ASSOCIATION BETWEEN LACTATE LEVELS AND APPROPRIATENESS OF EMPIRIC ANTIBIOTIC TREATMENT IN SEPTIC PATIENTS IN THE INTENSIVE CARE UNIT

A PROSPECTIVE COHORT STUDY

FINAL DEGREE PROJECT

Universitat de Girona
Facultat de Medicina

Hospital Universitari de Girona Doctor Josep Trueta
Institut Català de la Salut
Servei de Medicina Intensiva (UCI)

Author: LAURA VIVES COLILLES
Tutor: DR. JOSEP-MARIA SIRVENT
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A special mention to Doctor Sirvent,
and all the personal in the intensive care unit,
who have patiently taught me.
And all those who have taken the time to read this work.

"Preventable death is a tragic waste for which nothing can compensate and from which we can look for no crumb of comfort."
Henry James

INDEX

1. ABREBIATIONS

ER	Emergency room
HJT	Hospital Josep Trueta
ICU	Intensive care unit
MAP	Mean arterial pressure
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential [Sepsis-related] Organ Failure Assessment

2. ABSTRACT

ASSOCIATION BETWEEN LACTATE LEVELS AND APPROPRIATENESS OF EMPIRIC ANTIBIOTIC TREATMENT IN SEPTIC PATIENTS IN THE ICU

Introduction: Sepsis is a major health issue nowadays. A massive progress has been done since the creation of the Surviving Sepsis Campaign in 2001 in terms of diagnosis, management and outcome, but there still is a long way to go.
Still between 10 and 30 per cent of prescribed empirical antibiotics in the ICU are inappropriate (1). It has been proven that inappropriateness of empiric antibiotic treatment is independently associated with a higher mortality (2).

Objectives: The goal of this study is to determine if there is an independent association between lactate measurements 24h after diagnosis of sepsis (lactate normalization and lactate clearance) and appropriateness of antibacterial treatment. In order to contribute to reduce the rate of patients receiving inappropriate empiric antibiotics.

Methodology: Longitudinal prospective cohort performed in the ICU of the third level teaching facility, Hospital Josep Trueta, in Girona. The study will be performed between 2016 and 2019.

Participants: All patients with a community-acquired sepsis or septic shock admitted in the ICU between January 2017 and December 2019.

Key words: (MeSH terms) sepsis, septic shock, lactic acid, cohort studies, intensive care units, anti-bacterial agents.

3. BACKGROUND

3.1. What is sepsis?

It is important to set the definition of sepsis and the concepts related to it to understand the aim of this work. Since these definitions have been in constant revision, we will use the ones stated in the most recent update about the matter.

Sepsis[1] is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (3,4). Sepsis is a syndrome conditioned by both pathogen and host factors. This fact contributes to the heterogeneity of the syndrome, and makes it very diverse and difficult to define with exactitude.

Sepsis is not the result of adding up the signs and symptoms of an infection and an inflammatory response or SIRS, it also includes an organ dysfunction caused by a very complex pathobiology. It seems that the host response amplifies the pathogenic effect of the infection per se. It involves early activation of both pro- and anti-inflammatory responses, along with major modifications in non-immunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation (3).

[1] Sepsis: etymologically comes from Greek, it means putrefaction.

3.2. Epidemiology

Sepsis is indubitably a universal main health issue. Sepsis and Septic shock incidence is not only very high but it has also been increasing over the last three decades (5,6). True incidence of sepsis is unknown and there is a disparity between the epidemiological studies that have researched into it.

Even though there are more modest estimates, the last evidence published states that incidence of sepsis and severe sepsis during the last ten years in high income countries is 437 and 270 cases per 100.000 person-years for sepsis and septic shock respectively (6). Sepsis incidence is increasing mainly due to aging of population and its consequential raise of chronic health conditions, such as diabetes, chronic lung disease, chronic kidney failure, human immunodeficiency virus, and iatrogenic immunosuppression (7). It has also been found to have an increased risk of developing or worsening a chronic illness such as chronic kidney failure (8).

Septic patients in the developed world, have a hospital mortality rate of 25,8% outside ICU and 16,2% in the ICU, according to recent studies. Septic shock patients have a mortality rate of almost 50% (6,8–10). This data sets sepsis as a leading cause of morbidity and mortality, and it has encouraged researchers around the world to find evidence about every different aspect of sepsis, such as epidemiology, diagnosis and management.

3.3. Diagnosis

The current clinical characterization of sepsis (3) has been simplified in comparison to precedent definitions, published in 1991(11) and 2001(12). Nowadays it only distinguishes two concepts: **sepsis** and **septic shock**.

Sepsis is clinically defined as an organ dysfunction consequent to an infection. Currently the best approach to assessing organ dysfunction is using a scale that objectifies the diagnostic process. SOFA[2] is the scale which has proved to discriminate mortality the best, compared to others (3).

Septic shock is an aggravation of sepsis, in which underlying circulatory and cellular metabolism abnormalities are severe enough to substantially increase mortality. Clinically, it translates into persisting hypotension requiring vasopressors despite an adequate volume resuscitation, to attempt maintaining both parameters, **mean arterial pressure** (***MAP)*** above 65mmHg and ***serum lactate*** levels below 2mmol/L, explained in detail as follows. With these criteria, hospital mortality of septic shock is 40% (3).

- ***Mean arterial pressure***[3] is the main indicator used to asses hypotension in septic patients. It has been proven that an MAP higher than 65 mmHg ensures a correct organ perfusion (13).

[2] SOFA includes the following variables: PaO_2, Glasgow coma scale score, MAP, administration of vasopressors, serum creatinine or urine output, bilirubin and platelets. To evaluate respiration, central nervous system, cardiovascular, renal, liver and coagulation.

[3] MAP = (2 Diastolic Pressure + Systolic Pressure)/3

- Even though ***serum lactate*** is a more controversial concept, because of the complexity of its metabolism, it irrefutably is a valuable severity and mortality predictor (3). It will be explained more thoroughly in the section 3.5.

3.4. Management of sepsis

Management of severe sepsis and septic shock syndrome has changed drastically since the beginning of the new century. The foundation of the surviving sepsis campaign in 2001 promoted the creation of an international guideline to standardize the critical care of the septic patient.

The last published guidelines were in 2012 (14), and there was a brief update in 2015 that has also been considered (15). This section will summarize the actions recommended in the mentioned guidelines which we consider the most relevant to the study.

We identify three main pillars in the initial management of sepsis (16). They should be controlled among the first 24 hours. Hemodynamic resuscitation, broad spectrum antibiotic therapy and source control.

- **Hemodynamic resuscitation**: Using crystalloid fluids and vasoactive agents if needed to ensure a correct perfusion of the organs.

  The physiopathology behind this step is quite clear. The cytotoxic effect of sepsis produces hypotension, for two main reasons: relaxation of smooth muscle tissue of the vessels, which reduces peripheral vascular resistances and hypovolemia (4). Hypotension leads to organic hypoperfusion, therefore,

restitution of normal organic arterial blood flow is a critical step to revert the severe state the septic patient is in.

The current guidelines consider reanimation with fluids one of the most urgent measures, to be performed during the first three hours. Firstly 20-30 ml/kg of crystalloid fluids have to be administered, to recover volume. If MAP or lactate persist lower than 65 mmHg or higher than 4 mmol/l respectively, a vasopressor needs to be administered, preferably norepinephrine, and the patient needs to be monitored with more aggressive measures (14,15).

There also has to be a strict control of fluid balance. On one hand, volemia and tension has to be under control, keeping the MAP higher than 65 mmHg and ensuring a minimum amount of diuresis (0,5 ml/kg/h). And on the other hand, it is crucial to make sure the patient isn't overcharged with fluids maintaining a negative balance of liquids, meaning that the amount of diuresis should be higher than the liquid intake of the patient. A positive balance of liquids has been proven to increase mortality (17).

Therefore, a patient is considered to be correctly reanimated taking in account the following parameters at 24h after diagnosis of sepsis: MAP, lactate measurements, diuresis and clinical evolution.

- **Broad spectrum antibiotic therapy**: It is the second pillar of management of sepsis, and the one that concerns the current work the most. There are two main factors related to antibiotics that have an impact on mortality. Time to empiric antibiotic and appropriateness of empirical antibiotic.

Time to empiric antibiotic

Early administration of antibiotics after diagnosis of sepsis is important for a good outcome (14), every hour of delay represents an increase in mortality of 7% (18).The current guidelines recommend administering the antibiotic within the first hour after diagnosis of sepsis (14).

Appropriateness of empirical antibiotic

In this work, the concept of ***appropriate empirical antibiotic*** means having treated the patient empirically with a sensitive antibiotic in the antibiogram, and ***inappropriate empirical antibiotic*** means failing to do so.

Inadequate empirical antibiotics are associated to higher morbidity and mortality rates in septic patients (1,2,19–21).

Unfortunately, it's impossible to be certain of the most adequate antibiotic needed until the results of the bacterial cultures and the antibiogram are available, which can prolong between 48 and 72 hours. During this period, empirical antibiotics will have to be administered, taking into account local hospital protocols[4] and clinical singularities of each patient.

The most important characteristics of the patient that should be considered are three. Firstly, common aspects of any pharmacological prescription (age, hepatic and renal insufficiencies, pregnancy, intolerances and allergies, etcetera). Secondly the site of infection, it will provide orientation for the spectrum that should be covered. And thirdly those characteristics that suggest

[4] Attached in ANNEX 1.

a resistant infection, which is related to a higher rate of inappropriate antibiotic treatment (22), such as a prolonged stay in the hospital or another health care facility or an antibiotic treatment during the past month. (23)

Having to consider these many factors, makes the choice of an empirical antibiotic quite complex. We want to prescribe an antibiotic therapy that has a high probability of covering the microorganisms responsible for the infection, without producing more harm to the patient with the toxicity of an unnecessary overly intense treatment (24). Meaning that, although it would be ideal, covering the totality of the microorganism spectrum isn't an option.

Although being thorough when chooseing the most suitable antibiotic can prevent a lot of inappropriate choices, still between 10 and 30 per cent of critically ill septic patients have been found to be treated with inappropriate empirical antibiotics depending on the series (1,25,26). Therefore, we consider it is imperative to decrease this rate to improve ICU outcomes.

- **Source control**: Defined as drainage of infected fluids, debridement of infected soft tissues and removal of infected devices or foreign bodies (27).

  As the best way to reduce the bacterial inoculum, the guidelines recommend to determine the need for source control and to perform the least invasive procedure possible if the action is needed within the first 12 hours after the diagnosis of sepsis (grade of recommendation 1C) (14).

3.5. Lactate, a biomarker of sepsis

Lactate is considered to be an indicator of anaerobic cellular activity in sepsis. It rises when organ perfusion is menaced. When oxygen is not present in high enough concentrations, the compromised cells switch to anaerobic metabolism in order to function, leading to a higher lactate production. Theoretically, it can also be altered by many other processes such as insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, inhibition of pyruvate metabolism, and reduced hepatic clearance (28,29).

Nevertheless, the prognostic value of lactate is irrefutable. It is known for being the best surrogate of anaerobic metabolism related to cellular hypoxia, over venous oxygen saturation and central venous pressure. Lactate is often used for diagnosis and management of sepsis as an indicator of global hypoperfusion and shock (14). It has been found to be the best mortality predictor after resuscitation (30), an indicator of severity, and a predictor of short-term and long-term mortality (31).

Many different ways to interpret lactate have been explored; we will expound the two that have a higher level of evidence behind them. We can analyse lactate as a single measurement in time, as in lactate normalization, or use it as a dynamic parameter, calculating lactate clearance.

- Lactate normalization: Defined as a value of lactate below 2 mmol/l[5] at a certain time (30).
- Lactate clearance: It represents the variation of lactate concentration during the first 24 hours. A significant decrease is considered to be higher than 10% or more of initial lactate by most publications about this topic.

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

[5] The reader might have noticed that the guidelines use 4 mmol/l of lactate as the end point for resuscitation. But most of the studies about the subject use 2 mmol/l of lactate as a cut off point and also, it is the one used most commonly in the clinical practice. In this work, we will apply the second, 2 mmol/l.

4. JUSTIFICATION

In 2003 a multicentre prospective cohort performed in Spain demonstrated that patients with a community-acquired sepsis admitted in the ICU that were treated with inadequate empirical antibiotics had a higher mortality rate (2). This study demonstrates that choosing the wrong empirical antibiotic is an important risk factor for bad prognosis for the population of the current study. Consequently, we believe that some actions should be taken to reduce the rate of patients treated with an inadequate empirical antibiotic.

Given that the choice of an empirical antibiotic is highly complex, we suggest studying the relationship between lactate blood levels and appropriateness of empirical antibiotics so that, if the results are favourable, a usable indicator can be incorporated into the said choice. We believe that lactate might be a useful biochemical parameter because it has already been related to better outcomes after using other treatments, such as reanimation therapies that revert hypotension.

To accomplish our objective, we propose measuring lactate at the moment of diagnosis and 24 hours after, when according to current guidelines, hemodynamic resuscitation and source control should already be under control. Therefore, these lactate measurements would mainly be predicting antibiotic appropriateness. We will study lactate in two forms: lactate normalization, which corresponds to the absolute lactate concentration at hour 24 and lactate clearance, which is a relative value that also takes in account the initial lactate concentration.

If the results of the study are favourable, when lactate measurements indicate so, we will suggest to amplify the spectrum of the chosen antibiotic therapy.

5. HYPOTHESIS

We believe that blood lactate levels higher than 2 mmol/l, at 24 hours of the first antibiotic administration, in patients with community-acquired sepsis in the ICU, are associated with an inappropriate choice of empirical antibiotic therapy.

We presume that a lactate clearance, at 24 hours of the first antibiotic administration, lower than 10%, in patients with community-acquired sepsis, is associated with an inappropriate choice of empirical antibiotic therapy, in the ICU.

6. OBJECTIVES

One objective of this study is to determine if there is an independent association between blood lactate levels, at 24 hours of administration of the first antibiotic, and appropriateness of empirical antibiotic in patients with community-acquired sepsis admitted in the ICU.

Another objective of this study is to determine weather there is an independent association between lactate clearance, at 24 hours of administration of the first antibiotic, and appropriateness of empirical antibiotic or not in patients with community-acquired sepsis admitted in the ICU.

7. METHODOLOGY:

7.1. Study design

According to the characteristics of the study we are planning, the most suitable design is a prospective cohort.

7.2. Setting and population of the study

The study will be performed in the ICU of the third level teaching facility, Hospital Josep Trueta in Girona, Catalonia, Spain.

The goal population of the study is any patient admitted in the ICU with a community-acquired sepsis.

7.2.1. Inclusion criteria

- Patients older than 18 years old.
- Community-acquired sepsis: patients without a prior stay in the hospital longer than 48h.
- With signed informed consent.

7.2.2. Exclusion criteria

- Terminal malignancy.
- Documented immunosuppression (caused by an illness or pharmacological).
- Patients with HIV: this disease can cause a very abnormal cellular behaviour.

7.3. Patient selection and sample size

To calculate sample size, we have used the POISSON approximation. Accepting an alpha risk of 0.05 and a beta risk inferior to 0.2 in a bilateral sampling. We need at least **291** patients with a lactate clearance higher than 10% and **192** patients with a lactate clearance lower than 10%, to detect a minimum relative risk of 1.5, estimating the expected incidence in patients with a lower lactate clearance to be 0.25, and expecting a rate of loss during follow up of 1%.

The sampling method selected will be consecutive. Considering the ICU in HJT admits around 300 patients with the requested characteristics, we will recruit patients during 2 years.

We have only calculated the sample size once, we consider that the value of expected incidence will be similar for both independent variables: lactate normalization and lactate clearance. After recruiting all the subjects, the sample size will be revaluated.

7.4. Variables

All information will be collected from the digital medical history of the patient, into the case report form attached in the annex 5.

7.4.1. Independent variables

Our independent variables will be determined using two measurements: lactate at diagnosis of sepsis (L0) and lactate 24 hours after diagnosis (L24).

- **Lactate normalization:** Dichotomous variable with the following two categories. Accomplishment of lactate normalization, defined as L24<2 mmol/L or non accomplishment of lactate normalization, defined as L24>2 mmol/L.
- **Lactate clearance:** Defined as $\mathrm{LC} = \frac{(\mathrm{L0}-\mathrm{L24})\times 100}{\mathrm{L0}}$. Also a dichotomous variable, with the following two categories. High lactate clearance (LC>10%) or low lactate clearance (LC<10%).

An arterial blood sample will be extracted, using the same tube as the arterial blood gas analysis. The first sample will be taken at the time of diagnosis of sepsis, in the emergency room or in it's defect, in the ICU. The second sample will be taken 24h after diagnosis of sepsis, in the ICU.

The samples will be processed and analysed properly in the emergency laboratory of the hospital.

7.4.2. Dependent variable

The outcome variable is the **appropriateness of antibiotic treatment**. There are two outcome options: Appropriate antibiotic treatment or inappropriate antibiotic treatment.

A blood sample and samples of any possible origin of the infection (sputum, urine, intra-abdominal pus, skin injuries, among others) will be collected before starting the empirical antibacterial treatment. They will be processed and cultivated in the microbiology laboratory of HJT. An antibiotic sensitivity test will be performed as standardised by the local protocol.

As soon as the microbiology sample is extracted the empirical antibiotic treatment will be started. The exact time of initiation of treatment, name of the chosen drug/s and dose will be registered to the case report form.

When the antibiogram results are available, the patient will be classified as treated with an appropriate antibiotic treatment or else an inappropriate antibiotic treatment. This process won't affect the need of reassessment of the current antibiotic treatment, considering the antibiotic sensitivity.

7.4.3. Covariates

- Concerning the patient's demographics
    - **Age** (measured in years, at the time of diagnosis of sepsis).
    - **Gender** (female or male).
- Concerning the patient's medical history
    - **History of antibiotic treatment during the previous 30 days** (yes or no).
    - **Acute physiology and chronic health evaluation score II (APACHE II score)** (discrete continuous variable, 0-71) (32): It is a severity of disease classification system tested in the ICU, that correlates to severity of disease and mortality. It takes into account the age of the patient, the most important chronic impairments and 12 physiological parameters, to calculate the acute physiology score. Every study on the subject of sepsis adjusts the statistical analysis with this variable. It will be calculated with a digital calculator (33).
    - **Institutionalized patient** (yes or no): we will consider so a patient that has had a prolonged stay at any health care facility.
- Concerning medical decisions and current episode:
    - **Severity of sepsis** (sepsis or septic shock): We define septic shock as the use of vasopressors to accomplish hemodynamic resuscitation.
    - **Time to antibacterial treatment** (measured in hours): from the admission time to the time of administration of the empirical antimicrobial drug.

- **Site of infection** (urinary tract infection, pneumonia, intra-abdominal infection, skin or soft tissue infection, meningitis, bone or joint infection, endocarditis, implantable device infection, others (specify), unknown)**:** Categorical variable.
- **Empiric antibiotic**: the generic name, dose and means of administration.
- **Appropriate reanimation during the first 24 hours** (yes, MAP>65mmHg or no, MAP<65mmHg).
- **Appropriate evacuation of local infection during the first 24 hours** (yes or no)
- **Aisled microorganisms**: scientific name.

8. STATISTICAL ANALYSIS

All statistical analysis will be performed using the IBM Statistical Package for Social Science (SPSS) 22.0 program. Microsoft Excel tool will be used to manage computed data.

Univariate analysis:

In the univariate analysis, we will define variables as categorical or quantitative. Categorical variables will be described using percentages and proportions. Quantitative variables will be described using mean ± standard deviation or median and interquartile range (25-75) depending on whether they were normally distributed or not.

Bivariate analysis:

In the bivariate analysis, the independent and dependent variables are categorical. Therefore, the comparison between the independent (high lactate clearance or low lactate clearance and high lactate normalization at 24h or low lactate normalization at 24h) and dependent (appropriate empirical antibiotic or not) variables will be carried out with Chi-Square test.

Multivariate analysis:

The multivariate analysis will be executed using a logistic regression test to estimate odds ratio and 95% confidence intervals. It will be used adjust the relationship between lactate and appropriateness of empirical antibiotic for the potentially confounding effects of the selected covariates.

9. ETHICAL CONSIDERATIONS

This research protocol will be presented to the Clinical Research Ethical Committee (CEIC, Comitè d'Ètica d'Investigació Clínica) of Hospital Universitari Josep Trueta in Girona. They will assess if the study fulfils the required criteria for being approved. Moreover, the recommendations given by the committee will be taken into account to carry out the study.

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 (last actualization October 2013). Furthermore, we will take into consideration the Spanish Organic Law 14/2007, de Investigación Biomédica, which regulates biomedical investigation involving human beings in Spain.

The subjects will participate voluntarily in the study after giving their informed consent. Patients admitted in our ICU 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.

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. All data will only be used for the purpose of the research.

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

10. LIMITATIONS

We have chosen to perform a prospective cohort because we believe it is the best choice for the objective of our study, but we acknowledge the intrinsic limitations of this type of study. We acknowledge that a prospective, controlled, randomized clinical trial is the optimal means of demonstrating causality, but appropriately designed observational studies with the right analytical strategies can provide valuable information on treatment effectiveness.

There is a possible selection bias, firstly related to the selected non-probabilistic sampling method and also related to the fact that the location of the study is an intensive care unit, which only admits severe patients, whose clinical evolution could differ from non-ICU patients. For that reason, we believe that if the results of this study are relevant, they will only be applicable to intensive care units.

We have only decided to follow the subjects until the results of the antibiogram are available, this has advantages and disadvantages. On one hand, it reduces follow up losses to almost 0, given that patients are necessarily hospitalized in the ICU at least until then. In the other hand, we don't have information about mortality, which could be useful additional information.

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 when applied to clinical practice, lactate measurements are used to complement the other clinical data available.

11. WORK PLAN

This study is expected to last 2 years and 8 months. All activities carried out during this time will be organized in the following 4 phases.

1. Preparation and coordination phase (4 months).

This first phase of the study consists in the elaboration of the current protocol from September 2016 to October 2016.

The entire team participating; investigators, collaborators, and statisticians, will meet in order to specify which will be the tasks of every member of the team. The chronogram will be corrected with the collaboration of the other members of the research team and the methods for data collection will be discussed and set up.

Once the protocol is ready, we will present it to the Ethical Committee of Hospital Josep Trueta for its evaluation and approval.

During the two years of field work and data collection, the researchers will meet periodically (every 4 months, and more frequently towards the start and the end of the study) in order to control the data collected and asses the progress of the study and to identify deficiencies and correct methodological flaws.

2. Field research and data collection (2 years)

Subjects will be selected with the inclusion/exclusion criteria described before. The data collection will start when the first participant is recruited and will end after the outcome variable of the last recruited subject is registered.

The data collection will be carried out using a pre-established form attached in annex 5, which won't contain the subject's name. One of the main investigators/coordinators will encode each patient with a number, from 001 to 999. In order to protect personal information. The forms will be revised by two different investigators, in order to ensure the data's liability.

3. Data analysis and final evaluation (3 months).

After processing the database, all data will be analysed using the appropriate statistical tests by an external statistician.

The results will be evaluated by the research team and final conclusions will be extracted.

4. Publication and dissemination (2 months).

The researchers will write and edit a scientific paper to publish.

CHRONOGRAM:

TASKS	PERSONAL	2016				2017												2018												2019			
		S	O	N	D	J	F	M	A	M	J	A	S	O	N	D	J	F	M	A	M	J	A	S	O	N	D	J	F	M	A
PREPARATION AND COORDINATION PHASE																																	
Protocol elaboration and evaluation	LV, JMS																																
Research team coordination	All research team																																
FIELD WORK AND DATA COLLECTION																																	
Field work	Clinical researchers																																
Data collection	Clinical researchers																																
DATA ANALYSIS																																	
Statistical analysis	Statistician																																
Interpretation and discussion of results	All research team																																
PUBLICATION AND DISSEMINATION OF THE RESULTS																																	
Scientific publication	All research team																																

12. BUDGET AND FESIABILITY

EXPENSES	COSTS
PERSONAL EXPENSES	
Investigation team	0€
EXECUTIVE EXPENSES: MATERIAL AND SERVICES	
Statistical specialist (30h, per 35 €/h)	1050€
Office consumables and others	300€
PUBLICATION AND DISSEMINATION	
Publication costs	2000€
	TOTAL: 3350€

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.

If the study is accepted by the ethics committee and the budget is approved, it can correctly be carried out, complying with all aspects with this protocol, given that the means in terms of personal and material, are already available.

13. IMPACT

The final aim of this work is to improve the rate of adequate empirical antibiotics prescribed in the ICU. And doing so by means of a highly applicable tool, **lactate**.

If the results obtained in our study are relevant and conclude that lactate levels and/or lactate clearance are a good predictor for antibiotic appropriateness, we will be able to use them the day after the validation of the results. Moreover, the analytical parameters used for management of sepsis at the moment in any ICU in the world, will not even change, because lactate is already a parameter used routinarily for management of sepsis. Instead, we will be giving an extra reading to an already very versatile parameter.

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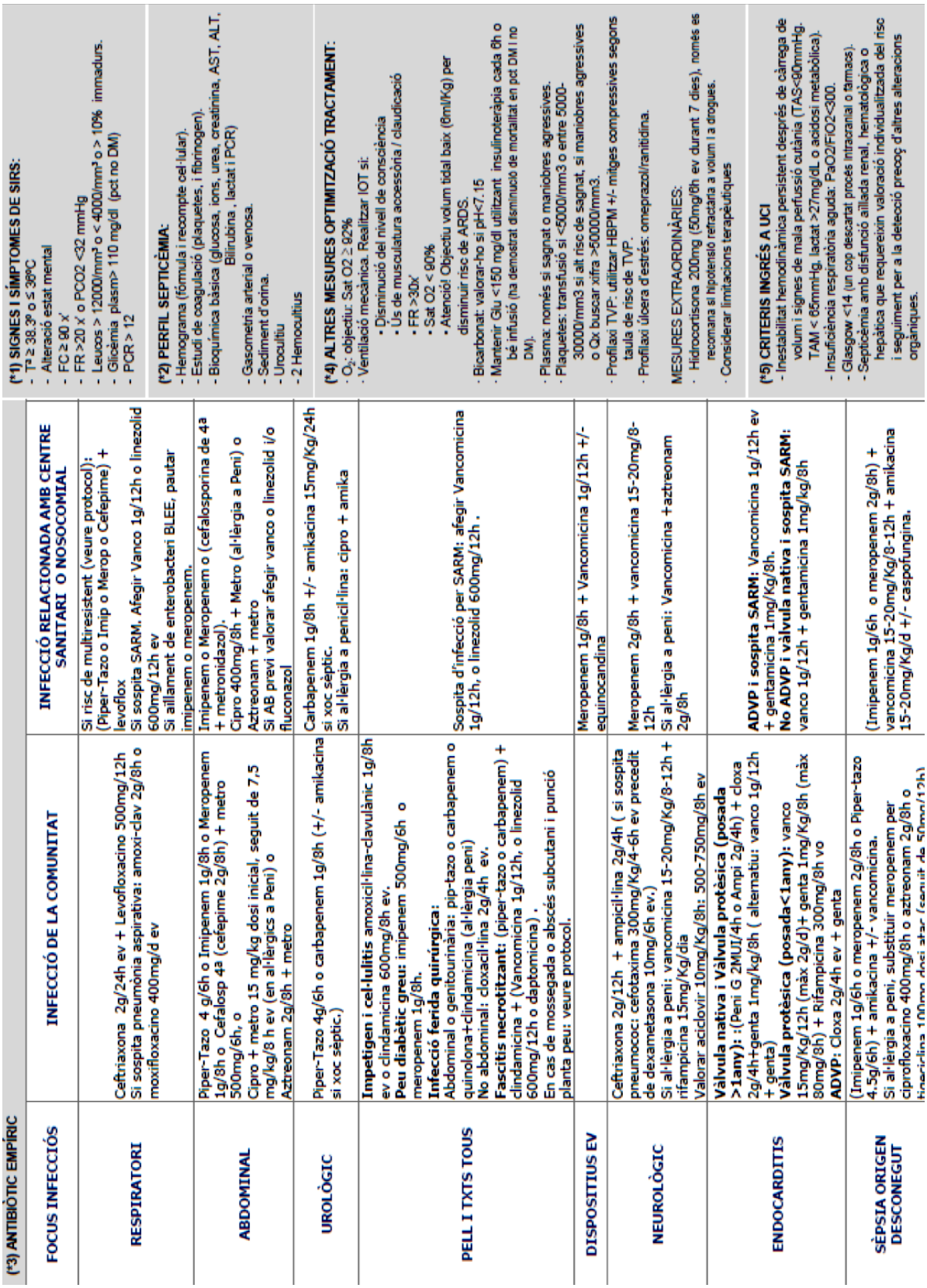
15. ANNEXS

ANNEX 1: HJT empiric antibiotic protocol (2012)



(*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) + levofloxacino Si sospita SARM. Afegir Vanco 1g/12h o linezolid 600mg/12h ev Si aïllament de enterobacteri BLEE, pautar imipenem o meropenem.
ABDOMINAL	Piper-Tazo 4 g/6h o 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	(Imipenem 1g/6h o meropenem 2g/8h) + vancomicina 15-20mg/Kg/8-12h + amikacina 15-20mg/Kg/d +/- caspofungina.

(*1) SIGNES I SÍMPTOMES DE SIRS:
- Tª ≥ 38,3º o ≤ 36ºC
- Alteració estat mental
- FC ≥ 90 x'
- FR >20 x' o PCO2 <32 mmHg
- Leucos > 12000/mm³ o < 4000/mm³ o > 10% immadurs.
- Glicèmia plasm> 110 mg/dl (pct no DM)
- PCR > 12

(*2) PERFIL SEPTICÈMIA:
- Hemograma (fórmula i recompte cel·lular).
- Estudi de coagulació (plaquetes, i fibrinogen).
- Bioquímica bàsica (glucosa, ions, urea, creatinina, AST, ALT, Bilirubina , lactat i PCR)
- Gasometria arterial o venosa.
- Sediment d'orina.
- Urocultiu
- 2 Hemocultius

(*4) ALTRES MESURES OPTIMITZACIÓ TRACTAMENT:
- O_2: objectiu: Sat O2 ≥ 92%
- Ventilació mecànica. Realitzar IOT si:
  - Disminució del nivell de consciència
  - Ús de musculatura acessòria / claudicació
  - FR >30x'
  - Sat O2 < 90%
  - Atenció! Objectiu volum tidal baix (6ml/Kg) per disminuir risc de ARDS.
- Bicarbonat: valorar-ho si pH<7.15
- Mantenir Glu <150 mg/dl utilitzant insulinoteràpia cada 6h o bé infusió (ha demostrat disminució de mortalitat en pct DM I no DM).
- Plasma: només si sagnat o maniobres agressives.
- Plaquetes: transfusió si <5000/mm3 o entre 5000-30000/mm3 si alt risc de sagnat, si maniobres agressives o Qx buscar xifra >50000/mm3.
- Profilaxi TVP: utilitzar HBPM +/- mitges compressives segons taula de risc de TVP.
- Profilaxi úlcera d'estrès: omeprazol/ranitidina.

MESURES EXTRAORDINÀRIES:
- Hidrocortisona 200mg (50mg/6h ev durant 7 dies), només es recomana si hipotensió refractària a volum i a drogues.
- Considerar limitacions terapèutiques

(*5) CRITERIS INGRÉS A UCI
- Inestabilitat hemodinàmica persistent després de càrrega de volum i signes de mala perfussió cutània (TAS<90mmHg. TAM < 65mmHg, lactat >27mg/dL o acidosi metabòlica).
- Insuficiència respiratòria aguda: PaO2/FiO2<300.
- Glasgow <14 (un cop descartat procés intracranial o tarmacs).
- Septicèmia amb disfunció allada renal, hematològica o hepàtica que requereixin valoració individualitzada del risc i seguiment per a la detecció precoç d'altres alteracions orgàniques.

ANNEX 2: Patient information sheet

FULL D'INFORMACIÓ PEL PARTICIPANT

INVESTIGADORS PRINCIPALS: Josep-Maria Sirvent , Laura Vives

CODI DEL PROJECTE: _____

1) **Generalitats del projecte:** El present estudi serà dut a terme per la unitat de cures intensives de l'Hospital Universitari de Girona Doctor Josep Trueta, en un període de temps aproximat de dos anys 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 el tractament antibiòtic empíric, en pacients que presenten una sèpsis adquirida a la comunitat. Per tal de millorar la tria de l'antibiòtic empíric a la unitat de cures intensives.
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 establer ts 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, tan 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.

ANNEX 3: Informed consent

CONSENTIMENT INFORMAT

Declaració del participant: Jo, _____ o jo, _____ representant legal de _____. Declaro que:

- He llegit la fulla informativa 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 .
- **Concenteixo l'ús de les meves dades o del meu representat legal per fins relacionats amb el projecte anomenat: Association between lactate and appropriateness of empiric antibiotic treatment in septic patients in the ICU.**

Firma del participant	Firma de l'investigador
Data: __ / __ / __	Data: __/__/__

ANNEX 4: Researcher's commitment form

RESEARCHER'S COMMITEMENT

Dr./Mr./Mrs._____

Service:

Center:

Exposes:

I have evaluated the protocol of this clinical trial titled:

Association between lactate and appropriateness of empiric antibiotic treatment in septic patients in the ICU.

Referring to these aspects:

- The clinical trial respects the ethical rules relevant to these kind of studies, according to good clinical practice recommendations, in Helsinki, Declaration of World Health Organization (15 January of 2001), and to the legal normative applicable.
- I agree to participate as the main researcher in this clinical trial.
- I have all the material and human resources necessary to carry on the clinical trial

without affecting the performance of other studies or my usual duties.

Girona, ___/___/20___

ANNEX 5: Case report form

CASE REPORT FORM for the study named: Association between lactate and appropriateness of empiric antibiotic treatment in septic patients in the ICU.

Instructions:

- *Please write the patient's identification number in the boxes above.*
- *Read carefully and marck 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:*
  - Terminal malignancy.
  - Documented immunosuppression
  - HIV
- *If you have doubts or you have problems with any answer or item, please contact with the email address lauravivess@hotmail.com, and you will receive an answer shortly.*

DATE: _ _ / _ _ / _ _
INVESTIGATORS NAME AND ID:

- _____
- _____

SIGNATURES

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

- DATE AND TIME OF ADMISSION AT THE HOSPITAL: _ _ / _ _ / _ _ at _ _:_
- DATE AND TIME OF ADMISION IN THE ICU: _ _ / _ _ / _ _ at _ _:_ _

MEDICAL HISTORY:

- ANTIBIOTIC TREATMENT THE PREVIOUS 30 DAYS: YES__ / NO__/ UNKNOWN__
- HOSPITAL ADMISSION PREVIOUS TO 48h: YES__/ NO__
- INSTITUCIONALIZED PATIENT: YES__ / NO__/ UNKNOWN__
- APACHE II SCORE: __/71
  - APS: __
  - Chronic health evaluation: __

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 __
- DATE AND TIME OF DIAGNOSTIC OF SEPSIS (as accurate as possible): _ _ / _ _ / _ _ at _ _:_ _
- SEVERITY OF SEPSIS (X)
    - SEPSIS (no need for vasopressors to maintain MAP and lactate) __
    - SEPTIC SHOCK (need for vasopressors to maintain MAP and lactate) __

EMPIRICAL ANTIBIOTIC:

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

MANAGEMENT (values at 24h after first antibiotic administration if not specified otherwise. Choose the closest value to the time demanded):

- Local infection:
    - Is there a drainable focus? YES__ / NO__
    - Has the focus been successfully drained before 24h? YES__ / NO__
- Mean arterial pressure (mmHg): _____
- Diuresis (ml/kg/h): _____
- Lactate (mmol/l):
    - At time of administration of antibiotic: _____
    - At 24h: _____

CULTURE RESULTS:

- aisled microorganism (scientific name): _____
- Microorganism sensitive to empirical antibiotic: YES__/ NO__