Universitat de Girona
Facultat de Medicina

EVALUATING THE USE OF END-TIDAL CARBON DIOXIDE IN A SEPSIS CODE PATIENT AS A GOAL FOR THE EARLY RESUSCITATION TREATMENT IN THE EMERGENCY DEPARTMENT

FINAL DEGREE PROJECT

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“Estimar és el gran do de l’home, ser estimat el seu gran desig. Allò que no poden fer les medicines ni els tractaments més enèrgics ho aconsegueix una paraula amable, un suau somriure, un gest afectuós.”

Pere Tarrés

I would like to express my sincere gratitude to all the staff of the emergency departments of Hospital Universitari Doctor Josep Trueta and Parc Hospitalari Martí i Julià for having received me so well. I have learnt a lot from each one of them and from the patients as well.

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1. ABSTRACT

Background: Sepsis is a major healthcare problem with high mortality and an increasing incidence (1). A huge progress reducing mortality has been made since the creation of the Surviving Sepsis Campaign in 2001 but there is still a long way to go.

In the management of septic patients, blood lactate is one of the most important measures as a goal for the early resuscitation treatment (2). Because of its physiology (3), $ETCO_2$ seems to be an ideal indicator and a reference goal for the sepsis management as well.

Justification: $ETCO_2$ could be a real-time, dependable, not invasive and easily obtained measurement of early resuscitation treatment in sepsis code patients, instead of invasive blood extractions for lactate measurements.

Objectives: The goal of this study is to determine if there is a correlation between blood lactate levels and $ETCO_2$ during early resuscitation treatment in patients with sepsis. Secondary objectives: A cut-off point of $ETCO_2$ equivalent to lactate levels <2mmol/L as an early resuscitation goal and the relationship between $ETCO_2$ values and in hospital mortality will also be evaluated.

Methods: This study is an observational longitudinal prospective cohort study that will include 120 patients admitted to the Hospital Josep Trueta emergency department due to sepsis and older than 18 years. The sepsis code protocol must be activated, with the following criteria: Suspected infection and tachypnea, hypotension or mental status disorders. Exclusion criteria are vital prognosis <6 months, immunosuppression, asthma or chronic obstructive pulmonary disease and intubated patients. Patient's recruitment will last 6 months. Main variables: Blood lactate and $ETCO_2$ measurements will be taken during the first 6 hours of sepsis resuscitation treatment in order to evaluate the correlation between both measures.

Key word: Sepsis, $ETCO_2$, lactate, emergency department

2. ABBREVIATIONS

CO_2	Carbon dioxide
ED	Emergency department
$ETCO_2$	End-tidal carbon dioxide
HJT	Hospital Josep Trueta
ICU	Intensive care unit
qSOFA	Quick sequential organ failure assessment score
MAP	Mean arterial pressure
O_2	Oxygen
$PaCO_2$	Partial pressure of carbon dioxide
SIRS	Systemic inflammatory response system
SOFA	Sequential organ failure assessment score

3. INTRODUCTION

3.1. Background

Although sepsis has long been recognized, there was no clinical definition until the last 20th century. In 1991 a consensus statement of different international societies was developed and then revised in 2001, in which they introduce the concept of **SIRS**[1] as a part of sepsis definition. They also define severe sepsis and septic shock as a continuum of acute inflammation and organ dysfunction (4,5).

Nevertheless, these definitions of sepsis have been revised currently since they were outdated and confusing. **Sepsis** is now defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (6,7). Sepsis is not a specific illness but a syndrome characterized for a multifaceted host response to an infecting pathogen that is amplified by endogenous factors.

The original definition of sepsis as an infection with SIRS criteria (4) is now not enough, since the organ dysfunction is produced by a complex pathobiology. It involves an early activation of the pro and anti-inflammatory responses, along with some changes in other physiologic pathways such as cardiovascular, neuronal, hormonal, metabolic and coagulation. (6)

Therefore, the importance of the interaction of both pathogen factors and host factors, contributes in the heterogeneity of the syndrome that makes it difficult to describe and identify.

[1] SIRS (Systemic Inflammatory Response Syndrome) Two or more of: Temperature >38°C or <36°C, Heart rate >90/min, Respiratory rate >20/min or PaCO2 <32mmHg (4.3 kPa), White blood cell count >12 000/mm3 or <4000/mm3 or >10% immature bands

3.2. Clinical definitions

The current clinical identification of sepsis includes only the concepts of sepsis and septic shock, simplifying the 1991 and 2001 classification (4,5). The old definition of sepsis was very sensitive but all kinds of infection could be included, making it less specific (Figure 1) (7).

Sepsis is clinically defined as an organ dysfunction caused by an intercurrent infection. In a recent study, the best way to assess the organ dysfunction is the SOFA[2] score (8). The qSOFA score (quick SOFA score) is useful for the first assessment of a septic patient. (ANNEX I)

Septic shock is when in the subset of sepsis, the underlying circulatory and cellular or metabolic abnormalities are profound enough to increase mortality substantially. In clinical terms, it is traduced to a need of vasopressor therapy despite adequate volume resuscitation in order to increase the mean arterial pressure (MAP) above 65mmHg and maintain the serum lactate levels below 2mmol/L (8).

Category	Definition
PREVIOUS DEFINITIONS	
SIRS (systemic inflammatory response syndrome)	Two of the following: • Temperature >38°C or <36°C • Heart rate > 90 beats/min • Respiratory rate >20 breaths/min or arterial carbon dioxide pressure <32 mm Hg • White blood cell count >12×10⁹/L or <4×10⁹/L
Sepsis	SIRS with infection (presumed or proven)
Severe sepsis	Sepsis with evidence of acute organ dysfunction (hypotension, lactic acidosis, reduced urine output, reduced PaO_2/FIO_2 ratio, raised creatinine or bilirubin, thrombocytopenia, raised international normalized ratio)
Septic shock	Sepsis with persistent hypotension after fluid resuscitation
REVISED DEFINITIONS	
Sepsis	Life threatening organ dysfunction* caused by a dysregulated host response to infection
Septic shock	Sepsis and vasopressor therapy needed to increase mean arterial pressure to ≥65 mm Hg and lactate to >2 mmol/L despite adequate fluid resuscitation

***Figure 1**: Clinical definitions of sepsis before and after revision* (6).

[2] SOFA score: sequential organ failure assessment score. Assessed by an acute change of ≥2 points.

3.3. Epidemiology

Sepsis is a leading cause of mortality and critical illness worldwide (1). Despite advances in treatment and care, existing epidemiologic studies suggest that sepsis remains a huge burden across all regions (1,9).

It is difficult to know the true incidence of sepsis since there is a huge heterogeneity between studies. This disparity could be because there is no gold standard for sepsis diagnose and the sepsis definitions are non-standardized. Despite difficulties, last evidence published states that in high-income countries the incidence of sepsis is 437 cases per 100.000 person-years. About severe sepsis, the incidence is 270 cases per 100.000 person-year (1,10). The evaluation of global incidence of sepsis is limited due to missing data from low and middle-income countries, but the estimate extrapolations suggest a global number of more than 31 million sepsis cases and 5 million deaths. However, the true incidence of sepsis in low and middle-income countries may be higher since infection disease are more prevalent at these regions (1).

The incidence of sepsis is increasing, reflecting the higher life expectancy of population with comorbidities, such as chronic kidney disease, diabetes, heart insufficiency and immunocompromising, and the grater detection of the illness (11). Furthermore, the patients who survive sepsis often have long-term physical and cognitive disabilities with significant health care and social implications.

In the developed world, the mortality rate among septic patients is 20-35.8% outside Intensive care unit (ICU) and 15-25.8% in the ICU, depending on the studies (1,10,12,13). About septic shock the mortality is higher, about 50% of the patients (12,14).

The infectious focus of sepsis differs on every patient but the most common focus are the pulmonary, followed by urinary tract and abdomen (13,15,16).

3.4. Sepsis management protocol

On Octuber 15th the CatSalut sepsis code protocol came into operation (17). It was created in order to standardize the sepsis management among all hospitals in Catalonia and to organize the circuit of septic patients. The CatSalut code pretends to improve the coordination of resources and facilitate the transfers of the patients to appropriate hospitals according to their severity. Furthermore, standards to provide better care and general recommendations for the management are made.

This protocol classifies all hospitals in different levels depending on the resources they have. Therefore, depending on the resources, each hospital develops a different function on the treatment of a septic patient. The protocol also stablish a direct communication between hospitals and SEM (Servei d'Emergències Mèdiques) and the criteria required to transfer patients in order to facilitate it.

With this classification, HJT has become a level SEP-2b hospital, the highest level of assistance for the management of sepsis. According that, HJT has the function of hemodynamic resuscitation, organ specific support and abdominal/skin/soft tissues/urologic and non-abdominal focus control during 24h. As it is the reference hospital of the health network around Girona, all patients who meet the referral criteria in this area will be transported and treated in our hospital.

Regarding emergency department, the sepsis code actions are structured in a sequential, standard, multidisciplinary and time dependent process, which is developed in 3 principal phases:

1. **Detection and activation**: to differentiate the patients with an infection from those with sepsis. It is based on the identification of the organ dysfunction in a patient with suspected infection. The clinical criteria for the sepsis code activation are the following:

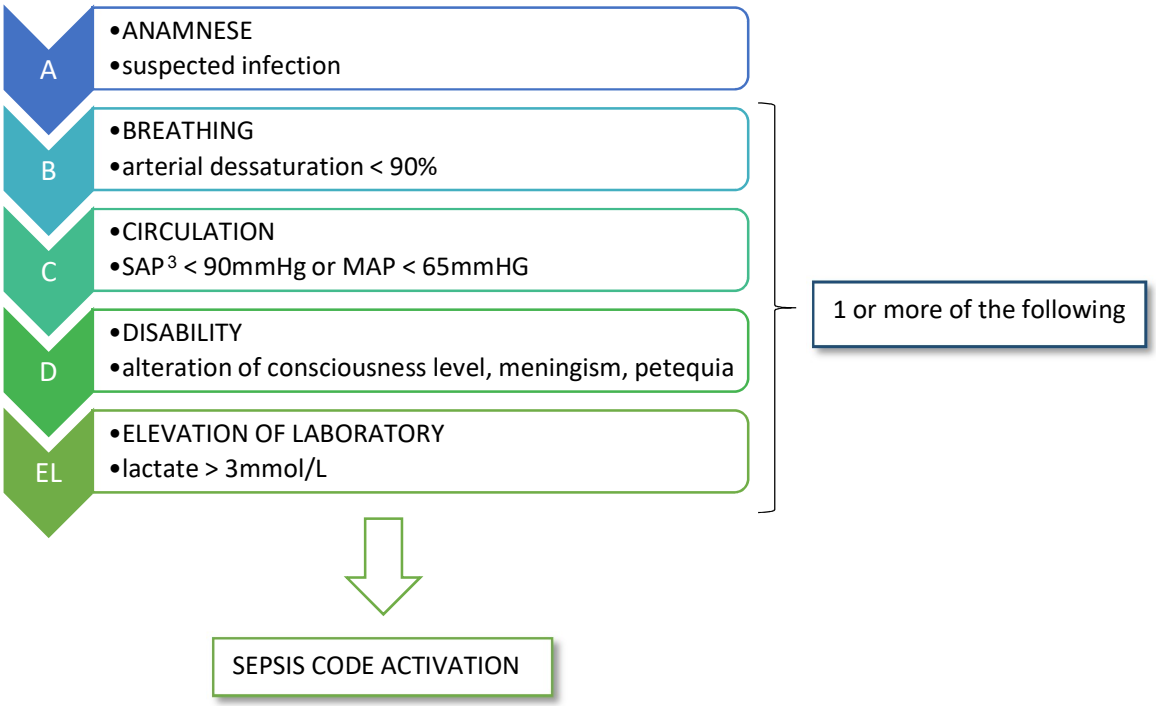

Figure 2: *Sepsis code activation criteria. Adaptation* (17)

2. **Resuscitation and focus control**: the main objectives are to achieve a correct perfusion and oxygenation of the tissues, to complete the syndromic diagnose and to administrate early empiric antibiotic treatment during the first 6 hours.

   It is based in 4 fundamental pillars:

   - Assessment of the gravity of the organ dysfunction
   - Hemodynamic early resuscitation treatment
   - Infectious focus management (empiric antibiotic and focus control)
   - Monitoring the response

[3] *SAP: Systolic arterial pressure*

The actions needed to achieve these basic objectives are described in a time-dependent sequential list:

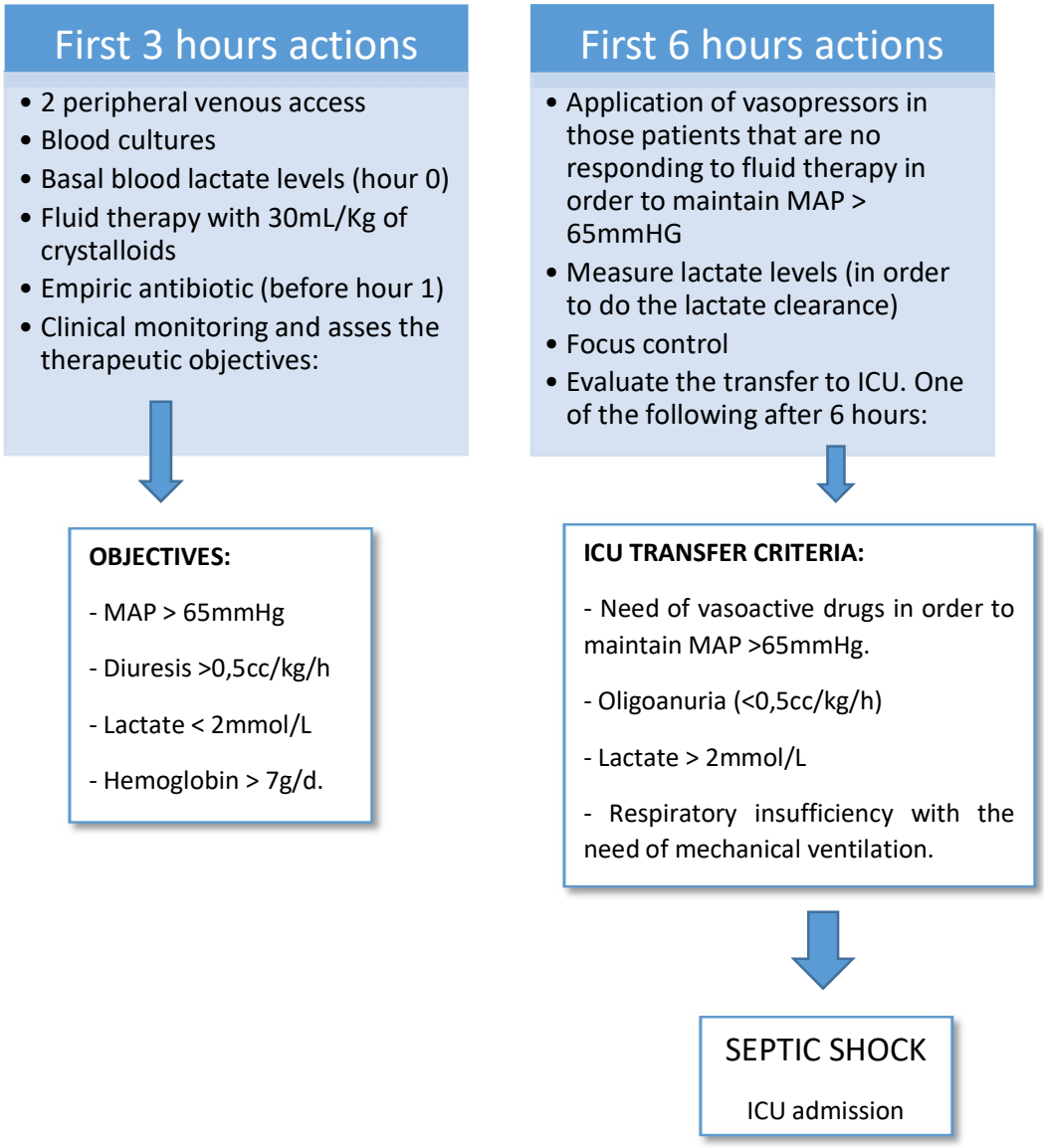

***Figure 3**: Actions and objectives of the early resuscitation treatment. Adaptation* (17)

3. **Monitoring and specific support**: this phase consists on the measures needed to maintain or increase the tissue perfusion in those patients that are no responding to the early resuscitation treatment. It normally requires the admission to the UCI when the patient meets one of the criteria in the Figure 3. According

to the sepsis definitions, these patients are also fulfilling the Septic shock diagnose.

In Doctor Josep Trueta Hospital a sepsis code has been made in order to accomplish the CatSalut sepsis protocol (ANNEX II). Furthermore, an empiric antibiotic treatment guideline has been elaborate depending on the infection focus and the most prevalent microbiological pathogens of the area (ANNEX III). In our study, we will be using this protocol for treating our patients in the emergency room.

3.5. Lactate

Lactate is considered an indicator of anaerobic cellular activity. When organ perfusion is menaced, such in a sepsis patient, oxygen concentrations are not high enough for cellular aerobic metabolism. In this scenario, compromised cells switch to anaerobic metabolism, leading to a higher lactate production (18). Although there are other many processes that can increase lactate production such as reduced hepatic clearance or inhibition of pyruvate metabolism, most frequent causes are the ones related to a decreased O_2 delivery to tissues (18,19)

Therefore, lactate value is the best surrogate of anaerobic metabolism related to tissue hypoxia. It has been found to be the best mortality predictor after early sepsis resuscitation treatment (2) a severity indicator and general mortality predictor (19,20).

There are many different ways to interpret lactate levels. The most frequent used to assess a septic patient evolution will be exposed.

- **Lactate levels**: single measure of lactate in time. It is defined as lactate normalization, with a value <2mmol/L (18g/dl) at a certain time (normally 6 hours after initial resuscitation treatment) (2,21).
- **Lactate clearance**: dynamic parameter. It represents the variation of lactate concentration during the first 6 hours of treatment. A significant decrease is considered to be higher than 10% or more (20,22).

*Lactate clearance = (initial lactate – final lactate)/initial lactate * 100*

However, blood lactate has some limitations. Lactate levels cannot be provided in real time and require serial blood extractions, which correspond to an invasive measure.

3.6. End tidal carbon dioxide

The end tidal is a non-invasive measurement of the carbon dioxide (CO_2) elimination when the patient is exhaling. It is reflected as a curve of the changing concentration of CO_2 while breathing called capnogram (Figure 4) (3).

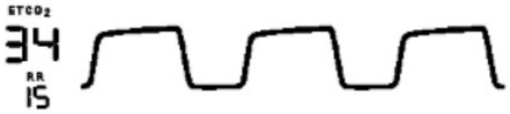

***Figure 4**: Capnography display* (24)

3.6.1. Capnogram analysis

A capnogram is a plot of CO_2 concentration over time and has 4 phases (Figure 5)(23):

- **Phase I**: (A-B) It corresponds to late inspiration and early expiration. In early expiration, the air expired is from the dead space, where there is no CO_2.
- **Phase II**: (B-C) It corresponds to the middle expiration, with a combination of death space and alveolar air.
- **Phase III**: (C-D) Plateau. It represents expired air from alveoli with almost constant CO_2. Point D is the highest point of the plateau and correspond on the maximal concentration of expired CO_2. It is called **end-tidal carbon dioxide ($ETCO_2$)**.
- **Phase 0**: (D-E) It is the rapid descent of CO_2 concentration during inspiration. It falls until zero in the baseline.

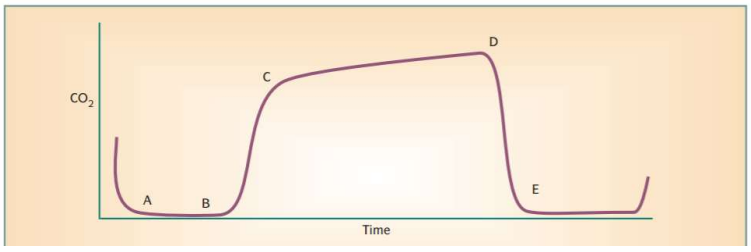

***Figure 5**: Normal capnogram. AB phase I, BC phase II, CD phase III, DE phase 0* (3).

3.6.2. Physiology

Capnography is based on the carbon dioxide gas properties. CO_2 is produced as a consequence of aerobic cellular metabolism as the waste product of combining oxygen and glucose to produce energy. CO_2 diffuses out of the cell and into the capillaries where it is transported to the right heart by the venous circulation. The right ventricle pumps the venous blood to the lungs, where the carbon dioxide is diffusing across the blood gas barrier of the alveolar wall, interstitial fluid and pulmonary capillary endothelium to the pulmonary alveoli (24–26). Carbon dioxide then exits the body via the lungs and it can be measured by a capnograph.

$ETCO_2$, therefore, is a reflection of metabolism, circulation and ventilation. Changes in the CO_2 levels in expired air reflect changes in one or more of these systems. If any two systems are kept relatively constant, the changes in $ETCO_2$ will reflect some kind of change in the third system (23,25,26). For example, in the case that there is no cardiac output or minute ventilation changes, hypermetabolic states will show increase levels in $ETCO_2$ (26).

Measurements of $ETCO_2$ constitute a useful non-invasive tool to monitor Partial pressure of carbon dioxide ($PaCO_2$) and hence the ventilator status of patients. CO_2 production normally remains constant, so the $ETCO_2$ is reflecting the $PaCO_2$. In normal individuals, where the ventilation and perfusion remains stable, the difference between $ETCO_2$ and $PaCO_2$ may vary from 2-5 mmHg. This value can vary from patient to patient and is dependent on several factors such as age, pulmonary disorders and hypovolemia (27). $ETCO_2$ represents $PaCO_2$ from all ventilated alveoli and $PaCO_2$ represents $PaCO_2$ of all perfused alveoli. Therefore, $ETCO_2$ usually underestimates or overestimates the $PaCO_2$ in cases of ventilation/perfusion (v/q) mismatch. For example, insufficient ventilation will increase $PaCO_2$ (it cannot be eliminated) and $ETCO_2$ will decrease, increasing $ETCO_2$-$PaCO_2$ difference (23,28).

3.6.3. Capnography waveforms patterns

Changes in capnography are immediate and provide a breath-to-breath status of ventilation. Capnography waveform can help us to identify different ventilation patterns. It is sometimes more important to pay attention to the ETCO2 trend than to the actual value since it shows more information about the ventilation status.

- **Normal**: $ETCO_2$ range is 35-45mmHg.
- **Hyperventilation**: respiratory frequency rate is increased and CO_2 goes down, so $ETCO_2$ value decrease.
- **Hypoventilation**: respiratory frequency rate is decreased and CO_2 and $ETCO_2$ increase.
- **Bronchospasm**: Due to airway obstruction, phase II and phase III are increased. The capnogram will show a characteristic waveform called “shark fin” as the patient has to struggle to exhale the alveolar air.

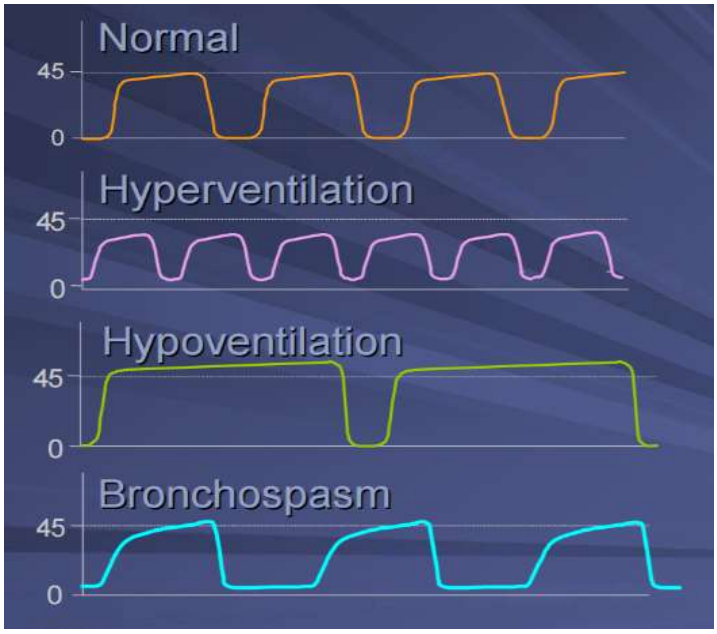

Figure 6: *Capnogram waveform patterns* (24)

3.6.4. Methods

There are two different equipment used for measuring the expired carbon dioxide. It can be measured directly at the patient ventilator interface (mainstream sensor), or a sample of gases can be collected and transported to the monitor for measurement (sidestream) (3).

3.6.5. Indications

Although commonly used in anaesthesiology for intubated patients receiving mechanical ventilation, this technique is now sometimes used in nonintubated patients (3,23,25).

Capnography was first advocated as a method for ensuring endotracheal rather than esophageal intubation (26). Since then, due to its physiology and non-invasive and quick measurement, many studies have been done for new indications. $ETCO_2$ measurements during cardiopulmonary resuscitation reflect variable cardiac output over time, and low values have been associated with decreased survival (29). It is also useful for detecting diabetic ketoacidosis among patients who present to the emergency department with a glucometer >550 mg/dl (30).

$ETCO_2$ monitoring is now being implemented to the emergency departments since it is a non-invasive, quick and reliable measurement of a wide variety of pathological processes.

4. JUSTIFICATION

Sepsis is a severe evolution of an infection with a life-threatening organ dysfunction and it has a mortality rate greater than 20% (1,12,16). Although its incidence is increasing and hospitalization rates are higher every year, rapid diagnosis and treatment improves the prognosis.

In 2010, the demonstrated non-inferiority of lactate clearance to $SCVO_2$ as a goal for early sepsis therapy, changed practice patterns (31). In addition, the strength of using lactate as a goal of sepsis therapy lied in its simplicity and availability.

Blood lactate levels are a key part as a goal for the early resuscitation treatment since they indicate the organ dysfunction by assessing the metabolic acidosis in the body (19). By improving lactate levels, we can assume that the organ dysfunction is also getting better. However, the only inconvenience of using lactate is that levels cannot be provided in real time and require serial blood extractions, what is painful for the patients.

For its physiology, $ETCO_2$ also seems to be an ideal indicator as a reference goal for the early resuscitation treatment. When a patient becomes septic, cellular hypoperfusion leads to a metabolic acidosis that result in a compensatory increase of the respiratory rate, which leads to an alkalosis in order to maintain homeostasis. An increase respiratory rate produces a higher CO_2 exhalation. Thus, $ETCO_2$ should reflect these physiologic changes by decreasing its value. $ETCO_2$ is also a non-invasive, simple and quick method, instead of gasometry or blood analysis procedure for acquiring blood lactate levels (32).

There are few recent studies comparing $ETCO_2$ to lactate and lactic acidosis in which they found a similar inverse relationship between them, so, when lactate levels increase, $ETCO_2$ decrease (32,33). No studies have compered the relationship between the two measures during early sepsis therapy, not have they yet established a cut-off point for

$ETCO_2$ equivalent to the lactate clearance >10% or blood lactate levels <2mmol/L used as an objective for the first 6 hours of treatment in sepsis patients.

For all these reasons, we suggest to measure $ETCO_2$ and lactate levels in 4 separate occasions during early sepsis resuscitation over the first 6 hours of therapy. This could allow us to compare the changes in $ETCO_2$ with the lactate, and also find a value for an end point as a sepsis treatment goal. Furthermore, we believe that changes in $ETCO_2$ will be produced earlier during the sepsis management, allowing us to know if the patient is progressing well in a quicker way.

$ETCO_2$ could be a real-time, dependable, not invasive and easily obtained measure of early resuscitation on a sepsis code patient.

5. HYPOTHESIS

There is a good correlation between $ETCO_2$ and lactate levels; $ETCO_2$ monitoring may be used in the early resuscitation treatment in a sepsis code patient.

$ETCO_2$ levels in first 6 hours of treatment of a sepsis code patient are associated with in-hospital mortality.

6. OBJECTIVES

The main objective of this study is to determine if there is a correlation between blood lactate levels and $ETCO_2$, both being measured at 0, 1, 3 and 6 hours of early resuscitation treatment, in patients in whom both the sepsis code has been activated and they have been admitted to the HJT's emergency department.

Secondary end points of this study are:

- To determine a cut-off point for the $ETCO_2$ equivalent to the blood lactate level <2mmol/L as an early resuscitation goal.
- To determine the increase of $ETCO_2$ equivalent to the lactate clearance >10% as an early resuscitation goal.
- To determine if there is a relationship between $ETCO_2$ values after early resuscitation treatment and in-hospital mortality.

7. METHODOLOGY

7.1. Study design

The present study will be an observational longitudinal prospective cohort study. A cross-sectional analysis will also be performed within this study.

We have chosen a prospective cohort design in order to study the $ETCO_2$ change during the early resuscitation of sepsis and its correlation with lactate blood levels over time. Furthermore, the in-hospital mortality within the 28 first days will be also analyzed as compared to that based on the $ETCO_2$ values. The cross-sectional analysis will be performed in order to determine a cut-off point for $ETCO_2$ equivalent to blood lactate levels as an early resuscitation goal.

7.2. Setting and population of the study

The study population will be all patients admitted to the Hospital Josep Trueta of Girona emergency department due to sepsis, with the following inclusion and exclusion criteria:

7.2.1. Inclusion criteria

- Adults 18 years old or older.
- Sepsis code activation: patients with suspected infection or fever and one or more of the three following criteria (hypotension, tachypnea or mental disorders).
- Signed informed consent.

7.2.2. Exclusion criteria

- Vital prognosis < 6 months.
- Documented immunosuppression.
- History of asthma exacerbations or chronic obstructive pulmonary disease: The v/q mismatch in these patients could modify $ETCO_2$ values.

- Intubated patients: $ETCO_2$ monitoring in these patients is different from non-intubated patients.

7.3. Sample size

A non-probabilistic and consecutive sample recruitment will be applied to this study. All patients admitted to the HJT emergency department fulfilling the inclusion criteria will be possible candidates.

Sample size calculation is based on the free GRANMO software (34).

According to our main objective, we calculate the sample size for two quantitative variables: lactate values and $ETCO_2$. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, we need at least 103 patients with sepsis, with a correlation coefficient of 0.3 between the abovementioned variables. A dropout rate of 15% has been estimated.

The sampling method selected will be consecutive and we know that, every year, approximately 240 patients with sepsis are admitted to the emergency department of HJT. Considering that, the recruitment of the patients will be completed in 6 months (n=120).

As regards the secondary objective of in-hospital mortality, the estimated sample size, will allow us to detect a difference in the mortality hazard ratio of at least 2 units between patients with low and high ETCO2 values.

7.4. Variables

All the variables will be collected prospectively into the case report form attached in ANNEX IV.

In the context of our project, we cannot technically define our variables as independent and dependent, since it is a descriptive study and we are not looking for causality.

7.4.1. Main variables and measurement methods

- **Blood lactate levels**

The variable will be determined using four measurements: first measurement of lactate at sepsis code activation (L0), and then 3 more measurements after early resuscitation measures are initiated: at 1st hour (L1), 3rd hour (L3) and lactate at 6th hour (L6).

There are 3 different ways to express the variable:

- **Lactate levels**: Continuous quantitative variable
- **Lactate normalization**: Dichotomous variable with the following two categories. Accomplishment of lactate normalization, defined as L6 <2mmol/L or non-accomplishment of lactate normalization, defined as L6 >2mmol/L.
- **Lactate clearance**: Defined as LC= ((L0–L6) ×100)/L0. Also a dichotomous variable, with the following two categories. High lactate clearance (LC>10%) or low lactate clearance (LC<10%).

Arterial blood and venous blood have a different cut-off point for the lactate levels in order to predict organ dysfunction in a septic patient. Therefore, in our study we will use an arterial blood extraction following the reference value of lactate >2mmol/L as a sepsis criteria for severity.

Arterial blood will be drawn, using the same line as that used for the measurement of arterial blood gases. The first extraction will be taken at the time of diagnosis and before treatment. The 3 consecutive extractions will be taken at 1st hour, 3rd hour and 6th hour after early resuscitation treatment is started.

All the samples will be processed and analyzed in the emergency laboratory of HJT. The samples will be analyzed during the first 20 minutes of extraction to prevent false lactate

elevations. An amperometric lactate biosensor will be used for the lactate measurement since it is incorporated to the gasometer.

- **$ETCO_2$ value**

The variable will be determined using four measurements: first measurement of $ETCO_2$ at sepsis code activation (ET0), and then 3 more measures after early resuscitation measures are initiated: at st1 hour (ET1), 3rd hour (ET3) and at 6th hour (ET6).

There are 2 different ways to express the variable:

- **$ETCO_2$ levels**: Continuous quantitative variable
- **ETCO2 normalization**: It cannot be categorized because a cut-off point is not stablish yet. It is one of the secondary objectives.
- **$ETCO_2$ clearance**: Defined as $ETCO_2C$ =((ET0–ET6) × 100)/ET0. A dichotomous variable, with the following two categories. High $ETCO_2$ clearance ($ETCO_2C$>10%) or low $ETCO_2$ clearance ($ETCO_2C$<10%).

Continuous monitoring will be done with the capnography, but the value will be collected at the same time of the blood extraction for the lactate levels.

A portable constant monitor will be used for the $ETCO_2$ measurement. In the emergency department of HJT there are 2 different monitors, Philips IntelliVue MMS X2 and Philips IntelliVue MP70 bedside monitor (ANNEX III), both used in the management of septic patients. With these devices, the $ETCO_2$ measurement will be done with a mainstream sensor when the patient is intubated or with a sidestream sensor in the non-intubated patients. Both devices use the infrared absorption spectroscopy to continuously measure CO_2 values and provide a real-time CO_2 waveform and numeric values.

There are no important differences in the $ETCO_2$ monitoring between both devices since the mechanism of measurement is the same and both are calibrated.

The only differences are the parameters monitored and the way that the values are presented. However, during the study, all the patients will be monitored with the Philips IntelliVue MP70 bedside monitor as the first option, and only in case of unavailability or need of transfer, the Philips IntelliVue MMS X2 will be used. Thereby, we will minimize the possible bias.

- **In-hospital mortality**

It is a nominal dichotomous qualitative variable (Yes/ No). It only includes deaths at the hospital during first 28 days (emergency department, ICU, hospitalization…). It will be expressed as a percentage.

In the longitudinal prospective study of mortality, it will be described as a dependent variable, and $ETCO_2$ will be the independent variable.

7.4.2. Covariates

- **Age** (measured in years, at the moment of sepsis code activation)
- **Gender** (male or female)

Related to patient medical history:

- **Diabetes Mellitus** (Yes or No). Acute decompensations during sepsis could modify $ETCO_2$ values.
- **Cardiac insufficiency** (Yes or No). Acute decompensations during sepsis could modify $ETCO_2$ values.

Related to current episode:

- **Severity of sepsis** (sepsis or septic shock). We define septic shock as the need of vasoactive drugs in order to accomplish the early resuscitation goals at 6 hours of treatment.
- **Time to resuscitation treatment** (measured in hours).

- **Site of infection** (pneumonia, urinary tract, intra-abdominal, skin or soft-tissue, bone, meningitis, endocarditis, others (specify) and unknown. Pulmonary infection could modify the $ETCO_2$ measurement due to changes in v/q.
- **Appropriate resuscitation at 6 hours** (Yes: TAM above 65mmHg, diuresis > 0.5cc/h, Hb > 7 or No: TAM < 65mmHg, diuresis < 0.5cc/h, Hb < 7)

To sum up the variables, we have elaborate the table below:

	Variables		Description	Categories or value	Measurement
Main variables	Lactate	Lactate levels	Continuous quantitative	mmol/L	Blood extraction
		Lactate normalization	Categorical dichotomous	- Accomplishment (L6 <2mmol/L) - Non-accomplishment (L6 >2mmol/L)	Blood extraction at 6 hours
		Lactate clearance	Categorical dichotomous	- High clearance (>10%) - Low clearance (<10%)	LC= ((L0–L6) ×100)/L0
	$ETCO_2$	$ETCO_2$ levels	Continuous quantitative	ETCO2	Blood extraction
		$ETCO_2$ clearance	Categorical dichotomous	- High clearance (>10%) - Low clearance (<10%)	$ETCO_2C$=((ET0–ET6) × 100)/ET0
	In-hospital mortality		Nominal dichotomous qualitative	Yes/No	Death during 28 days in-hospital
Covariates	Age		Discrete quantitative	Number of years	Patient documentation
	Gender		Nominal qualitative	- Male - Female	Patient documentation
	Diabetes Mellitus		Nominal dichotomous qualitative	Yes/No	Patient medical history
	Cardiac insufficiency		Nominal dichotomous qualitative	Yes/No	Patient medical history
	Severity of sepsis		Nominal dichotomous	- Sepsis - Septic shock	Need of vasoactive drugs at 6 hours (septic shock)
	Time to resuscitation treatment		Continuous quantitative	Hours	Hours to first treatment action
	Site of infection		Discrete qualitative	- pneumonia, - urinary tract abdominal - skin, soft-tissue - bone - meningitis - endocarditis - others (specify) - unknown	Blood cultures, additional exams (Rx, CT, lumbar puncture…)
	Appropriate resuscitation at 6 hours		Nominal dichotomous	Yes/No	YES: the following: - TAM above 65mmHg - diuresis > 0.5cc/h - Hb g/dL> 7

7.5. Data collection and procedure

All data will be collected prospectively using a case report form elaborated for this study (ANNEX V), with the aim to collect all the needed information from patients admitted to the emergency department (ED) of HJT with sepsis.

Before the study starts, all the emergency physicians of HJT will attend an information session where important aspects of the sepsis code will be explained and also all the necessary information to assist the patients included in the study will be given.

Patients admitted to the ED of HJT who meet the inclusion criteria will be appropriately informed (ANNEX VI) about the procedures of the project and an informed consent (ANNEX VII) must be signed before inclusion in the study. In case of incapacity, consent will be required to first-degree relatives.

The data collection will be structured as follows:

- **Hour 0**: After the sepsis code activation, 2 peripheral venous lines will be places and a blood test (hemogram, coagulation, biochemistry) will be extracted. Then, an arterial blood extraction will be done for the **lactate (L0)** measurement. $ETCO_2$ monitoring will also be performed and **$ETCO_2$ ($ETCO_2$ 0)** value will be measured at the same time of blood extraction. Blood cultures will be extracted before initiating the empiric antibiotic. Early resuscitation treatment with crystalloids will also be performed according to the patient hemodynamic state and the sepsis protocol.
- **Hour 1**: A second arterial blood extraction will be done in order to obtain lactate **(L1)** levels. $ETCO_2$ **($ETCO_2$1)** value will be measured also at the time of blood extraction. Resuscitation treatment and monitoring will be performed according to the patient evolution and the sepsis code protocol.
- **Hour 3**: Same procedure that in hour 1. **(L3, $ETCO_2$3)**

– **Hour 6**: Same measurements as hour 1 and hour 3 **(L6, $ETCO_2$6)** According to the sepsis code protocol, if the patient meets one of the ICU transfer criteria (table 2), the ICU admission needs to be considered.

	Hour 0	**Hour 1**	**Hour 3**	**Hour 6**
Measurements	- Blood test - Arterial blood test (lactate) - Blood cultures - $ETCO_2$	- Arterial blood test (lactate) - $ETCO_2$	- Arterial blood test (lactate) - $ETCO_2$	- Arterial blood test (lactate) - $ETCO_2$
Treatment	- Empiric antibiotic - Early resuscitation treatment with crystalloids			
Monitoring (objectives)	- MAP > 65mmHg - Diuresis >0,5cc/kg/h - Lactate < 2mmol/L - Hemoglobin > 7g/d.			<u>ICU transfer criteria</u> - Need of vasoactive drugs to maintain MAP >65mmHg. - Anuria (<0,5cc/kg/h) - Lactate > 2mmol/L. - Respiratory insufficiency with the need of MV.

Table 1: *Data collection*

No more measurements will be done after 6 hours of patient admission to the ED. Only in-hospital mortality during the first 28 days will be taken into account and collected into the case report form.

Then, after completing the recruitment of patients 6 months after the start of the study, the data from these case report forms will be typed in a database created for this study in order to analyze all the information obtained.

8. STATISTICAL ANALYSIS

8.1. Univariate analysis

In the univariate analysis, we will define variables as categorical or quantitative. Results will be expressed using percentages and proportions for the categorical variables and using mean ± standard deviation or median (interquartile range Q1-Q3) for continuous quantitative variables, depending on whether they are normally distributed or not.

8.2. Bivariate analysis

In the bivariate analysis, the main variables are quantitative. Therefore, the correlation between blood lactate levels and $ETCO_2$ values will be analyzed with the Pearson correlation coefficient.

As regards the secondary objectives, the cut-off point of $ETCO_2$ equivalent to lactate clearance <2mmol/L will be identified with ROC curves since the variables are quantitative and categorical, respectively.

The clearance of $ETCO_2$ will be measured with the chi-square (X^2) test because both (lactate clearance and $ETCO_2$ clearance) are categorical variables.

Finally, the mortality will be measured with the Kaplan-Meier survival curves.

8.3. Multivariate

The multivariate analysis for the main objective will be analyzed using a multiple lineal regression test, adjusted for the potentially confounding effects of the selected covariates (age, gender, severity of sepsis, site of infection, appropriate resuscitation treatment).

The secondary objectives will also be adjusted for the potentially confounding effects of abovementioned covariates as follows:

The sensitivity and specificity of the cut-off point of $ETCO_2$ previously identified will be tested in multiple logistic regression analysis adjusted for the potential confounding variables.

$ETCO_2$ clearance previously identified to be equivalent to lactate clearance <2mmol/L in the bivariate analysis will also be tested using a multiple logistic regression test.

In case a confounding variable modifies the sensitivity or specificity of the cut-off point, or the $ETCO_2$ clearance, we will consider performing sub-analysis by categories for the confounding variables.

Finally, the mortality will be analyzed with the cox model.

9. ETHICAL CONSIDERATIONS

This research protocol will be presented to the Clinical Research Ethical Committee (CEIC, Comitè d'Ètica d'Investigació Clínica) of Hospital Josep Trueta in Girona and it can only be carried out after their approval.

The project will be executed according to the ethical principles established by World Medical Association in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects. Furthermore, we will take into consideration the Spanish Organic Law 14/2007, de Investigación Biomédica, which regulates biomedical investigation involving human beings in Spain.

According to "Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal", personal and clinical information of participants will be confidential and only used for the purpose of the research. Moreover, all data will be analysed anonymously. A separate document from the data collection sheet will be created to encode the name of the subject, assigning a number to each subject.

An information document about the study procedures will be given and the subjects will participate voluntarily in the study after giving their informed consent signed. Patients admitted to the emergency department who meet the inclusion criteria will be suggested to participate in the study as soon as they are capable. In case of incapability, we will seek informed consent from their legally authorized representative.

All the investigators will have to declare no conflict of interest.

10. LIMITATIONS

Analyzing our study, we acknowledge as follows:

Our study is designed as an observational longitudinal prospective cohort. We have chosen this design because we believe it is the best choice for our objective, but we acknowledge the intrinsic limitations of this type of study. We know that a prospective, controlled, randomized clinical trial is the best study for determining causality, but first we need to find if there is a correlation between $ETCO_2$ values related to lactate values in order to find a cut-off point for further studies such a clinical trial.

To collect data we will use a case report form filled for the ED physicians. This may cause an information bias if the form is incorrectly filled, so, an information session will be done before the study starts and all the physicians of the ED department will be taught on how to fill the case report form correctly. Furthermore, several meetings during the field work will be done in order to ensure good data collection and solve doubts.

We are aware of the fact that lactate measurements are a surrogate variable. For that reason, if the results of the study are relevant, we suggest that lactate measurements and $ETCO_2$ should be used to complement the other clinical data available.

About the procedure, we will measure blood lactate levels four times. We are aware that it is an invasive procedure but considering that sometimes our patients are critical, it is justified in order to do the best for treating them.

11. WORK PLAN AND CHRONOGRAM

This study is expected to last 1 year and 6 months. The sequence of activities that will be carried out during this time will be organized in the following 4 phases explained below:

- **Preparation and coordination phase – 6 months**

At the beginning of this study, the entire team of participants (investigators, collaborators and statisticians) will meet in order to specify the tasks of every member of the team and objectives and main variables will be determined.

After the meeting, the principal investigators will elaborate the current protocol. Once the protocol is definitely designed and before to proceed to the second phase, a positive evaluation to the CEIC may be required.

- **Field work and data collection - 7months**

During this stage, subjects will be selected with the inclusion/exclusion criteria described before and all the information about the study will be given to them. Data collection will start when the first patient will sign the informed consent, and it will end after 28 days in-hospital (or after discharged from the hospital or death) of the last recruited subject.

Data collection will be done in the pre-stablish form attached in ANNEX V. The form will not contain the patient name. An encoded number from 001 to 120 will be written in the form instead, in order to protect personal information.

During the field work, researchers will meet periodically (every month in the beginning and less frequently at the end) in order to ensure a good data collection and to identify deficiencies and correct methodologic flaws.

Data collection will last 6 months. Once all the data is collected, principal investigators of the study will introduce it in a database created for this study.

- **Data analysis - 3 months**

After all the data collection sheets are processed, an external statistician will analyze all the data obtained using the appropriate statistical tests.

- **Publication and dissemination - 3 months**

Final analysis of the results and the researchers will edit a scientific paper to publish and diffuse the results.

To better understand the work plan, it is resumed into a chronogram:

TASKS	PERSONAL	2016		2017													2018		
		N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	
PREPARATION AND COORDINATION																			
Protocol elaboration	Investigation team																		
Research team meeting and coordination	All research team																		
DATA COLLECTION AND FIELD WORK																			
Data collection	Physicians of HJT ED.																		
Data introduction to the database	Investigation team																		
DATA ANALYSIS																			
Statistical analysis	Statistician																		
Interpretation of the results and discussion	All research team																		
PUBLICATION AND DISSEMINATION																			
Scientific publication	Investigation team																		

12. BUDGET

STUDY BUDGET	COST
Personal expenses	
- Investigation team	0 €
Goods and services costs	
- Qualified statistician: - 30€/h x 3h/day x 2day/week x 8 week……. - Physicians formation (qualified physician in sepsis): - 30€/h x 2h/day x 2 days…….	 1440 € 120 €
	Subtotal: 1560 €
Publication and dissemination	
• Travel and subsistence costs - National conferences attendance - Inscription……. - Transport costs…… - Accommodation…… - International conferences attendance - Inscription…… - Transport costs…… - Accommodation…… • Publication costs ……	 300 € 150 € 250 € 300 € 450 € 250 € 1000€
	Subtotal: 2700 €
	TOTAL: 4260 €

Neither personal expenses nor diagnostic procedures have been included in the budget. We consider that none of the activities needed for the study differ from normal clinical assistance.

13. FEASIBILITY

The physicians of HJT emergency department will perform the study. They are all experienced doctors and well trained in the sepsis code protocol in the ED. Furthermore, an information session will be performed before the study starts.

In order to develop this study, we need to have access to blood analysis and a capnogram. Both services are already available in the normal clinical assistance in the emergency department.

14. IMPACT

The final aim of this study is to improve the sepsis management protocol in the emergency department. If the results obtained in our study are relevant and show a good correlation between $ETCO_2$ values and lactate levels, we might use $ETCO_2$ monitoring for the early resuscitation treatment in a septic patient.

The use of $ETCO_2$ as a measurement in sepsis monitoring would be a step forward in the sepsis management, since it is more accessible, non-invasive and provided on a real-time basis. Moreover, the $ETCO_2$ monitoring is nowadays widely used in the ED for the early evaluation of patients, so, with increasing knowledge in this field, new functions could be considered in order to detect people who are in lactic acidosis.

Further research is necessary to determine which of the measures (lactate or $ETCO_2$) is better for the management of septic patients and whether the outcome is even better if both measures are used in combination.

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16. ANNEXS

16.1. Annex I

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Table 1: SOFA score

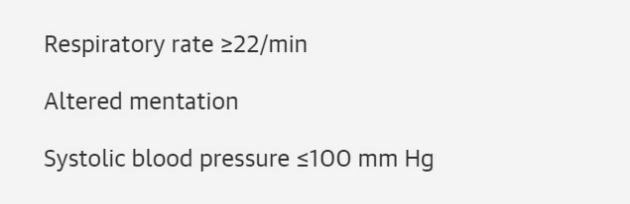
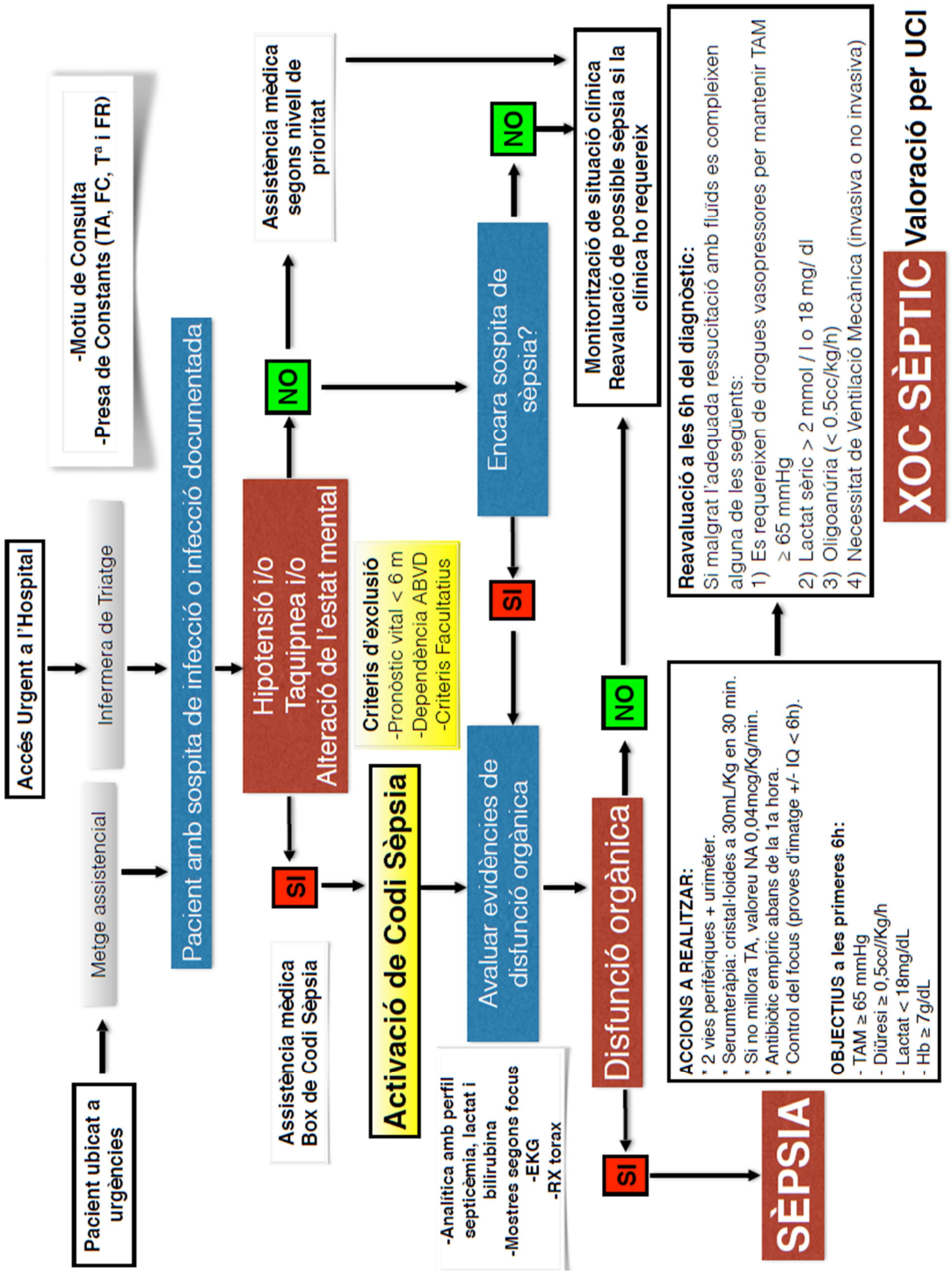


Figure 1: Quick SOFA score (qSOFA)

16.2. Annex II


Pacient ubicat a urgències
Accés Urgent a l'Hospital
Metge assistencial
Infermera de Triatge
-Motiu de Consulta
-Presa de Constants (TA, FC, Tª i FR)
Pacient amb sospita de infecció o infecció documentada
Hipotensió i/o Taquipnea i/o Alteració de l'estat mental
NO
Assistència mèdica segons nivell de prioritat
SI
Assistència mèdica Box de Codi Sèpsia
Activació de Codi Sèpsia
Criteris d'exclusió
-Pronòstic vital < 6 m
-Dependència ABVD
-Criteris Facultatius
-Analitica amb perfil septicèmia, lactat i bilirubina
-Mostres segons focus
-EKG
-RX torax
Avaluar evidències de disfunció orgànica
Encara sospita de sèpsia?
NO
SI
Disfunció orgànica
NO
Monitorització de situació clínica
Reavaluació de possible sèpsia si la clínica ho requereix
SI
SÈPSIA
ACCIONS A REALITZAR:
* 2 vies perifèriques + urimèter.
* Serumteràpia: cristal·loides a 30mL/Kg en 30 min.
* Si no millora TA, valoreu NA 0,04mcg/Kg/min.
* Antibiòtic empíric abans de la 1a hora.
* Control del focus (proves d'imatge +/- IQ < 6h).
OBJECTIUS a les primeres 6h:
- TAM ≥ 65 mmHg
- Diüresi ≥ 0,5cc/Kg/h
- Lactat < 18mg/dL
- Hb ≥ 7g/dL
Reavaluació a les 6h del diagnòstic:
Si malgrat l'adequada ressucitació amb fluïds es compleixen alguna de les següents:
1) Es requereixen de drogues vasopressores per mantenir TAM ≥ 65 mmHg
2) Lactat sèric > 2 mmol / l o 18 mg/ dl
3) Oligoanúria (< 0.5cc/kg/h)
4) Necessitat de Ventilació Mecànica (invasiva o no invasiva)
XOC SÈPTIC Valoració per UCI

16.3. Annex III

(*3) ANTIBIÒTIC EMPÍRIC

FOCUS INFECCIÓS	INFECCIÓ DE LA COMUNITAT	INFECCIÓ RELACIONADA AMB CENTRE SANITARI O NOSOCOMIAL
RESPIRATORI	Ceftriaxona 2g/24h ev + Levofloxacino 500mg/12h Si sospita pneumònia aspirativa: amoxi-clav 2g/8h o moxifloxacino 400mg/d ev	Si risc de multiresistent (veure protocol): (Piper-Tazo o Imip o Merop o Cefepime) + levoflox Si sospita SARM: Afegir Vanco 1g/12h o linezolid 600mg/12h ev Si aillament de enterobacteri BLEE, pautar imipenem o meropenem.
ABDOMINAL	Piper-Tazo 4 g/6h Þ Imipenem 1g/8h o Meropenem 1g/8h o Cefalosp 4ª (cefepime 2g/8h) + metro 500mg/6h, o Cipro + metro 15 mg/kg dosi inicial, seguit de 7,5 mg/kg/8 h ev (en al·lèrgics a Peni) o Aztreonam 2g/8h + metro	Imipenem o Meropenem o (cefalosporina de 4ª + metronidazol). Cipro 400mg/8h + Metro (al·lèrgia a Peni) o Aztreonam + metro Si AB previ valorar afegir vanco o linezolid i/o fluconazol
UROLÒGIC	Piper-Tazo 4g/6h o carbapenem 1g/8h (+/- amikacina si xoc sèptic.)	Carbapenem 1g/8h +/- amikacina 15mg/Kg/24h si xoc sèptic. Si al·lèrgia a penicil·lina: cipro + amika
PELL I TXTS TOUS	**Impetigen i cel·lulitis** amoxicil·lina-clavulànic 1g/8h ev o clindamicina 600mg/8h ev. **Peu diabètic greu:** imipenem 500mg/6h o meropenem 1g/8h. **Infecció ferida quirúrgica:** Abdominal o genitourinària: pip-tazo o carbapenem o quinolona +clindamicina (al·lèrgia peni) No abdominal: cloxacil·lina 2g/4h ev. **Fascitis necrotitzant:** (piper-tazo o carbapenem) + clindamicina + (Vancomicina 1g/12h, o linezolid 600mg/12h o daptomicina) . En cas de mossegada o abscés subcutani i punció planta peu: veure protocol.	Sospita d'infecció per SARM: afegir Vancomicina 1g/12h, o linezolid 600mg/12h .
DISPOSITIUS EV		Meropenem 1g/8h + Vancomicina 1g/12h +/- equinocandina
NEUROLÒGIC	Ceftriaxona 2g/12h + ampicil·lina 2g/4h (si sospita pneumococ: cefotaxima 300mg/Kg/4-6h ev precedit de dexametasona 10mg/6h ev.) Si al·lèrgia a peni: vancomicina 15-20mg/Kg/8-12h + rifampicina 15mg/Kg/dia Valorar aciclovir 10mg/Kg/8h: 500-750mg/8h ev	Meropenem 2g/8h + vancomicina 15-20mg/8-12h Si al·lèrgia a peni: Vancomicina +aztreonam 2g/8h
ENDOCARDITIS	**Vàlvula nativa i Vàlvula protèsica (posada >1any):** :(Peni G 2MUI/4h o Ampi 2g/4h) + cloxa 2g/4h+genta 1mg/kg/8h (alternatiu: vanco 1g/12h + genta) **Vàlvula protèsica (posada<1any):** vanco 15mg/Kg/12h (màx 2g/d)+ genta 1mg/Kg/8h (màx 80mg/8h) + Rifampicina 300mg/8h vo **ADVP:** Cloxa 2g/4h ev + genta	**ADVP i sospita SARM:** Vancomicina 1g/12h ev + gentamicina 1mg/Kg/8h. **No ADVP i vàlvula nativa i sospita SARM:** vanco 1g/12h + gentamicina 1mg/kg/8h
SÈPSIA ORIGEN DESCONEGUT	(Imipenem 1g/6h o meropenem 2g/8h o Piper-tazo 4.5g/6h) + amikacina +/- vancomicina. Si al·lèrgia a peni, substituir meropenem per ciprofloxacino 400mg/8h o aztreonam 2g/8h o tigeciclina 100mg dosi atac (seguit de 50mg/12h)	(Imipenem 1g/6h o meropenem 2g/8h) + vancomicina 15-20mg/Kg/8-12h + amikacina 15-20mg/Kg/d +/- caspofungina.

16.4. Annex IV

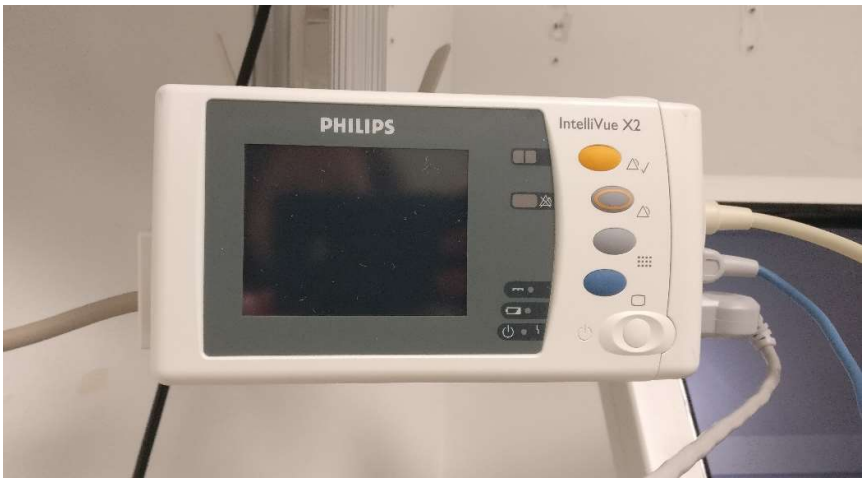


Image 1: Philips IntellVue MMS X2

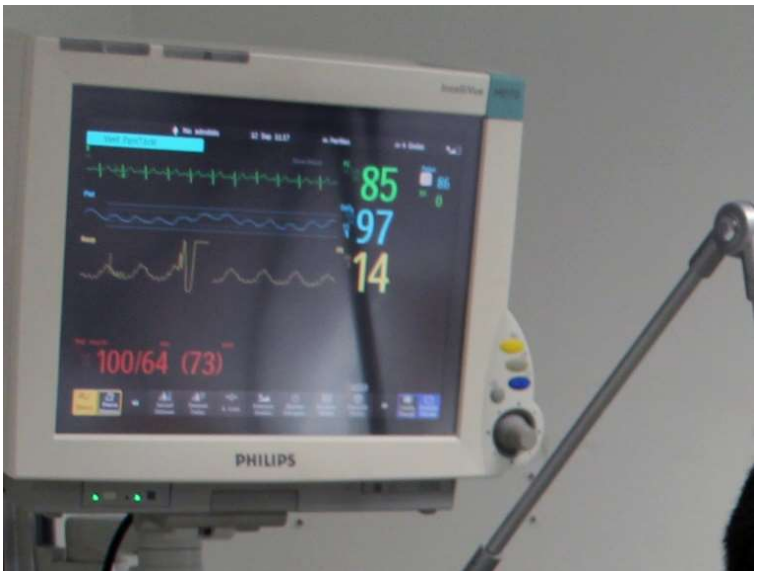


Image 2: Philips IntellVue MP70 bedside monitor

16.5. Annex V

CASE REPORT FORM for the study named: Evaluating the use of ETCO2 in a sepsis code patient, as an objective for the first 6 hours resuscitation treatment in the emergency department of HJT.

Instructions:

- *Please write the patient's identification number in the boxes above.*
- *Read carefully and mark with "X" in the most suitable option in the boxes.*
- *Please mark all the boxes. Verify you have marked the right box and that the X is clear.*
- *Search carefully for exclusion criteria:*
  - Vital prognosis <6 months
  - Documented immunosuppression
  - History of asthma or chronic obstructive pulmonary disease
- *If you have doubts or you have problems with any answer or item, please contact with the email address reserch.trueta.sepsis@gmail.com, and you will receive an answer shortly.*

DATE: _ _ / _ _ / _ _

INVESTIGATORS NAME AND ID:

- _____
- _____

SIGNATURES

PATIENT INFORMATION

- PATIENT'S IDENTIFICATION NUMBER: _ _ _
- DATE OF BIRTH: _ _ / _ _ / _ _
- GENDER: F__/M__
- SIGNED CONSENT? YES__

SEPSIS CODE ACTIVATION

- DATE AND TIME OF SEPSIS DIAGNOSE: _ _ / _ _ / _ _ at _ _:_ _
- INITIAL VITAL CONSTANTS: BP _ _/_ _ mmHg
  Tª _ _._ ºC
  CR _ _ x'
  RR _ _ x'
  Glasgow _ _

MEDICAL HISTORY:

- HISTORY OF ASTHMA EXACERBATIONS: YES__ / NO__/ UNKNOWN__
- HISTORY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: YES__/ NO__
- DIABETES MELLITUS: YES__ / NO__
- CARDIAC INSSUFICIENCY: YES__ / NO__
- INTUBATED PATIENT: YES__ / NO__

INFECTION:

- SITE OF INFECTION (X)
  - urinary tract infection __
  - pneumonia __
  - intra-abdominal infection __
  - skin or soft tissue infection __
  - meningitis __
  - bone or joint infection __
  - endocarditis __
  - implantable device infection __
  - others (specify) _____
  - unknown __

MANAGEMENT

HOUR 0

- Local infection:
  - Is there a drainable focus? YES__ / NO__
- Mean arterial pressure (mmHg): _____
- Diuresis (ml/kg/h): _____
- **Lactate** (mmol/l): _____
- **$ETCO_2$**: _____

HOUR 1

- **Lactate** (mmol/l): _____
- **$ETCO_2$**: _____

HOUR 3

- **Lactate** (mmol/l): _____
- **$ETCO_2$**: _____
- Mean arterial pressure (mmHg): _____
- Diuresis (ml/kg/h): _____

HOUR 6

- MAP (mmHg): _____
- Diuresis (ml/kg/h): _____
- **Lactate** (mmol/l): _____
- **$ETCO_2$**: _____
- Need of vasoactive drugs to maintain MAP >65mmHg: YES__ / NO__
- Respiratory insufficiency with the need of MV: YES__ / NO__

RESUSCITATION TREATMENT:

- DATE AND TIME OF ADMINISTRATION OF EARLY RESUSCITATION TREATMENT (CRYSTALLOIDS): _ _ / _ _ / _ _ at _ _:_ _
- CRYSTALLOIDS (note pharmacological name and dose (30mL/Kg)): _____

EMPIRICAL ANTIBIOTIC:

- DATE AND TIME OF ADMINISTRATION OF EMPIRICAL ANTIBIOTIC: _ _ / _ _ / _ _ at _ _:_ _
- EMPIRICAL ANTIBIOTIC (note pharmacological name, dose and means of administration): _____

SEVERITY OF SEPSIS (at 6 hours of resuscitation treatment)

- SEPSIS (no need for vasopressors to maintain MAP and lactate) __
- SEPTIC SHOCK (need for vasopressors to maintain MAP and lactate) __

FOLLOW-UP OF THE MORTALITY IN-HOSPITAL

- DEATH IN-HOSPITAL DURING FIRST 28 DAYS: YES__ / NO__
- CAUSE OF DEATH: _____
- SERVICE OF DEATH: _____

16.6. Annex VI

FULL D'INFORMACIÓ PEL PARTICIPANT

CODI DEL PROJECTE: _____

1) **Generalitats del projecte:** El present estudi serà dut a terme per el departament d'urgències de l'Hospital Universitari de Girona Doctor Josep Trueta, en un període de temps aproximat d'un any i mig. Es tracta d'un estudi observacional. El projecte de recerca ha estat valorat i aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Doctor Josep Trueta. Els participants en l'estudi participaran facilitant les seves dades.
2) **Objectius i finalitats de l'estudi:** Amb aquest estudi es pretén estudiar la relació entre el lactat, una molècula que es troba a la sang, i l'$ETCO_2$, una mesura que valora la quantitat de CO_2 durant l'espiració, en pacients que presenten una sèpsia. La finalitat del projecte és trobar una prova menys invasiva per a la monitorització dels pacients amb sèpsia.
3) **Participació:** La seva participació en l'estudi és totalment voluntària i no s'obtindrà cap compensació econòmica. La tasca del participant, donat que es tracta d'un estudi observacional, consta únicament en facilitar l'accés i l'ànalisi de les seves dades als investigadors.
4) **Confidencialitat i protecció de dades:** S'adoptaran les mesures per garantir la confidencialitat de les seves dades en compliment de la Llei Orgànica 15/1999 i les dades recollides seran gestionades de forma anònima i només utilitzades amb fins d'investigació. També es garantiran els principis establerts per la Llei d'Investigació Biomèdica 14/2007.
5) **Resultats i beneficis de la investigació**: El pacient està en el seu dret de ser informat dels resultats de la investigació. Els beneficis derivats de la investigació, tant poden beneficiar al participant com a altres persones, i aquests seran adequadament utilitzats per assolir els objectius de l'estudi i serviran de base per futures investigacions en aquest àmbit.

Gràcies per la seva participació.

16.7. Annex VII

CONSENTIMENT INFORMAT

Declaració del participant: Jo,

_____ o jo,

_____ representant legal de

_____.

Declaro que:

- He llegit el full informatiu sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte l'estudi.
- He rebut suficient informació sobre l'estudi.
- He estat informat per l'investigador.....de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària.
- Entenc que s'adoptaran les mesures per garantir la confidencialitat de les meves dades en compliment de la Llei Orgànica 15/1999 .
- **Lliurament, dono la meva conformitat a l'ús de les meves dades per fins relacionats amb el projecte anomenat: Evaluating the use of $ETCO_2$ in a sepsis code patient, as an objective for the early resuscitation treatment in the emergency department of HJT.**

Firma del participant Firma de l'investigador

Data: __/__/__