Can capnography use during sepsis treatment reduce mortality by improving hemodynamic management?

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Also, Dra. Gispert and Dr. Marcos thanks for guiding me through this adventure, it also wouldn't have been possible without your invaluable assistance.

List of abbreviations

SEMES	Sociedad Española de Medicina de Urgencias y Emergencias
SOFA	Sequential Organ Failure Assessment
qSOFA	Quick Sequential Organ Failure Assesment
HUDJTG	Hospital Universitari Doctor Josep Trueta de Girona
ID	Infectious diseases
ED	Emergency department
MAP	Mean arterial pressure
SAP	Systolic arterial pressure
ETCO2	End-tidal carbon dioxide
RR	Respiratory Rate

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Abstract

Background: Sepsis and septic shock are life-threatening pathologies with an elevated mortality. Recent scientific evidence is showing that the most decisive period to affect mortality and prognosis when treating those pathologies is the first hour of treatment, named "*Golden Hour".* Also, new evidence has shown the utility of capnography as a perfusion monitoring tool, even showing to be a better measurement than MAP for volume responsiveness.

Objective: This study aims to demonstrate that a new protocol in hemodynamic management, using capnography as a volume responsiveness monitoring tool, in order to detect earlier those patients in which vasoactive drugs will be needed to guarantee perfusion, can reduce mortality by letting ED teams act earlier, as it is indicated in the new scientific consensus.

Design: This is a randomized, controlled, transversal study carried out by the Emergency Department of Hospital Universitari Doctor Josep Trueta de Girona. A non-probabilistic sampling method will be performed, including all patients for which septic code is activated in this centre from February 2021 to January 2024.

Key words: Capnography, ETCO2, sepsis, septic shock, ED, crystalloids, noradrenaline, PAM, SAP, SOFA, qSOFA.

Introduction

INFECTION, INFECTIOUS DISEASES, SEPSIS AND SEPTIC SHOCK

One of the most accepted definitions for infection is “any pathological process secondary to the invasion by pathogenic or potentially pathogenic microorganisms of a tissue, fluid or anatomical cavity that under normal conditions must remain sterile”. However, this definition is not perfect, since, for example, the colon is not sterile, and a Clostridium difficile infection can be generated there(1). Another definition for infection, more accurate, is “the invasion of the host organism by microorganisms, their toxins or by parasites that can cause pathological conditions or diseases(2). This pathological conditions or diseases is what we call infectious diseases. Infectious diseases can be classified by their origin, the pathogen which causes it, or by the severity of the patient clinical situation.

In this last way to classify it we must talk about two important concepts: sepsis and septic shock.

There has always been a lot of discussion about which should be the definition of sepsis. The first person to use this term was Hipócrates in IV century b.C. who defined it as a process by which meat decomposes and wounds become infected. In our times, until 2015, the definition accepted by the scientific community for sepsis was based on the concept of systemic inflammatory response syndrome (SIRS), but since 2017 the accepted definition is the one published by Sepsis Definitions Task Force that has introduced a new

concept of sepsis as a “life-threatening organ dysfunction caused by a dysregulated host response to infection”. Until 2015 it was also accepted the term “severe sepsis”, which was defined as the presence of sepsis in association which organ disfunction manifestations, such as hypoxemia, oliguria, bleeding disorders, lactic acidosis or mental disturbance among others; since 2015 severe sepsis concept was no longer accepted due to its redundancy, because sepsis itself is always severe(3,4).

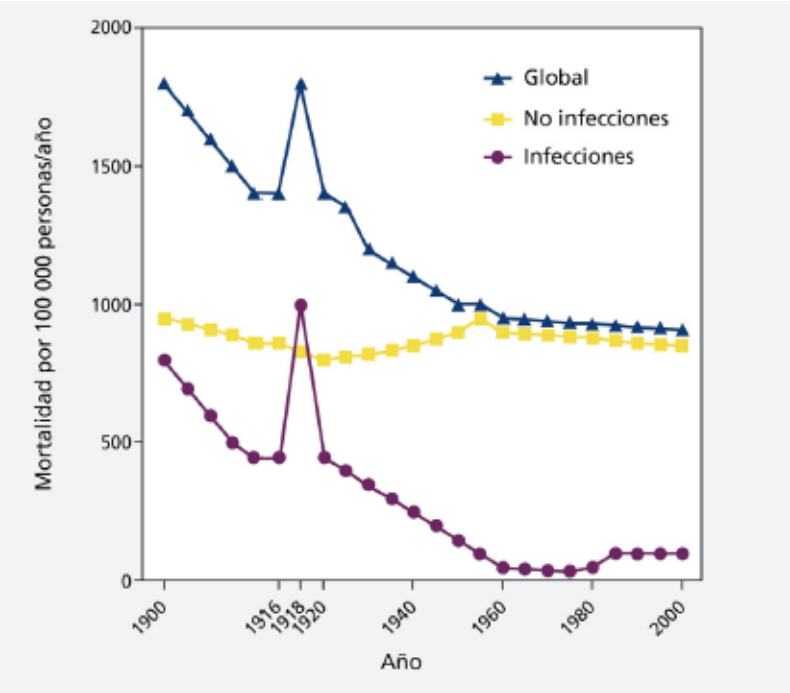
The other important concept to define before continuing is the concept of septic shock:

In medicine, a shock is defined as the clinical context in which, as a result of varied causes, there is a sudden deficit in blood supply (and therefore oxygen and nutrients) to tissues, that conditions a cellular metabolic suffering such that, if not resolved, it will inexorably lead to the death of tissues and the organisms that sustains them.

Septic shock is classified as a distributive shock, also called vasogenic, which originates from a pressure drop in the circuit as a consequence of vasodilation.

The most accepted definition for septic shock is “a subcategory of sepsis in which circulatory and metabolic alterations are deep enough to considerably increase mortality risk”. Sepsis Definition Task Force also purposed the criteria that defines the occurrence of septic shock: hypotension, sustained requirement of vasopressors to maintain MAP (mean arterial pressure) ≥ 65 mmHg and a serum lactate level > 2 mmol/L (5).

EPIDEMIOLOGY



Infectious diseases have been, and in many countries still be the most frequent cause of mortality. About 12 million people worldwide die from infectious diseases, which represents 21% of total causes of death. In developing countries, the numbers are even more alarming: In those countries ID are causing around 50% of deaths(6). In developed countries the situation was similar last century, but nowadays has changed a lot due to the introduction of antibiotics towards the middle of XX century; however, the improvement of life expectancy, which leads to a greater number of chronic processes in the population and also the realization of a major number of invasive techniques, states of immunosuppression for drug or patients treated with chemotherapy, among other factors has led to an increase in mortality from infectious diseases.

In the Spanish health system, according to SEMES and recent studies(7,8):

- Sepsis is the most prevalent pathology in the ICU.

- 10.4% of patients attending the emergency department are diagnosed of an infectious disease (being the most prevalent those of respiratory origin).

- Between 5-10% of that patients meet criteria for sepsis.

- 30% of them will develop a septic shock.

- In the Catalan health system, the incidence registered for sepsis between 2008 and 2012 was 213 cases/100.000 habitants, with a 21.6% hospital mortality(8).

Worldwide epidemiological data is also alarming; according to WHO, who has published its first world report about septicaemia(9):

- Every year 49 million people are diagnosed of septicaemia worldwide.

- The first infectious focus is the hospital: 49% of patients with sepsis attended at ICU have been infected in-hospital.

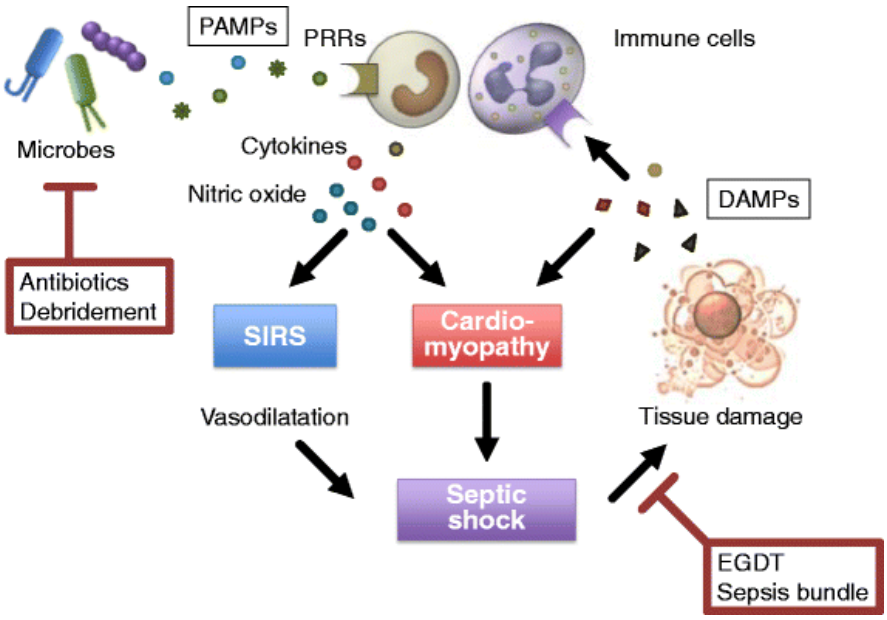
- 11 million people will die from sepsis every year.

- In-hospital mortality rates are alarming: 27% of mortality in hospital and 42% of mortality in ICU.

- The ones who survive the septic episode aren't out of risk: In one-year period 50% of them will die or develop complications that will lead to disability.

PHYSIOPATHOLOGY

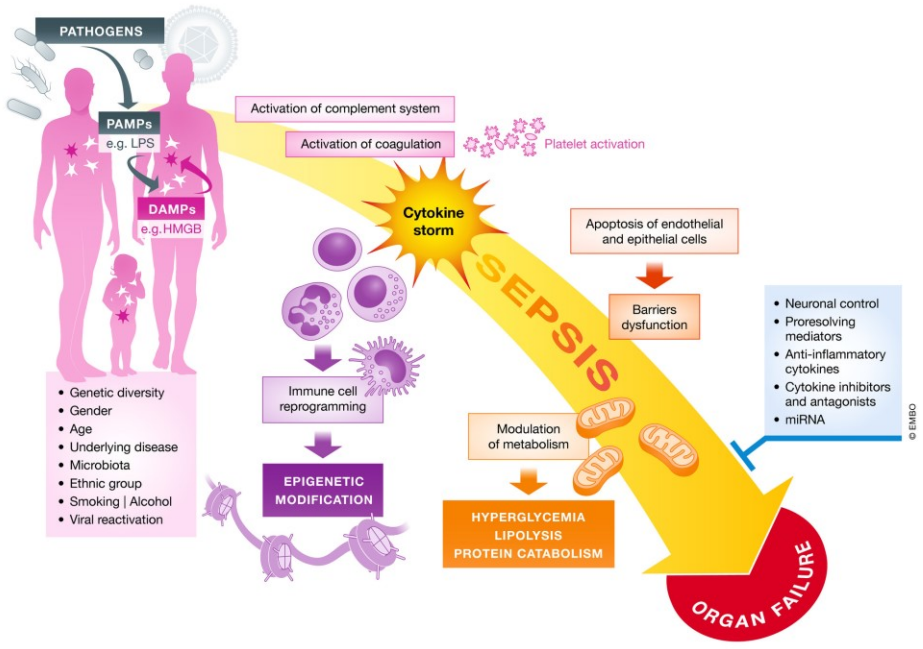
The first step in the initiation of the host response to the pathogen is the activation of innate immune cells, which are basically macrophages, monocytes, neutrophils, and natural killer cells. This happens by the union of pathogen associated molecular patrons (PAMP), such as bacterial endotoxins or fungal β-glucans, to a specific patron recognition receptor of this cells(10,11). Another way to initiate this inflammatory process are the damage associated molecular patrons (DAMP), which basically are intracellular material from death host cells, such as ATP or mitochondrial DNA.



These molecules bind to specific receptors in monocytes or macrophages, such as toll-like receptors (TLR, leptin type C receptors, NOD receptors (nucleotide-binding oligomerization domain-like receptors) and RLRs (RIG-1-like receptors). The activation of these receptors results in the activation of intracellular pathways in those immune cells

that cause the transcription and release of pro-inflammatory cytokines, such as TNFα, IL-1 and IL-6.

In addition to the inflammatory response, the haemostatic pathway is also activated in sepsis, with the simultaneous inflammatory and coagulation cascades activation. The spectrum of this interaction can range from mild thrombocytopenia to a fulminant disseminated intravascular coagulation (DIC)(12). The etiology of this coagulation's dysregulation is multifactorial, however it is believed that the hypercoagulability in sepsis it's due to the liberation of altered endothelial cell tissue factor(10). The tissue factor causes the systemic activation of the coagulation cascade, resulting in the production of thrombin, platelet activation and formation of platelet and fibrin clots. These microthrombi can cause local perfusion defects resulting in tissue hypoxia and organ dysfunction.



The initial pro-inflammatory state of sepsis is often replaced by a prolonged state of immunosuppression. There is a decrease in the number of T cells (helper and cytotoxic) as a result of apoptosis and a decreased response to inflammatory cytokines. The post-mortem studies of ICU who died of sepsis demonstrated a global depletion of CD4+ and CD8+ T cells, most notably in lymphoid organs like the spleen(11,13–15). The above findings suggest that the immune system in a septic patient cannot organize an effective immune response to infections.

Talking about the shock, this can be produced by three ways:

-By a volume deficit: hypovolemic

-By a fail in cardiac contraction: cardiogenic

-By alterations in the vascular tone: distributive

Septic shock brings together aspects of the 3 pathophysiological alterations mentioned.

As it is mentioned above, in sepsis there is a liberation of endogen and exogen toxins, which lead to a proinflammatory mediators liberation that cause peripheral vasodilation and the formation of microemboli.

The CNS and endocrine system are also activated, producing adrenalin, noradrenalin, glucocorticoids, aldosterone, glucagon and renin, which lead the patient to an hypermetabolic state, and, as a consequence, to a pulmonary, renal and splenic vasoconstriction, which can lead to a multisystemic fail.

The septic shock goes through different phases: the initial, the compensatory, the progressive and the refractory.

The initial phase is characterized by a generalized vasodilatation, manifested in the decrease in blood pressure as a consequence of the reduction of preload and afterload. In the compensatory phase increased heart rate may be evident, and hemodynamically the cardiac output and the cardiac index are increased, while the ventricular ejection volume is altered due to a decrease in the myocardial contractility. Other evident signs and symptoms in this phase are hypoxemia, tachypnoea, rales, altered state of consciousness or oliguria.

During the progressive phase, the hypoperfusion is severe, and it is manifested by global cyanosis and oxygen desaturation; it also can appear generalized edema (anasarca) due to failure of the sodium-potassium pump.

Finally, the patient can enter a refractory phase. In this there is no response to any treatment, due to massive cell destruction, which causes a multi-organ failure. In a high percentage, death is the end result of this phase.

SEPSIS CODE

Sepsis and septic shock are time-dependent pathologies. It's management requires a fast identification and an acute treatment, as scientific evidence has demonstrated that diagnostic or therapeutic delay negatively influences in patient's evaluation: depending on whether appropriate antibiotic therapy is administered in the first 30 minutes after diagnosis or between 9-12h, mortality varies between 17% and 74%, respectively(16–18).

According to that, and with the aim of initiate early diagnostic-therapeutic measures, including adequate antibiotic treatment and hemodynamic support, the Catalan public health system implemented in all its sanitary territory the sepsis code, which is an emergency protocol with an integrated model of care that standardizes and accelerates decision making, establishing clear diagnostic and therapeutic criteria without space for interpretation, which minimize the loss of time in the response of health teams.

In 2012 Sepsis Code was launched in HUDJTG, developing an action protocol with care recommendations. This protocol was updated in 2016, adapting it to the recommendations of the Third International Consensus on Sepsis(18). In 2018, an update was done with the Surviving Sepsis Campaign Bundle(17), which highlights the relevance of action in the first hours especially the first (also called *the Golden Hour*), in the outcome of the septic process.

The sepsis code in HUDJTG has 3 basic pillars:

- Early antibiotic therapy (< 1h.).
- Focus control (microbiological culture < 1h; surgical debridement (if needed) < 6h.).
- Hemodynamic stability (SAP > 90 mmHg. /MAP > 65 mmHg. during first 3-6 h.).

In the emergency department of HUJTG sepsis code can be activated, even in the triage, if the patient presents both criteria:

- Suspected infection, hypothermia (Tª < 36 °C) or hyperthermia (Tª>37'5°C).

-1 out of 3 qSOFA (quick SOFA) criteria.

Quick Sequential Organ Failure Assessment (SOFA) score

qSOFA (Quick SOFA) Criteria	Points
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mmHg	1

qSOFA is the simpler version of SOFA (Sequential Organ Failure Assessment Score), made to be used in the triage in a fastest and simpler way than SOFA, to initiate the sepsis code. Unlike SOFA, qSOFA does not include analytical parameters, so it allows ED professionals to discern those patients who present a high risk to suffer organic dysfunction, and therefore they need priority attention, in a much faster way than SOFA.

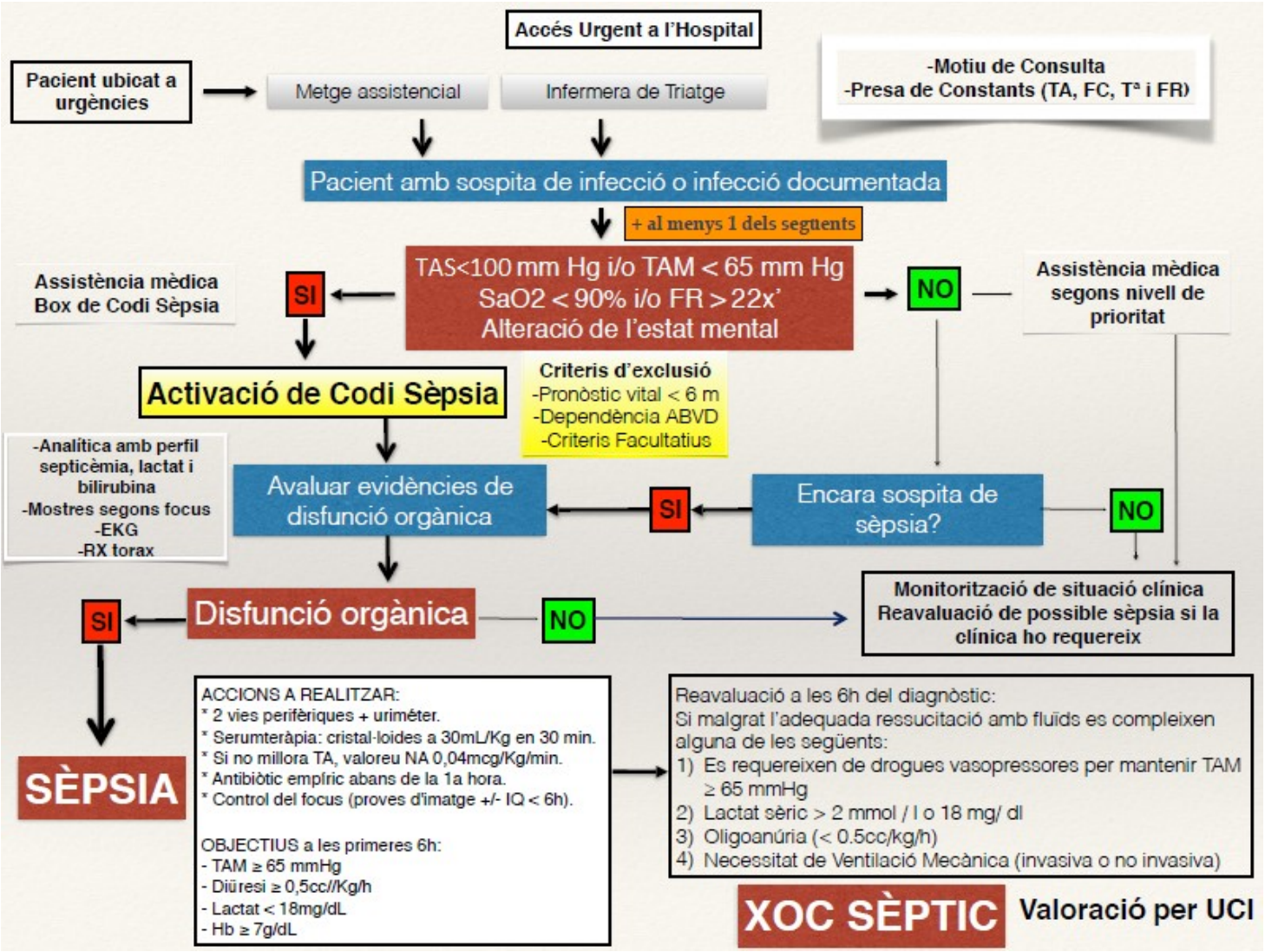
SOFA is a scoring system made to classify septic patients in order to its gravity and also determine the rate of organ failure. This score evaluates 6 parameters (PaO2/FiO2, platelets, bilirubin, cardiovascular, GCS Score, and creatinine/urine output). Each parameter is punctuated between 0-4, according to the values in the table. A SOFA score ≥ 2 points is diagnostic of sepsis. Beyond that, as the score rises, so does the rate of organ failure and the risk of mortality(19).

	Score				
	0	1	2	3	4
Respiratory system					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Hepatic system					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular system					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Coagulation					
Platelets $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Central nervous system					
Glasgow coma scale	15	13–14	10–12	6–9	<6
Renal system					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (mL/d)				<500	<200

Notes: [a]All catecholamine doses represent μg/kg/min. Organ dysfunction is identified as an increase in the SOFA score of ≥2 points. In patients with not known preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. *Intensive Care Med*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. 22(7), 1996, 707–710, Vincent JL, Moreno R, Takala J, et al. With permission of Springer.[17]

Abbreviations: PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure.

Once sepsis code is activated, the patient is automatically ubicated in the critic patient's area of the emergency department to initiate this treatment algorithm:



Hemodynamic support tasks during first hours focus on recover SAP and MAP. This is done by resuscitation with crystalloids, and the response is monitored with MAP and lactate clearance, assessed 3 hours after the start of resuscitation: 3 hours after initiating

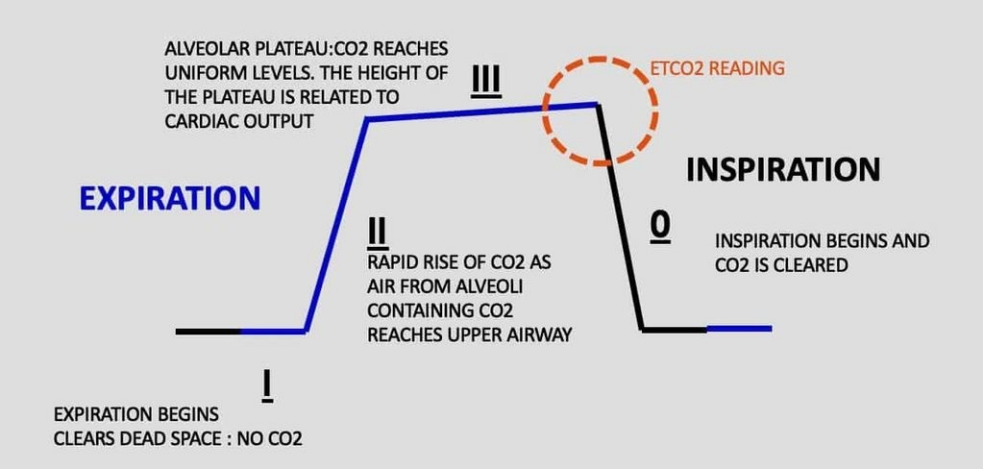
crystalloids a blood gas test (venous or arterial) with lactic acid analysis is performed, and compared with the lactate level at the arrival. If this lactate clearance is > 10%, lactate levels < 18 mg/dL or MAP is ≥ 65 mmHg. it is considered that resuscitation progress is satisfactory and hemodynamic support keeps at this stage. If lactate clearance is < 10%, lactate levels > 18 mg/dL and MAP is < 65 mmHg. it is considered that there is no response to resuscitation and vasoactive drugs are needed. Then it is indicated to initiate noradrenaline perfusion at a 0,04mcg/Kg/min with the aim of recovering MAP and correct perfusion.

CAPNOGRAPHY AND ETCO2

Capnography is the monitoring of the concentration or partial pressure of carbon dioxide in the respiratory gases. It is usually presented as a representation graph of the airway CO2 wave as a function of time, including inspirations and expirations. It is connected with nasal glasses, which directly collect the respiratory gases of the patient.

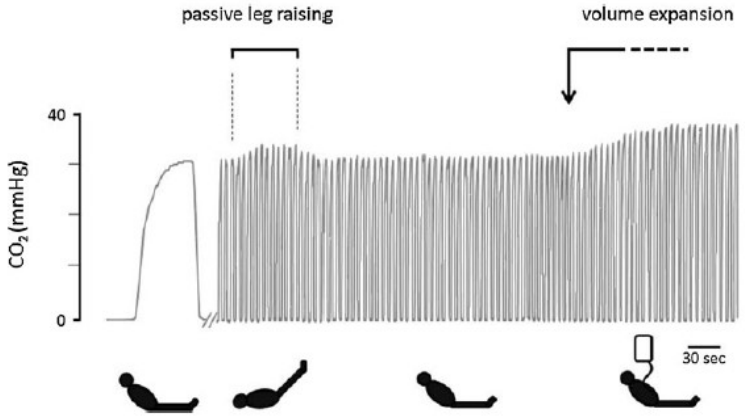
Capnography can analyse RR, rhythm, morphology of the wave, tendency, and the numeric ETCO2 value (end tidal carbon dioxide).

ETCO2 is the end tidal carbon dioxide, in other words, the average amount of CO2 at the end of expiration. It is a really valuable tool, in both anaesthesiology and emergencies fields, as it is an indicator of pulmonary ventilation/perfusion ratio and also systemic perfusion.



Its profits in those fields range from the evaluation of the correct placement of an endotracheal tube, evaluation of a CPR, monitoring sedation, monitoring carbon dioxide insufflation during gastroscopy, measuring acidosis in children with gastroenteritis, diagnose and monitor a patient suffering a diabetic ketoacidosis or a major trauma with hypovolemia, to diagnose sepsis and predict mortality or elevated SOFA scores in those patients(20,21,30,31,22–29).

Recent studies even demonstrated the ability of ETCO2 in predicting volume responsiveness. *Monnet et al.* published in 2013 "*End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test*", a study which results demonstrated



that a PLR-induced increase in ETCO2 ≥ 5% predicted a fluid-induced increase in CI (cardiac index) ≥ 15% with sensitivity of 71% (95% confidence interval; 48-89%) and specificity of 100% (82-100%). With these results, *Monnet et al.* concluded that "*the changes in ETCO2 induced by a PLR test predicted fluid responsiveness with reliability, while the changes in arterial pulse pressure did not*".

Justification

When treating sepsis and septic shock, its fundamental to accelerate and optimize the decision-making process. Early identification and treatment of septic shock have been shown to improve survival, and it is estimated that, when treating sepsis, mortality increases 8% for every hour of delay in starting treatment(32). Actual international consensus (Surviving Sepsis Campaign 1-Hour Bundle, 2019) recommends early start (during 1st hour after diagnosing) of serum therapy and vasoactive drugs if needed(18).

These protocols establish that initial treatment of sepsis include resuscitation with crystalloids at a 30 ml/Kg dose, with monitored response with SAT, MAP, lactate clearing and Rising Test (*Annex 1*). Only if those monitored parameters show no response, normally checked 3 hours after initiating resuscitation with crystalloids, vasoactive drugs will be initiated. In that case, if TAM remains ≤65 mm Hg, lactate clearance is ≤ 10%, or there is lack of response to Rising test noradrenaline 0,04mcg/Kg/min infusion will be initiated.

According to previously cited recommendations those 3 hours couldº be a very valuable time to act early.

Lactic acidosis is a well-accepted marker for disease severity in this population, a good mortality predictor in ED patients with infection. However, it takes about 30 minutes to analyse lactate levels in a venous gasometry, and the information that gives you about the patient is static.

Some studies have tried to use ETCO2 measurement in the ED, in sepsis and septic shock, to predict mortality. Their conclusions were that ETCO2 concentration may perform similarly to lactate levels as a predictor for mortality in patients with suspected sepsis. However, those were studies with small sample of patients, and so they also concluded that "further studies are necessary to determine if ETCO2 can be used to decrease time to recognition and therapy of patients with sepsis"(30).

Capnography is a non-invasive, real-time and dynamic method of determining exhaled end-tidal carbon dioxide (ETCO2), which is a function of basal metabolic rate, cardiac output and ventilation status, so it is, somehow, a direct indicator of tissue perfusion. In recent studies, it has been shown that ETCO2 can predict severe metabolic acidosis in diabetic ketoacidosis(24,33) and gastroenteritis(27).

Other studies have also shown that ETCO2 levels are low in patients suffering hypovolemic shock, and that ETCO2 can be used as a marker in injury severity and a predictor of mortality in major trauma patients(25). Low ETCO2 levels also have been associated with lactic acidosis and it's associated to organ dysfunction, leading us to postulate utility in another disease state where acidosis is a well-established marker of poor outcome, severe sepsis(28–30).

Hypothesis of the study

The application of capnography as a monitoring tool in the septic and septic shocked patients management can decrease mortality and predict complications, such as lactic acidosis.

Study Objectives

MAIN OBJECTIVE

The main objective of this study is to demonstrate that the application of capnography in septic and septic shocked patients can reduce the mortality in those pathologies, by letting ED professionals to early predict complications, and so, early initiate serum therapy and vasoactive drugs, if needed.

SECONDARY OBJECTIVES

1. Determine the incidence of septic and septic shocked patients in HUDJTG
2. Demonstrate that the use of capnography in septic processes can reduce the average number of days of hospital admission required in those patients.
3. Demonstrate that the use of capnography contributes to the early initiation of effective treatment.
4. Evaluate, through the analysis of independent variables, the risk factors of developing complications in septic processes.

Material and methods

STUDY DESIGN

This study will be a randomized, controlled, transversal study. It will be conducted in the Emergency Department of Hospital Universitari Doctor Josep Trueta de Girona

Subjects will be randomized in a 1:1 ratio to lactate determination group or capnography group as a monitoring tool.

STUDY POPULATION, INCLUSION AND EXCLUSION CRITERIA

The study population will be composed by all patients with sepsis/suspected sepsis or septic shock attended by the Emergency Department of Hospital Universitari Doctor Josep Trueta de Girona, with the following inclusion and exclusion criteria:

Inclusion criteria

Patients exhibiting qSOFA≥2 in HUJTG (patients with sepsis/suspected sepsis or septic shock in which sepsis code will be activated).

Exclusion criteria

1. Patients with expressed limitation of therapeutic effort on their clinic history, or dependant for activities of daily living: Barthel index ≥60, Rockwood Clinical Frailty Scale≥7 or Profund index≥11 (*Annexes 2,3 and 4*)

2. Patients that arrive at the ED with cardiorespiratory arrest.

3. Patients with oncologic pathology tributary of palliative treatment.

4. Those patients in whom they or their relatives do not give their informed consent.

SAMPLE

Sample size

The sample size was calculated using the free application *Calculadora de Grandària Mostral (GRANMO)*(34).

To calculate the size of the sample, it is needed a mortality proportion in septic patients using capnography and without using it. A previous meta-analysis was searched to get this data, but due to the lack of studies nowadays in this field, no one was found. Instead of that, the size-weighted mortality of participants from the three main studies found in which capnography was performed was calculated, giving a 13,245% average mortality(29–31).

In the non-performed capnography group, the average mortality of sepsis, which is 21,6% was taken from a recent thesis(8).

Getting this data, a bilateral contrast done with an alpha significance level of 5% and a power of 80% assuming that the differences detected were moderate, we will need 355 patients per arm of the clinical trial (total 710).

A dropout rate of 10% because of the possibility of incomplete data collecting sheets or their misplacing has been anticipated.

HUDJTG activates an average of 350 septic codes per year; about 3% of which are paediatric. That are not included in the study due to the different protocol, treatment and ED in HUDJTG. That reduces the annual cases that could be included in the study to 339. Assuming that among them some will have exclusion criteria, we estimate that a 3-year period will be needed to carry out the study, starting in February 2021 and ending in January 2024 (both months included).

Sample selection

To get the sample a non-probabilistic consecutive sampling method will be performed, selecting all patients that accomplish inclusion and exclusion criteria; to be included in the study patients will also have to give their informed consent (*Annex 5*).

The sample will be composed of two groups: a control group and an intervened group.

VARIABLES AND METHODS OF MEASUREMENT

All the variables of the study will be collected prospectively for 36 months (from February 2021 to January 2024) and are summarized below:

Independent variable

The independent variable is the capnography (ETCO2 measurement) monitoring intervention. Both groups will have the lactate level analysis done as it is in the analytical pre-set for septic code in HUDJTG. However, in only one group the capnography will be done.

- **Group A** is a control group, it will receive the protocolized attention in HUDJTG established by sepsis code, without capnography (*Annex 6*).

- **Group B** is an intervention group, it will be treated by the same protocol as group A, the sepsis code, but in addition, ETCO2 determination by capnography will be performed, to monitor the hemodynamic response of the patient, 1 hour after initiating resuscitation with crystalloids. In addition to lactate clearance > 10%, lactate < 18 mg/dL or MAP ≥ 65 mmHg, ETCO2 increase ≥ 5% determined by capnography 1 hour after initiating resuscitation with crystalloids will indicate considering the patient fluid responsive. If the patient is not considered fluid responsive 1 hour after initiating resuscitation with crystalloids, noradrenaline perfusion at a 0,04mcg/Kg/min will be started with the aim of recovering MAP and correct perfusion.

It is a dichotomous qualitative variable and will be expressed in a percentage.

Dependent variables

The main variable is the in-hospital mortality. It also is a dichotomous qualitative variable and will be registered at the hospital discharge.

Hospital length of stay due to the septic process will be taken as a secondary variable. It is a continuous quantitative variable, and it will be measured through the time expressed in hours, between the hospital admission and the hospital discharge; it will be expressed in hours, and it will be registered in the clinical history of the computer database.

Covariates

1. Age: measured as a continuous quantitative variable to later group it into age clusters, to become a discrete variable, defined as follows: adult population: (a)young adults up to 39 y.o., (b) intermediate adults up to 49 y.o., (c) mature adults up to 59 y.o. and Elderly population: (d) early or primary stage between 60 and 69 y.o., (e) intermediate phase from 70 to 84 y.o., and (f)advanced phase ≥ 85 y.o.

2. Sex: Measured as a nominal qualitative variable with the next categories: Male, Female or Other

3. Focus of infection: Measured as a nominal qualitative variable with the next categories: Respiratory focus, abdominal focus, urologic focus, skin and soft tissues focus, endovascular devices focus, CNS focus.

4. Pathogen: Measured as a nominal qualitative variable, with the scientific name of the pathogen.

5. Antibiotic prescribed and dose: Measured as a nominal qualitative variable, with the generic name of the antibiotic administrated to the patient during hospitalization.

6. Time from the hospital admission until the antibiotic administration: Continuous quantitative variable expressed in minutes.

7. Time from the hospital admission until the administration of vasoactive drugs in patients that need them: The average mean will be calculated, and it will be expressed in minutes as a continuous quantitative variable.

8. Time from the hospital admission until the beginning of resuscitation with crystalloids: Expressed in minutes, as a continuous quantitative variable.

9. Patient SOFA score: Is a discrete quantitative variable, from 0 to 4, which corresponds as the SOFA score given to the patient at his/her arrival. (*Annex 7*)

10. Patient qSOFA score: Is a discrete quantitative variable, from 0 to 4 which corresponds at the quick SOFA score given to the patient at the triage. (*Annex 8)*

11. MAP at the arrival: Measured in mm Hg. as a continuous quantitative variable to later group it into clusters, to become a discrete variable defined as follows: (a) <45 mm Hg; (b) 45-49 mmHg; (c) 50-54 mmHg; (d) 55-59 mmHg; (e) 60-64 mmHg; (f) 65-69 mmHg; (g) 70-75 mmHg; (h) >75 mmHg.

12. Oxygen Saturation: Measured as a continuous quantitative variable.

13. PAFI index (PaO2 / FIO2): Measured as a continuous quantitative variable.

14. Coagulation platelets (× 10^9/L): Measured as a continuous quantitative variable to later group it into clusters, to become a discrete variable defined as: (a) >150, (b) <150, (c) <100, (d) <50, (e) <20.

15. Liver bilirubin (mg/dL): Measured as a continuous quantitative variable to later group it into clusters, to become a discrete variable, defined as: (a) <1.2, (b)1.2-1.9, (c) 2.0-5.9, (d)6.0-11.9, (e) >12.0.

16. Glasgow coma scale score (*Annex 9*): Measured as a discrete quantitative variable to later group it into clusters, to become a discrete variable defined as: (a)15, (b)13-14, (c)10-12, (d)6-9, (e)<6.

17. Creatinine (mg/dL): Measured as a continuous quantitative variable to later group it into clusters, to become a discrete variable defined as: (a)<1.2, (b)1.2-1.9, (c)2.0-3.4, (d)3.5-4.9, (e) >5.0.

18. Urine output on the first 24h. (mL): Measured as a continuous quantitative variable to later group it into clusters, to become a discrete variable defined as: (a)800-2.000, (b)799-650, (c)649-500, (d)<500, (e)<200.

19. Charlson comorbidity index: It is a discrete quantitative variable, from 0 to 33, which corresponds to the index given to the patient. (*Annex 10*)

20. Barthel scale: It is a discrete quantitative variable, from 0 to 100, which corresponds to the punctuation given to the patient according to Barthel scale. (*Annex 2*)
21. Rockwood scale: It is a discrete quantitative variable, from 0 to 7, which corresponds to the punctuation given to the patient according to Rockwood fragility scale. (*Annex 3*)
22. ETCO2 levels (in those patient's in which capnography is performed): It is a continuous quantitative variable expressed in mm. Hg.
23. Lactate levels: Measured as a continuous quantitative variable expressed in mmol/L.
24. Requirement for ventilatory support: None, IV (invasive ventilation), or NIV (non-invasive ventilation)

RANDOMIZATION TECHNIQUE

The patients who participate in this study after meeting all inclusion criteria and none of the exclusion criteria will be randomly assigned to one of two groups:

- **Group A** is a control group, it will receive the protocolized attention in HUDJTG established by sepsis code, without capnography (*Annex 6*)

- **Group B** is an intervention group, it will be treated by the same protocol as group A, but in addition, ETCO2 determination by capnography will be performed, to monitor patient's hemodynamic response, as explained above.

With the randomized selection we avoid selection bias. When the sepsis code is activated for a new patient meeting all inclusion and exclusion criteria and accepting his/her participation in this study, he/she will be assigned randomly through a computer program to group A or B.

DATA COLLECTION METHOD

Before joining the study, the attending doctors will give to the patient all the information about the study and it's aims, collected in the information document for the study (*Annex 11*), and this document will be signed by the patient, stating that he has received it, has been explained and has understood it correctly.

After that, the patient will be asked to sign the informed consent (*Annex 5*) to be included in the study, in which the doctor will highlight the confidentiality and voluntary aspects of it. As it is likely that the patient will not be able to sign it due to his/her serious condition, the informed consent will be required from a first-degree family member, representative or legal guardian if they are present. Once the patient is conscious, he/she will also be asked to sign the informed consent.

The informed consent forms and study information sheets will be available in Catalan, Spanish and English but only Catalan version is annexed.

All data will be collected prospectively during the 36 months of patient's recruitment using data collection sheets (*Annex 12*) as a collection method.

In each patient treated at the HUDJTG for which the sepsis code is activated, and after meeting all the inclusion and exclusion criteria, and giving his/her informed consent, a group (group A or group B) will be randomly assigned.

During the patient's treatment, or when it's finished, indifferently, the emergency sanitary team will fill in the data collection sheet. During the care process, the attending doctor will have the responsibility to indicate the nursing team the collection of information necessary to fill up this document a posteriori.

Statistical Analysis

All statistical variables analysis will be performed using the Statistical Package for Social Science (SPSS) version 26. The descriptive analysis of the variables will be performed to compare the characteristics of the population of both groups. It is expected that the basic demographics of the participants during the study will be similar and, therefore, comparable groups.

Statistical significance will be considered at p value < 0.5 and confidence intervals will be calculated at 95%.

DESCRIPTIVE ANALYSIS

Results of data collected will be presented as proportions and percentages for categorical variables. For quantitative variables, results of data collected will be presented as mean ± SD and interquartile range (25-75) depending on whether they have a normal distribution or not.

BIVARIATE INFERENCE

The difference of proportion of the qualitative variables (dependent and covariables) of both A and B groups will be contrasted applying the Chi square test ($\chi 2$) and Fisher's exact test when the expected frequencies are < 5.

To compare the means and the medians of the quantitative variables of both A and B groups the T Student's test and U-Mann-Whitney's test will be used.

MULTIVARIATE ANALYSIS

To give more external validity to our study a Logistic Regression will be conducted in order to adjust the relationship between changes in mortality in the different groups adjusted with potential confounders, which are collected as covariables.

In the case of secondary dependent variable, which is hospital length of stay, as it is a quantitative continuous variable, a Linear Regression will be estimated with the same independent variable, and adjustment for the same covariates will be performed.

The existence of possible interactions between the intervention and/or covariates will be assessed.

It will be considered that a significant difference between both groups exists when p-value < 0.05.

Ethical considerations

This study will respect the medical ethics principles of human experimentation, following what was established by the World Medical Association in the *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*(35).

Also, database will use the medical record number instead of the names of patients to guarantee the anonymity of all patient's data, according to *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*(36).

All participants will be personally informed by an ED doctor and an information document about the study will be given to them (*Annex 11*) together with the informed consent (*Annex 5*), which participants will have to voluntarily sign before joining the study. If the patient is under-aged, remains unconscious or inevitably dies, the informed consent will be requested to first-degree relatives or legal guardian.

The present project will be presented and evaluated by the Clinical Research Ethics Committee (CEIC) of the HUDJTG, and its approval will be obtained before initiating the study.

The investigators of this project declare that there are no conflicts of interest.

Study limitations

Several limitations of this study should be acknowledged.

Due to the lack of similar studies done before, the sample size was calculated using different population's mortality. When sample size was calculated, the expected mortality of group A (with the current sepsis code protocol) was obtained from a doctoral thesis based on the Catalan population, and the expected mortality of group B was obtained by calculating the mean mortality of the studies published to date in which similar protocols, although not the same, were used in American population. In order to minimize this bias, the sample of both groups was slightly increased.

Another limitation of this study that must be acknowledged is the fact that nowadays the Catalan public health system, specially its ICU's and ED's, like HUDJTG ED, are saturated due to the Coronavirus SARS-CoV-2 pandemic, and because of that, its professionals may not be able to give their fully attention and dedication to this study.

Interviewer bias it is also likely to appear in our study as some HUDJTG ED doctors are already familiar to the use of capnography, and some other are not. In order to reduce

that bias, an specific theoretical formation and practical training on capnograph use will be done to all HUDJTG ED doctors. Normally, to train the 21 doctors associated to the HUDJTG ED, two groups would be made, but due to the Coronavirus SARS-CoV-2 pandemic, and also the commitment of this study in the better training of health personnel in charge, 4 different groups will be made, and a 3-hour formation will be given to each one.

Working plan and chronogram

All the study process is expected to last 44 months, and all the activities carried out during this time will be organized in the following phases:

WORKING PLAN

Phase 1: Preparation, training and coordination

This first part of the study lasts five months and consists on the elaboration of the current protocol, and the training of HUDJTG ED professionals in capnography use and in the new protocol.

During this phase, also, investigators, collaborators and statisticians will meet in order to specify the tasks every member of the team will be in charge.

Phase 2: Patient recruitment and data collection

This part of the study lasts 3 years (36 months) and it consists on the selection of patients who accomplish the inclusion and exclusion criteria described before, the group

assignment to each patient, also according to randomization criteria described before, their treatment and the data collection, using the data collection form attached (*Annex 12*).

Phase 3: Statistical analysis

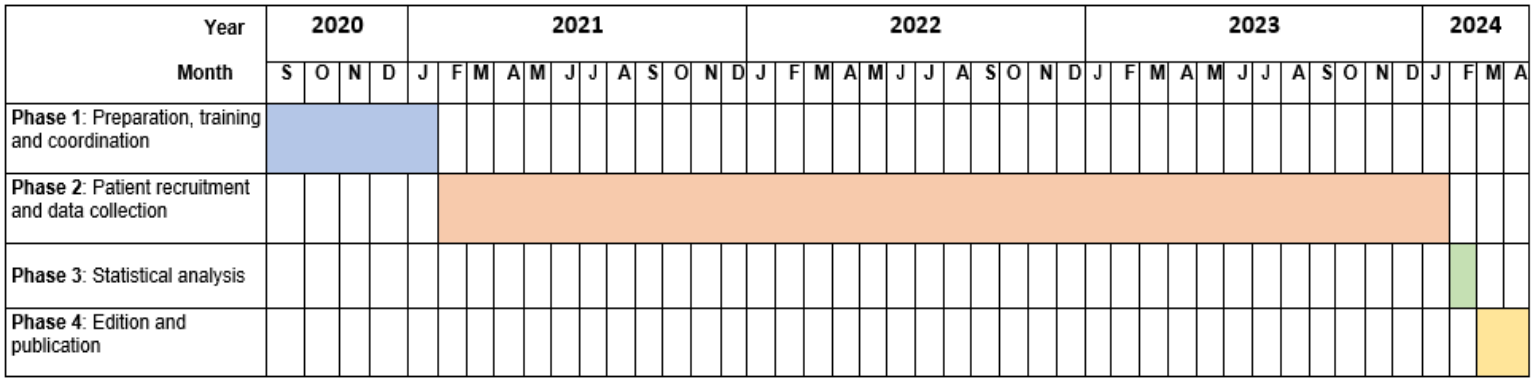
After processing the database, all data will be analysed using the appropriate statistical tests by an external statistician. This part of the study should last 1 month.

Results and conclusions will be extracted and evaluated by all the research team.

Phase 4: Edition and publication

During the last two months, the researchers will write and edit a scientific paper to be published.

CHRONOGRAM



Budget of the study

EXPENSES	UNIT COST	HOURS/UNITS	TOTAL
PERSONNEL/STAFF			
Formation of trainers	60€	12h.	720€
Data manager	40€	40h.	1.600€
Statistician	50€	48h.	2.400€
Subtotal:			**4.720€**
MATERIAL COSTS			
Capnography tube	6,9€	355	2.449,5€
Subtotal:			**2.449,5€**
PUBLICATION AND DIFUSSION COSTS			
Linguistic correction			150€
Article publication			1.500€
Subtotal:			**1.650€**
			TOTAL: 8.819,5€

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Bruno Carneiro, MD; Julie Pernet, MD; Pierre-Géraud Claret, MD P, Fabrice Dami, MD; Ben Bloom, MD; Bruno Riou, MD, PhD; Sébastien Beaune, MD P. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA. 2017;317(3):301–8.

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임성익•이성우•홍윤식•최성혁•문성우•김수진•김낙훈•박상민•김정윤 Shock Index, Serum Lactate Level, and Arterial-End Tidal Carbon Dioxide Difference as Hospital Mortality Markers and Guidelines of Early Resuscitation in Hypovolemic Shock. J Korean Soc Emerg Med. 2007;18(4):287–93.

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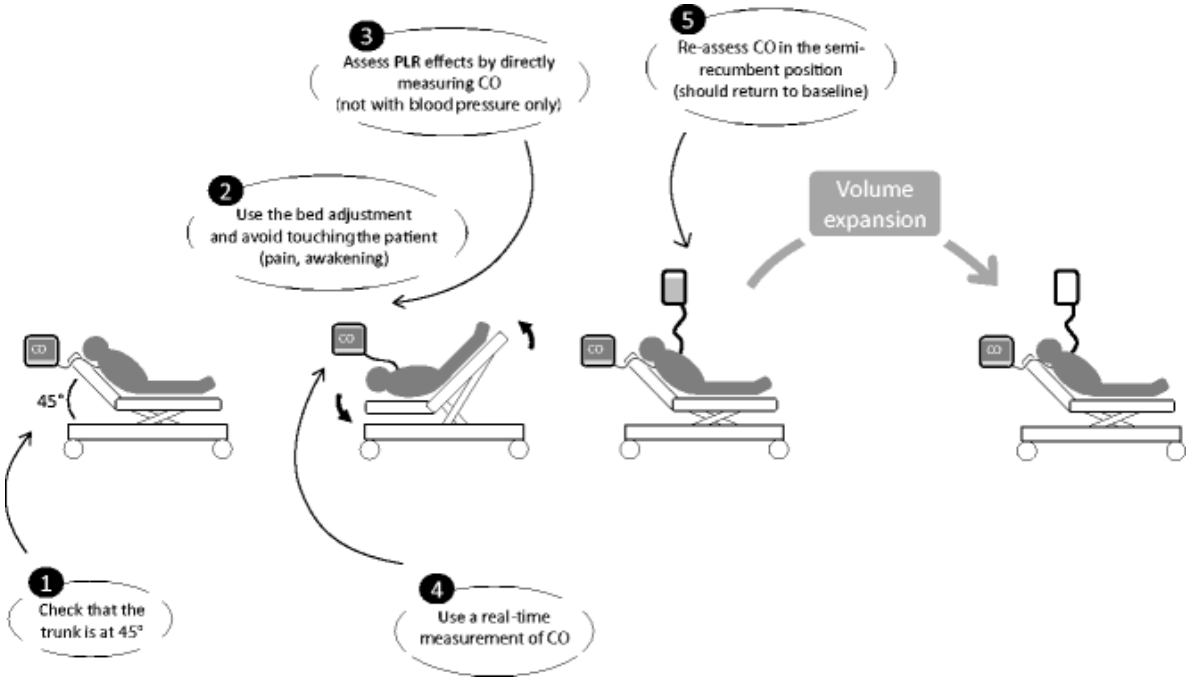
Annexes

Annex 1: Passive Leg Rising Test



Annex 2: Barthel Index

Barthel Index of Activities of Daily Living

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

The Barthel Index

Bowels
0 = incontinent (or needs to be given enemata)
1 = occasional accident (once/week)
2 = continent
Patient's Score: _____

Bladder
0 = incontinent, or catheterized and unable to manage
1 = occasional accident (max. once per 24 hours)
2 = continent (for over 7 days)
Patient's Score: _____

Grooming
0 = needs help with personal care
1 = independent face/hair/teeth/shaving (implements provided)
Patient's Score: _____

Toilet use
0 = dependent
1 = needs some help, but can do something alone
2 = independent (on and off, dressing, wiping)
Patient's Score: _____

Feeding
0 = unable
1 = needs help cutting, spreading butter, etc.
2 = independent (food provided within reach)
Patient's Score: _____

Transfer
0 = unable – no sitting balance
1 = major help (one or two people, physical), can sit
2 = minor help (verbal or physical)
3 = independent
Patient's Score: _____

Mobility
0 = immobile
1 = wheelchair independent, including corners, etc.
2 = walks with help of one person (verbal or physical)
3 = independent (but may use any aid, e.g., stick)
Patient's Score: _____

Dressing
0 = dependent
1 = needs help, but can do about half unaided
2 = independent (including buttons, zips, laces, etc.)
Patient's Score: _____

Stairs
0 = unable
1 = needs help (verbal, physical, carrying aid)
2 = independent up and down
Patient's Score: _____

Bathing
0 = dependent
1 = independent (or in shower)
Patient's Score: _____

Total Score: _____

(Collin et al., 1988)

Scoring:

Sum the patient's scores for each item. Total possible scores range from 0 – 20, with lower scores indicating increased disability. If used to measure improvement after rehabilitation, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable.

Sources:

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1

Annex 3: Rockwood Clinical Frailty Scale

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

Annex 4: Profund Index

Table 1. The PROFUND Index

Characteristic	PROFUND Index
Demographics	
≥85 Years	3
Clinical features	
Active neoplasia	6
Dementia	3
III–IV functional class on NYHA and/or MRC	3
Delirium in last hospital admission	3
Analytical parameters (blood plasma)	
Hemoglobin < 10 g/dL	3
Psychological–functional–sociofamilial features	
Barthel's index < 60	4
Caregiver other than spouse or no caregiver	2
Healthcare features	
≥4 hospital admissions in last 12 months	3
Total score items = 9	0–30 points

Notes: MRC, medical research council; NYHA, new york heart association.

Annex 5: Informed consent for this study

Full de consentiment informat per a la realització de l'estudi

Títol de l'estudi: Can capnography use during sepsis treatment reduce mortality by improving hemodynamic management?

Nom i Cognoms: .....

amb DNI:.....

Declaro sota la meva responsabilitat que:

- He estat informat adequadament pel Dr./Dra:.....
- He llegit el full d'informació que se m'ha lliurat, se m'ha explicat correctament i podré guardar-ne una còpia.
- He pogut fer totes les preguntes desitjades sobre l'estudi i els meus dubtes s'han resolt de forma satisfactòria.
- He rebut prou informació sobre l'estudi.
- He entès quin serà el meu paper durant l'estudi.
- He entès que totes les dades seran tractades de forma estrictament confidencial.
- Comprenc que la meva participació és voluntària.
- Comprenc que puc retirar-me de l'estudi quan vulgui, sense haver de donar explicacions, i sense que això repercuteixi en la meva atenció sanitària.

Accepto voluntàriament la participació a l'estudi i dono el meu consentiment per a l'accés i utilització de les meves dades, sempre en conformitat a l'establert al Reglament de Protecció de Dades (UE) 2016/679 del Parlament Europeu i del Consell, de 27 d'abril de 2017, relatiu a la protecció de les persones físiques en referència al tractament de dades personals i a la lliure circulació d'aquestes dades, i en el seu defecte, la Llei Orgànica de Protecció de Dades Personals i garantia dels drets digitals del 3/2018.

Desitjo rebre informació via telefònica o per correu electrònic sobre els futurs resultats de l'estudi:

□ Sí □ No

Correu electrònic.....Nº telèfon.....

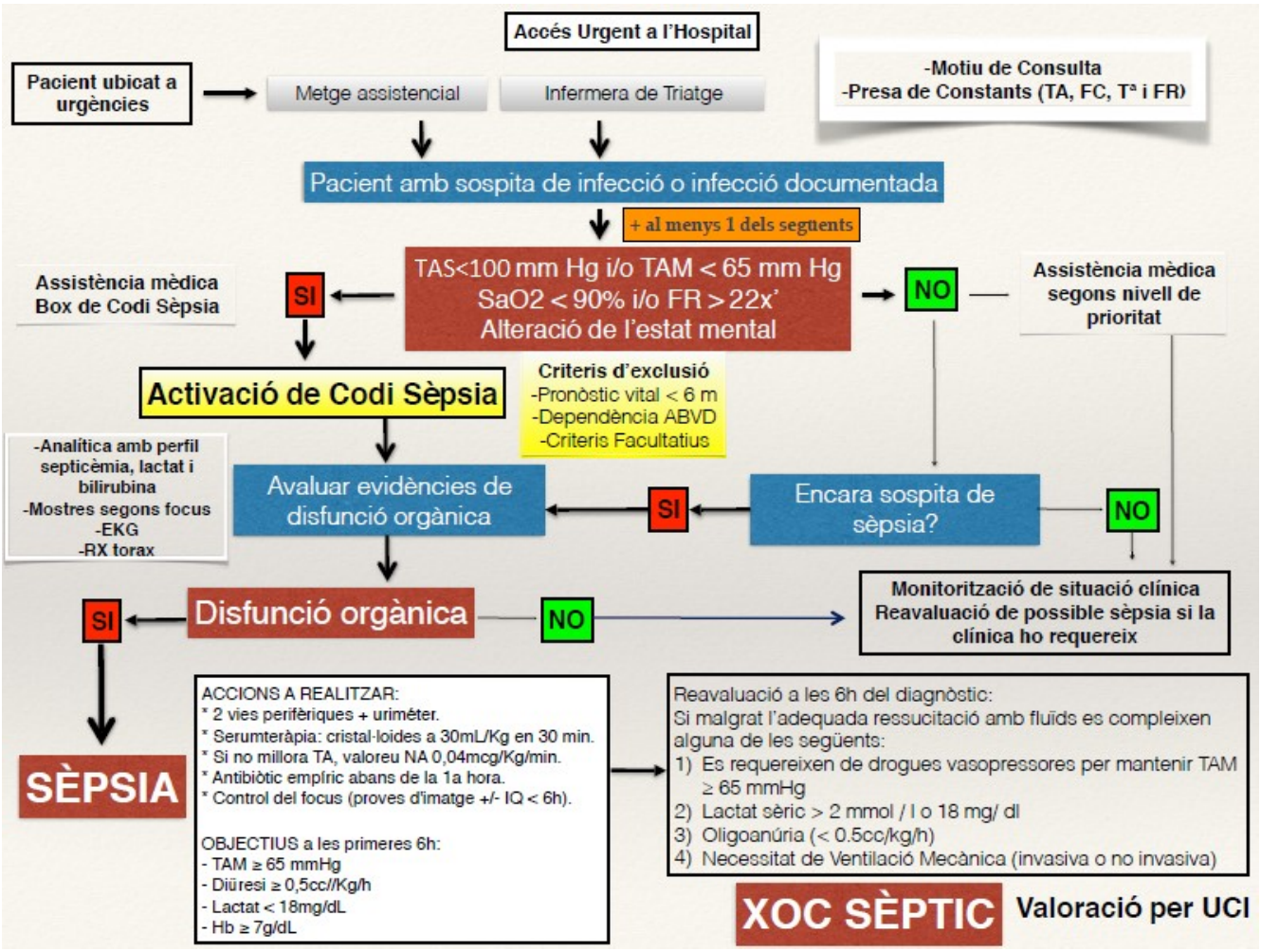
....., a.....de.....del 20.....

Firma del pacient: Firma de l'investigador:

Nom..... Nom.....

Aquest document s'ha de firmar per duplicat i se n'ha de quedar una còpia l'investigador i una altra el pacient

Annex 6: Current sepsis code protocol



Annex 7: SOFA scale

	Score				
	0	**1**	**2**	**3**	**4**
Respiratory system					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Hepatic system					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular system					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Coagulation					
Platelets $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Central nervous system					
Glasgow coma scale	15	13–14	10–12	6–9	<6
Renal system					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (mL/d)				<500	<200

Notes: [a]All catecholamine doses represent μg/kg/min. Organ dysfunction is identified as an increase in the SOFA score of ≥2 points. In patients with not known preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. *Intensive Care Med*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. 22(7), 1996, 707–710, Vincent JL, Moreno R, Takala J, et al. With permission of Springer.[17]

Abbreviations: PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure.

Annex 8: qSOFA scale

Quick Sequential Organ Failure Assessment (SOFA) score

qSOFA (Quick SOFA) Criteria	Points
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mmHg	1

Annex 9: Glasgow Coma Scale (GCS)

Glasgow Coma Scale		
Response	Scale	Score
Eye Opening Response	Eyes open spontaneously	4 Points
	Eyes open to verbal command, speech, or shout	3 Points
	Eyes open to pain (not applied to face)	2 Points
	No eye opening	1 Point
Verbal Response	Oriented	5 Points
	Confused conversation, but able to answer questions	4 Points
	Inappropriate responses, words discernible	3 Points
	Incomprehensible sounds or speech	2 Points
	No verbal response	1 Point
Motor Response	Obeys commands for movement	6 Points
	Purposeful movement to painful stimulus	5 Points
	Withdraws from pain	4 Points
	Abnormal (spastic) flexion, decorticate posture	3 Points
	Extensor (rigid) response, decerebrate posture	2 Points
	No motor response	1 Point
Minor Brain Injury = 13-15 points; **Moderate Brain Injury** = 9-12 points; **Severe Brain Injury** = 3-8 points		

Annex 10: Charlson comorbidity index

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	2
Moderate-to-severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno-deficiency syndrome (AIDS)	6

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Annex 11: Information document for the study

FULL D'INFORMACIO PEL PACIENT

Benvolgut / da Sr / a. Vostè/ o el seu familiar presenta una sèpsia, pel que requereix l'activació del codi sèpsia. Aquest és un protocol habitual i es realitzarà de manera normal seguint les guies de pràctica clínica. El doctor d'urgències de l'Hospital Universitari Doctor Josep Trueta de Girona que l'està atenent el convida a participar a l'estudi:

CAN CAPNOGRAPHY USE DURING SEPSIS TREATMENT REDUCE MORTALITY BY IMPROVING HEMODYNAMIC MANAGEMENT?

Aquest estudi el durà a terme l'investigador / a: Marc Marturià, Jordi Jiménez.

Abans de confirmar la seva participació en l'estudi de recerca, és important que entengui en què consisteix. Llegiu detingudament aquest document i faci totes les preguntes que li puguin sorgir.

Objectiu de l'estudi:
Aquest estudi pretén analitzar si un nou protocol basat en l'aplicació de la capnografia com a eina de monitoratge durant el tractament de la sèpsia disminueix la mortalitat en aquests pacients, permetent un millor maneig hemodinàmic.

Participació voluntària:
Vostè és completament lliure de triar participar o no en l'estudi. La seva decisió no influirà en la seva atenció mèdica.

Nombre de pacients i durada estimada de la participació dels pacients:
En aquest estudi es preveu la participació d'un total de 710 pacients atesos pel servei d'urgències de l'Hospital Universitari Doctor Josep Trueta de Girona que precisin l'activació del codi sèpsia. No es realitzarà seguiment dels pacients més enllà de l'atenció sanitària prestada durant l'ingrés.

Procediments de l'estudi
Recentment s'ha demostrat que l'actuació en la primera hora de tractament és la més decisiva en el pronòstic dels pacients amb sèpsia. En l'àmbit del maneig hemodinàmic els protocols actuals encara no contemplen aquesta consideració, i requereixen una actualització. Aquest estudi pretén demostrar la capacitat i la utilitat d'actuar precoçment en aquest sentit, permetent així reduir la mortalitat en aquest grup de pacients. Participant en aquest estudi, vostè/el seu familiar serà tributari de rebre tractament amb noradrenalina de forma precoç, si ho requerís. La resta del procediment de tractament de la sèpsia segons els protocols actuals no variarà si vostè decideix participar o no; Es farà de la mateixa manera en qualsevol cas. L'equip, durant o al final de l'assistència recollirà unes dades referents al seu estat i al procediment realitzat. Aquesta recol·lecció de dades es farà a través de formularis que completarà el personal sanitari.

Confidencialitat
D'acord amb la Llei Orgànica 15/1999, de 13 de desembre, de protecció de dades de caràcter personal (LOPD) i Reial Decret 1720/2007, les dades personals i de salut (ja constin en la seva història clínica ja els hagi proporcionat com conseqüència de la seva participació en aquest estudi) que es recullin amb motiu d'aquest estudi són els necessaris per cobrir els objectius d'aquest. Aquestes dades seran identificats per mitjà d'un codi per garantir la confidencialitat de la seva identitat i únicament el metge tindrà accés a aquesta informació.

Tanmateix, els representants autoritzats del promotor poden necessitar accedir a la seva història clínica que conté dades personals (no codificats) per tal de garantir que l'estudi s'estigui duent a terme de forma adequada i que les dades documentats són correctes. També podran accedir a aquestes dades les autoritats sanitàries i el Comitè Ètic d'Investigació Clínica. Tots ells mantindran en tot moment la confidencialitat d'aquesta informació.

Les dades que es recullin amb motiu d'aquest estudi, entre els quals es trobaran dades personals i de salut (ja constin en la seva història clínica ja els hagi proporcionat com a conseqüència de la seva participació en aquest estudi) seran processats i analitzats per l'equip investigador amb la finalitat d'avaluar-les científicament. Si vostè decideix participar en aquest estudi estarà consentint expressament en el tractament de les seves dades personals i de salut pel promotor. Tot això de conformitat amb la LOPD i amb la normativa que la desenvolupa.

Vostè podrà exercitar en qualsevol moment els seus drets d'accés, rectificació, cancel·lació i oposició dirigint-se al metge que l'atén en aquest estudi el qual ho ha de posar en coneixement del promotor.

Així mateix, els resultats de l'estudi poden ser comunicades a les autoritats sanitàries i eventualment a la comunitat científica a través de congressos i publicacions sense que la seva identitat sigui revelada en cap moment.

Preguntes / Informació:

Per fer alguna pregunta o aclarir algun tema relacionat amb l'estudi, o si necessita ajuda per qualsevol problema de salut relacionat amb aquest estudi, si us plau, no dubti en posar-se en contacte amb:

Dr: ..... Telèfon: .....

L'investigador li agraeix la seva inestimable col·laboració.

Annex 12: Data collection sheet

FULL DE RECOL·LECCIÓ DE DADES

Data: ..... / ..... / .....
Edat: ..... Sexe: ☐ Home. ☐ Dona. ☐ Desconegut.

Número d'història clínica:

Focus infecciós: Patogen:

Antibiòtic prescrit:

Temps des de l'admissió fins a l'administració d'antibiòtic:

Temps des de l'admissió fins a l'administració de noradrenalina si precisa:

Temps des de l'admissió fins a l'inici de la ressuscitació amb cristal·loides:

qSOFA: SOFA:

PAM (pressió arterial mitja) a l'admissió: Saturació d'oxigen:

Índex PAFI: Plaquetes ($\times 10^9$/L):

Bilirubina (mg/dL): Creatinina (mg/dL):

Puntuació escala de coma de Glasgow a l'arribada:

Producció d'orina primeres 24 h. (mL):

Índex de: Charlson: Barthel: Rockwood:

ETCO2 a l'arribada, al cap d'1 h. i al cap de 3 h: / /

Lactat (anotar totes les determinacions i hores):

El pacient ha requerit suport ventilatori? No VMNI VMI

Dies d'ingrés requerits:

Destí: Alta Èxitus