)
- Vasopressor-free days (from 1 to 28)
- Organ failure-free days (cardiovascular, CNS, renal, hepatic, coagulation abnormalities)
- ICU length of stay (days)
- Hospital length of stay (days)
- Renal function evolution (first 72h)
- Fluid Balance (first 72h)
- SOFA score evolution (first 72h)
- Mortality at 3 months (ICU, hospital)

3. **MATERIAL & METHODS**

**A. STUDY POPULATION**

1. Inclusion Criteria (all criteria must be present at the moment of inclusion)

   - Age > 18 years

   Clinical evidence of sepsis (microbiology confirmation, radiological or direct view - pus in biological fluid or surgical direct view-).
≥ 2 SIRS criteria:
- Temperature < 36.0°C or > 38.0°C
- Heart rate > 90 bpm
- Respiratory rate > 20 rpm or PaCO₂ < 32 mmHg or need of mechanical ventilation.
- Leukocytes > 12.0 x10⁹/L or < 4.0 x10⁹/L

Hemodynamic insufficiency defined as (at least one of the following):
- Sustained systemic hypotension (systolic arterial pressure ≤ 90 mmHg or MAP < 65 mmHg) or a decrease in MAP of > 30 mm Hg in a hypertensive patient.
- Need of vasopressors.
- Tachycardia (HR > 110 bpm) or bradycardia (HR < 55 bpm)
- Acute onset of oliguria, defined as a decreased urine output < 0.5 ml/kg/hr for ≥ 2 hours
- Serum lactate > 2 mmol/l
- Peripheral cyanosis, mottled skin, prolonged capillary refill

Mechanical ventilation without any kind of inspiratory effort and Vt 7-10 mL/Kg, Pplateau < 30 mmH₂O. Those patients with ARDS under mechanical ventilation will need to tolerate a tidal volume of at least 7 mL/Kg during 30 seconds while the plateau pressure remains < 30 mmH₂O.

Prior hemodynamic monitoring by arterial catheter.
Central venous catheter.

2. Exclusion criteria
Acute myocardial infarction < 7 days.
Pregnancy
Prior request of limited code status or expected life length lower than 3 months.
Shock > 12h
Cardiac arrhythmia
Aortic valvular disease
Inability to properly measure arterial pressure wave forms
B. STUDY DESIGN

- Prospective randomized multicenter study

40-60 general ICUs from Europe and Chile will participate. All ICUs are closed units with a critical care specialist on hand 24 hours per day, 365 days per year. The General Coordinator Center will be located at the Critical Care Center of the Hospital of Sabadell, Barcelona (Spain).

Each ICU from a geographical area is coordinated by an area coordinator and, at least, by one principal investigator in each center.

Early detection of patients with severe sepsis and septic shock should start in the emergency room, intensive care unit and even prehospital assistance. As soon as subjects are identified, the research team will be contacted, and the patients will be randomized within each center to one of the two groups. Inclusion in the study will start with the need for mechanical ventilation. Patients with clinical evidence of sepsis longer than 12 hours of evolution will be excluded.

- General recommendations

In both groups, we strongly recommend controlling the focus of infection and early administration (<3h) of broad-spectrum antibiotics after cultures samples are obtained (17). In case of persistent hemodynamic insufficiency despite high levels of vasopressor support, it is recommended to give high dose corticosteroids and also to evaluate cardiac function by using echocardiography +/- continuous hemodynamic monitoring device. Ensure calibration of arterial pulse contour system each 6-12h.

1. Randomization

When a septic patient is identified, the local research team will be contacted, and they will proceed to the randomization of the patient to one of the two study groups. This randomization will be performed following a 4 block design (2x2). The 2 study groups are defined as: “standard” and “intervention”.

2. Study protocol (see flow algorithm)
The “standard” group (Early Goal-Directed Therapy) follows a common resuscitation protocol based on Surviving Sepsis Campaign recommendations (14): Fluid loading in patients with hypotension or elevated lactates until normalization of MAP (> 65mmHg) or CVP > 12mmHg. If CVP reaches > 12 mmHg and MAP remains < 65mmHg, norepinefrin should be started to reach MAP > 65mmHg. Once MAP is restored, if hypoperfusion signs persist (elevated lactate or urine output < 0.5mL/Kg/h), ScvO2/SvO2 must be measured. In order to reach a ScvO2 ≥70% or SVO2 ≥65%, consider giving blood transfusion if hemoglobin level (Hb) ≤ 7g/dL, and also consider dobutamine (initial dose 2.5 µg/kg/min, increased by 2.5 µg/kg/min every 30 min up to a maximum dose of 20 µg/kg/min, presence of arrhythmia, or FC>110bpm). At that point, if hypoperfusion signs remain present, consider restart protocol from the beginning.

The “intervention” group (Volume Guided Therapy) follows a resuscitation protocol based on dynamic-parameters-guided fluid management.

- In preload-responsive patients defined by the following dynamic parameters:
  
  a. In patients with an arterial line (central monitorization, Phillips Intellivue, CE-mark) who are fully adapted to mechanical ventilation* and with sinus rhythm.
  PPV >12%.
  PPV: Pulse pressure variation
  \[ PPV = \frac{(PP_{max}-PP_{min})}{\left(\frac{PP_{max}+PP_{min}}{2}\right)} \times 100 \] (during 5 respiratory cycles)

  b. In patients with an arterial pulse contour system (PiCCO ® - PULSION Medical Systems AG, Germany, CE 0124-; LiDCO ® - LiDCO Ltd.,Cambridge, UK-) who are fully adapted to mechanical ventilation* and with sinus rhythm.
  SVV > 12% (15).
  SVV: Stroke volume variation
Pulse-pressure contour systems must be calibrated each 6-12h).

*A tidal volume (Vt) ≥ 7-10cc/kg in mechanically ventilated (in a controlled mode – control volume or control pressure) and well-adapted patients without any inspiratory effort should be guaranteed.

Fluid loading must be performed with cristaloids (10mL/Kg) or coloids (5ml/Kg) every 30 minutes until PPV or SVV < 12%, while hypoperfusion signs are present.

If hypotension (MAP < 65mmHg) persists despite negative fluid responsiveness parameters (PPV, SVV < 12%), norepinephrine (NE) must be started (equivalent to 15mL/h of a dilution of 16mg/50mL for a standard 70Kg patient, with a maximum dose of 1.2mcg/Kg/min) to reach MAP > 65mmHg. Once MAP is restored, if hypoperfusion signs persist with negative fluid responsiveness parameters (VPP, VVS < 12%), ScvO2/SvO2 must be measured. In order to reach a ScvO2 ≥70% or SVO2 ≥65%, consider giving blood transfusion if hemoglobin level (Hb) ≤ 7g/dL, and also consider dobutamine (initial dose 2.5 µg/kg/min, increased by 2.5 µg/kg/min every 30 min up to a maximum dose of 20 µg/kg/min, presence of arrhythmia, or FC>110bpm). At that point, if hypoperfusion signs remain present, consider restart protocol from the beginning.

- In non-preload responsive patients (defined as PPV or SVV < 12%) NE will be used (maximum dose 1.2mcg/Kg/min) to reach MAP > 65mmHg. Once MAP is restored, if hypoperfusion signs persist, ScvO2/SvO2 must be measured. In order to reach a ScvO2 ≥70% or SVO2 ≥65%, consider giving blood transfusion if hemoglobin (Hb) ≤ 7g/dL, and also consider dobutamine (initial dose 2.5 µg/kg/min, increased by 2.5 µg/kg/min every 30 min up to a maximum dose of 20 µg/kg/min, presence of arrhythmia, or FC>110bpm). At that point, if hypoperfusion signs remain present, consider restart protocol from the beginning.

3. Data collection and Follow up
The onset of sepsis (time zero: sepsis diagnosis) and the time of first fluid challenge (resuscitation) will be recorded. During guided resuscitation (at patient inclusion), Blood Pressure (BP), Heart Rate (HR), oxygen pulsioximetry (SpO2) and urine output will be recorded every two hours. Fluid loading and vasopressor and inotropic dose will be also recorded from patient inclusion. ScvO2 will be recorded almost every hour and after each intervention until end of the resuscitation period. Lactate levels will be also recorded at baseline and every 6 hours until end of the resuscitation period. Follow up will be performed until the end of resuscitation with a maximum of 72 hours. Daily, we will evaluate SOFA score, mechanical ventilation parameters, renal substitution and function, fluid balance, corticoid use and reactive C protein. Demographical data (age, gender, weight and height), comorbidities, and diagnosis at admission will be also recorded. Likewise, we will record the time of blood cultures, and also the time of initiation of broad-spectrum antibiotics, including their adequacy and de-escalation regimen.

**C. END OF STUDY CRITERIA**

Once hemodynamical stability is maintained over > 12h the protocol will be stopped. The weaning from vasoactive drugs will be progressive (18): once the resuscitation criteria have been achieved the norepinefrine dose will be reduced (0.02-0.04 mcg/Kg/h every 10 minutes) if MAP remains > 65 mmHg. Dobutamine dose will also be reduced in 25% maintaining resuscitation endpoints on target. In case of catecholamine reinstitution after 6h of stability, the resuscitation will be under medical criteria.

As a general recommendation for both study groups, once the protocol is stopped it is important to implement a conservative fluid management by trying to achieve even/negative fluid balance (or at least avoiding positive fluid balance) (19).
**D. STUDY PROTOCOL ALGORITHM**

- **Control infectious focus**
  - Broad-spectrum antibiotic <3h
  - Stress dose corticosteroids

- **Sepsis evidence, >2 SIRS criteria, MV, hemodynamic insufficiency**
  - Exclusion criteria

- **Fluid loading 10-20 mL/kg**
  - Start NE - medical indic. - (max. 1 g/Kg/min)

- **Hemodynamic insufficiency?**
  - No
  - **STOP RESUSCITATION**
  - Yes
  - Informed consent & randomization

- **VOLUME GUIDED THERAPY**
  - Fluid loading (PPV, SVV > 12%)
    - MAP < 65mmHg?
      - Yes
        - Start or ↑ NE
        - SvcO2<70% and Hb>7g/dL
          - Yes
            - Start or ↑ DBT
          - No
            - Hemodynamic insufficiency?
    - No
      - **STOP RESUSCITATION**

- **STANDARD**
  - Fluid loading until CVP ≥12 mmHg
    - MAP < 65mmHg?
      - Yes
        - Start or ↑ NE
        - SvcO2<70% and Hb>7g/dL
          - Yes
            - Start or ↑ DBT
          - No
            - Hemodynamic insufficiency?
    - No
      - **STOP RESUSCITATION**
4. EFFICACY EVALUATION

- **Primary objective:**
  
  **A. Twenty-eight-day mortality.** Survival time will be assessed. Patients will be classified as either “alive at study day 28” or, if dead, “dead at study day 28”. Differences between the two strategies in mortality rates will be evaluated using the assumption of asymptotic normality. Estimates of relative risks and odds ratios and the corresponding 95% interval of confidence intervals will be presented.

- **Secondary objectives:** The following measures will be used to assess the secondary efficacy endpoints.

  **A. Length and dose of resuscitation.**
  - Duration of the resuscitation period (from first fluid expansion until correction of hypoperfusion signs or first 72 hours).
  - Volume loading dose and type of fluid.
  - Vasopressor and inotropic dose.

  **B. Mechanical ventilation-free days.** Days free of mechanical ventilation over 28 days.

  **C. Vasopressor-free days.** Days free of vasoactive support over 28 days.

  **D. Organ failure-free days** (cardiovascular, CNS, renal, hepatic, coagulation abnormalities). Days free of any organ failure over 28 days.

  **E. ICU length of stay.** Days of admission in ICU.

  **F. Hospital length of stay.** Days of hospital admission.

  **G. SOFA score evolution.** SOFA score will be performed every day for the first 3 days.

  **H. Renal function evolution.** Creatinine clearance will be calculated every day for the first 3 days (Cockroft-Gault formula).

  **I. Mortality at 3 months** (ICU, hospital).

- **Quality control**
  To ensure patient’s safety and the availability of exact, complete and reliable data, education material will be released to every center taking part in the study. There will be a permanent way to contact the Coordinator Center via email, fax and phone.
All the data will be collected in an electronic database available through the EDUSEPSIS website with restricted access. 5% of global data will be revised to detect potential errors. Most of the monitors used to obtain PPV/SVV have an automatized algorithm to calculate PPV/SVV which ensures the correct value and minimize the possibility of errors. In those cases when PPV/SVV will be obtained manually, 10% of the registers used for the calculation will be revised by the Coordinator Center.

The IP will keep the curve registers, lab determinations, clinical notes and every medical document of the study. Those documents will be available to the Sanitary Agencies and Ethical Committees if required.

5. DATA ANALYSIS
We calculate a sample size of 952 patients necessary to detect a 10 % relative reduction in mortality- estimated at 47% (1, 2)- with a power of 90% and a type I error of 5%. One intern analysis is planned for this study after 400 patients have been included. The analysis will be conducted by an external and independent Data Safety Monitoring Board (see Ethics chapter for details).

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*Stop for efficacy*: CumAlpha1= 0.00305 (O’Brien-Flemming)  Cl for Z (-2.9626; 2.9626); CumAlpha2= 0.05 (O’Brien-Flemming)  Cl for Z (-1.6986; 1.6986)  

*Stop for futility*: CumAlpha1= 0.03101 (Pocock)  Cl for Z (-2.1570; 2.1570); CumAlpha2= 0.05 (Pocock)  Cl for Z (-2.2009; 2.2009)
6. ETHICS

a) Informed consent
The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have about the study. The informed consent will be used to explain the risks and benefits of the study participation to the patient in simple terms before the patient is entered into the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative including signatures and date on the informed consent document prior to the performance of any protocol procedures.

b) Ethical Review Board
This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. The investigator, head of the medical institution, will promptly submit the protocol to applicable ethical review boards.

c) Data safety
An identification code assigned by the investigator to each patient will be used instead patient’s name to protect patient’s identity when reporting trial-related data.

d) Data Safety Monitoring Board (DSMB)
The main mandate of the DSMB is to review interim trial data to ensure continuing safety of trial subjects as well as the continuing validity and scientific merit of the trial. DSMB will be responsible of notifying the steering committee if the on-going ethical validity of the trial is threatened by emerging safety concerns, loss of clinical equipoise, or evidence of futility. DSMB is not responsible for the design, approval, conduct, analysis or final publication. However, DSMB will review the design and analysis plans of the trial to ensure that all members of the DSMB are comfortable with the trial’s ethical validity.
and feasibility from the onset. First meeting will be at 400 patients enrolled (50% of the study sample) for analysis and interim control. Investigators will not receive any information about this interim analysis if there is no indication for stopping due to efficacy or futility. Following most of the guidelines, DSMB members should have no serious conflicts of interest – academic, financial, or otherwise - with the trial’s outcome and steering committee. According to this, the proposed DSMB members are:

- Massimo Antonielli
- Francisco Baigorri
- David Suárez
- Antoni Torres

8. FUNDINGS AND INSURANCE
At the present time, no financial contribution supports this trial. Pharmaceutical industry only supports logistical aspects but do not participate in any decision. We will apply for different national grants for research. Insurance will not be necessary according to Spanish law “Real Decreto 223/2004” that says no insurance is needed when using sanitary products with the purpose they were approved for and when the IRB considers the study interventions with a risk equal or lower than usual medical practice.

9. PUBLISHING POLICY
Access to electronic register will be restricted to each investigator and only for data from his own center. Steering committee and investigators from the Coordinator Center have access to general data until the first publication. Subsequently, every participating investigator could access to general data by a formal proposal to steering committee. Statistical support will be provided. In every publication, all participating investigators and centers will be referenced.

10. WORKING PLAN
   Study design
   Approval from different centers (director and investigator, ethics committee)
   Preparation of documents (web, spreadsheet program)
Recruitment 6 months

Data analysis
- Intermediate analysis (400 patients, external committee)
- Quality assurance (5% patients)

Publication

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