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Clínica Universitária de Medicina Intensiva

Metabolic resuscitation in septic shock

David Gonçalves Paixão

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Orientado por:

Susana M. Fernandes

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ABSTRACT

Background: Sepsis is a medical emergency responsible for about half of all admissions on intensive care units (ICU). Despite appropriate treatment, prognosis remains poor with mortality rates for sepsis and septic shock in developed countries of 30% and 45%, respectively. Recently, there has been mounting evidence suggesting mortality benefits using hydrocortisone and/or thiamine in addition to standard treatment (ST) in patients with sepsis and septic shock. In the present work, we sought to investigate the effects of thiamine, hydrocortisone and a combination of thiamine and hydrocortisone on the mortality of septic shock patients. Additionally, we provide a comprehensive review of the pathophysiological basis and rationale behind the use of these drugs as adjuvant therapies in sepsis.

Methods: This is a retrospective cohort study conducted at Hospital de Santa Maria. We searched the electronic health record for patients admitted to the ICU between January 2018 and January 2019 with a diagnosis of septic shock, further subdividing them into four groups: those treated with ST; those treated with ST plus thiamine; those treated with ST plus hydrocortisone; and those treated with ST plus a combination of thiamine and hydrocortisone. The main outcome of this study, hospital mortality, was then analyzed in each of these groups.

Results: Our search yielded 173 patients. Of these, 73 received ST, 24 received ST plus thiamine, 50 received ST plus hydrocortisone and 26 received ST plus a combination of thiamine and hydrocortisone. Patients treated with hydrocortisone, either alone or in combination with thiamine, represented a more severely ill population, with lower median systolic and mean blood pressure, as well as higher median SAPS II and SOFA score on ICU admission and required higher mean maximum dose of vasopressors for a longer duration of time than patients in the other groups. The hospital mortality adjusted for severity of illness was significantly lower in patients treated with ST plus thiamine alone (p-value of 0,043). Hydrocortisone, either alone or in combination with thiamine, had no significant effect on the mortality of septic shock patients.

Conclusions: This study supports the use of thiamine supplementation in septic shock as this drug was associated with a significant reduction in hospital mortality. There was no significant benefit with the use of combination therapy. Further randomized clinical trials are necessary to elucidate the effects of these therapies in sepsis.

Key words: critical care; sepsis; septic shock; thiamine; hydrocortisone.

RESUMO

Fundamento: A sépsis é uma emergência médica, responsável por cerca de 50% de todas as admissões em Unidades de Cuidados Intensivos (UCI) e com taxas de mortalidade de 30% e 45% para sépsis e choque séptico, respetivamente. Recentemente tem-se assistido a um acumular de evidência sugerindo um benefício na mortalidade de doentes com sépsis com o uso de hidrocortisona e/ou tiamina para além da terapêutica standard (TS). O objetivo deste trabalho é investigar os efeitos da tiamina, da hidrocortisona e da combinação de tiamina e hidrocortisona na mortalidade de doentes com choque séptico. Adicionalmente, discutimos as bases fisiopatológicas que justificam o uso destas terapêuticas na sépsis.

Métodos: Este é um estudo retrospetivo realizado no Hospital de Santa Maria. Os doentes admitidos na UCI com o diagnóstico de choque séptico entre Janeiro de 2018 e Janeiro de 2019 foram subdivididos em quatro grupos: aqueles que receberam TS; aqueles que receberam TS e tiamina; aqueles que receberam TS e hidrocortisona; aqueles que receberam TS e tiamina e hidrocortisona. A mortalidade hospitalar de cada grupo foi de seguida analisada.

Resultados: Incluímos 173 doentes nesta análise. Destes, 73 receberam TS, 24 receberam TS e tiamina, 50 receberam TS e hidrocortisona e 26 receberam TS e tiamina e hidrocortisona. Os doentes tratados com hidrocortisona, isoladamente ou em combinação com tiamina, encontravam-se num pior estado clínico, com menor pressão arterial sistólica e pressão arterial média, assim como com um SAPS II e score SOFA superiores à admissão na UCI e requereram, em média, maiores doses de vasopressores por um maior período que os doentes dos outros grupos. A mortalidade hospitalar ajustada para a gravidade de doença foi significativamente menor nos doentes tratados com tiamina (p-value de 0,043). A hidrocortisona, isoladamente ou em combinação com tiamina, não apresentou nenhum efeito significativo na mortalidade destes doentes

Conclusão: Este estudo apoia o uso de tiamina em doentes com choque séptico, uma vez que esta se encontra associada a uma redução significativa na mortalidade destes doentes. Não foi observado nenhum benefício significativo com o uso de terapêutica de combinação. São necessários ensaios clínicos randomizados adicionais para esclarecer o papel destas terapêuticas na sépsis.

Palavras-chave: cuidados intensivos; sépsis; choque séptico; tiamina; hidrocortisona.

O trabalho final exprime a opinião do autor e não da Faculdade de Medicina da Universidade de Lisboa

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INTRODUCTION

DEFINITION AND EPIDEMIOLOGY

Sepsis is one of the oldest known diseases in medicine, first described more than 3 000 years ago as putrefaction of blood and tissues with fever[1]. It is a common and elusive syndrome, clinically defined for the first time by a consensus panel in 1992 as a systemic inflammatory response to infection[2,3].

Although still embedded in controversy and disagreement, this syndrome is nowadays defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis can progress to septic shock, a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase mortality[4]. Septic shock should be considered a medical emergency and focus must be placed on timely intervention, including the early identification and treatment of infection through appropriate antimicrobial therapy and source control when applicable, as well as reversal of hemodynamic instability through fluid resuscitation and vasopressor use if necessary[5,6].

Sepsis is a leading cause of morbidity and mortality worldwide, affecting 15 to 20 million people annually and it is directly responsible for about half of all admissions in intensive care units. It is the primary cause of death from infection, with mortality rates for sepsis and septic shock of 30% and 45% in developed countries, respectively[7].

Despite timely intervention, however, there exists a small subgroup of patients with septic shock seemingly refractory to conventional therapy who develop progressive multi-organ failure with an associated mortality of up to 60%[8]. There is no consensual definition of refractory septic shock, although the use of more than 0.5 mcg/kg/min of norepinephrine or epinephrine to maintain target blood pressure is often used in clinical trials as a threshold. Nearly 6% of critically ill patients will develop refractory septic shock, which accounts for 18% of deaths in intensive care units.[9] This subgroup of patients is often poorly represented in large randomized clinical trials (RCT) assessing the efficacy of interventions in septic shock and, therefore, there is little significant evidence to guide management in this particular population.

PATHOGENESIS AND TREATMENT

The knowledge we currently possess of the pathogenesis of sepsis has, like its definition, evolved over the years.

Traditionally, it was believed that the host response to infection resulted in an initial hyperinflammatory phase which, after some days, would evolve into an immunosuppression state[10–12]. From a macrocirculatory point of view, this initial proinflammatory cytokine storm would lead, in one hand, alongside the blocked catecholamine-induced vasoconstriction caused by intracellular lactate accumulation and lower intracellular pH, to excessive generalized vasodilatation[13]; and on the other hand, as a result of endothelial activation in response to this proinflammatory environment, to an increase in permeability of the endothelial barrier with fluid loss to the third space[14,15]. These two phenomena would thus result in low systemic blood pressure and, accordingly, low organic perfusion pressure, culminating in an inadequate tissue oxygen delivery in face of its metabolic needs[16]. Deprived of the fundamental process of aerobic respiration given the insufficient quantity of oxygen, cellular metabolism would shift to a predominantly anaerobic metabolism with lactate formation[17]. This intermediate product of anaerobic metabolism is frequently used on a clinical practice basis as a biomarker of organic hypoperfusion and of septic shock.

It is based on this model, which assumes hypoperfusion as the cause of organ dysfunction, that we can theoretically justify the current treatment of sepsis and septic shock: antibiotics and, if applicable, infectious source control, in order to directly combat the triggering insult which led to the dysregulated host response; fluid resuscitation, in line with restoring the volume lost to the third space and thus maximizing oxygen delivery to cells and tissues; vasopressor support after adequate fluid resuscitation as means of compensating for the excessive systemic vasodilation[5].

This macrocirculatory view has, however, been questioned in the last years given the fact that **a)** organ dysfunction can occur even in the absence of significative macrovascular alterations[16]; **b)** even in lethal septic shock with multiorgan dysfunction there is relatively little cellular death[18,19], with organic histology preservation[16], contrary to what would be expected considering generalized hypoperfusion and subsequent organic ischemia.

At the same time, metabolic dysfunction, centered at the cellular level, has been gaining a lot of focus as a fundamental causal element of organ dysfunction in this disease.

In sepsis, high levels of reactive oxygen species[20] cause protein and mitochondrial DNA injury[20], with subsequent mitochondrial dysfunction[21], an organelle responsible for around 90% of total body oxygen consumption. With mitochondrial dysfunction, the intracellular levels of ATP invariably decrease and, with the aim of preventing lethal decrease of its levels, cells enter a hibernation-like state with reduction in energy expenditure[16], compatible with the finding of normal or even increased tissue oxygen tension in sepsis[22–25]. As the number of viable cells decreases, organ dysfunction settles or recrudesces. In harmony with this metabolic view, raised serum lactate levels are not specific of hypoperfusion but can be present even with normal tissue oxygen delivery in the presence of cellular dysfunction[26].

Importantly, besides a problem in oxygen delivery to cells, there is also a problem in oxygen utilization by cells[27,28].

In the light of the above, the current paradigm in sepsis contemplates macrocirculatory changes and subsequently decreased tissue oxygen delivery, as well as metabolic dysfunction and inability at the cellular level in oxygen consumption. As previously stated, although current treatment of sepsis focuses on the first mechanism, the mortality of this syndrome remains unacceptably high. Therefore, new therapeutic approaches in sepsis have been focusing on metabolic optimization and in the development of drugs targeting this last mechanism (**figure 1**). Thiamine and hydrocortisone are two such new approaches being used as adjuvant treatment in sepsis and septic shock.

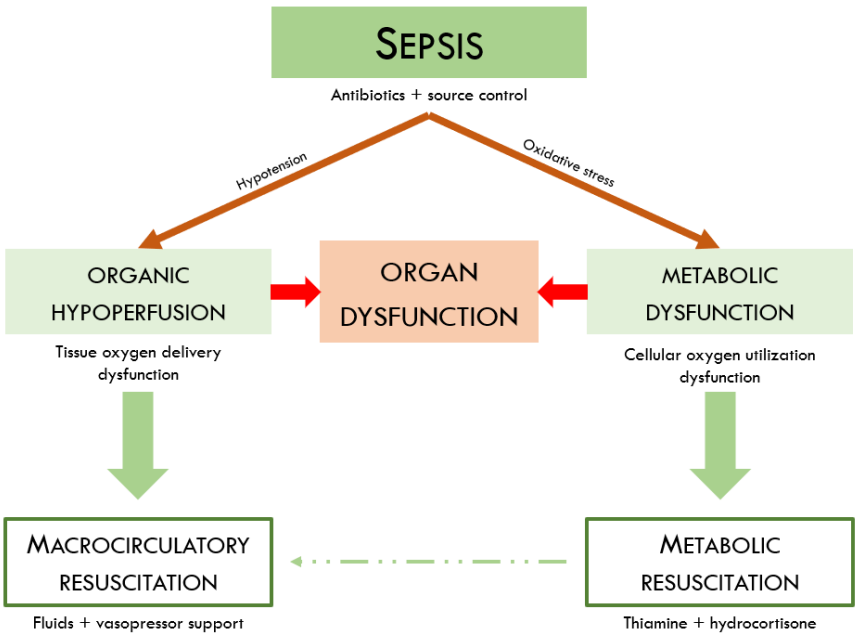

Figure 1. Therapeutic approaches in sepsis.

NEW THERAPEUTIC APPROACHES

Thiamine (Vitamin B1) is a vitamin found in the human body, obtained through feeding, present in a large variety of foods like meat, vegetables, cereals and dairy products and stored in the liver, kidney and central nervous system[29]. This vitamin exists in various forms, from free thiamine to phosphorylated ones. Its most active form, thiamine pyrophosphate, is fundamental in a series of cellular metabolic functions, the most important ones being carbohydrates metabolism and energy production and the pentose phosphate pathway (**figure 2**).

Regarding its role in energy production, thiamine acts as an essential cofactor of the enzyme pyruvate dehydrogenase, responsible for the conversion of pyruvate, obtained through glycolysis, to acetyl-CoA. This last substrate then enters the Krebs cycle, originating most of ATP used by all cells[30]. When thiamine levels are insufficient, the conversion of pyruvate to acetyl-CoA does not happen, compromising the aerobic respiration and forcing a cellular shift to an anaerobic metabolism, a less efficient process, energetically speaking. Concomitantly, lactate is produced as a byproduct of anaerobic metabolism, raising its serum levels[31,32].

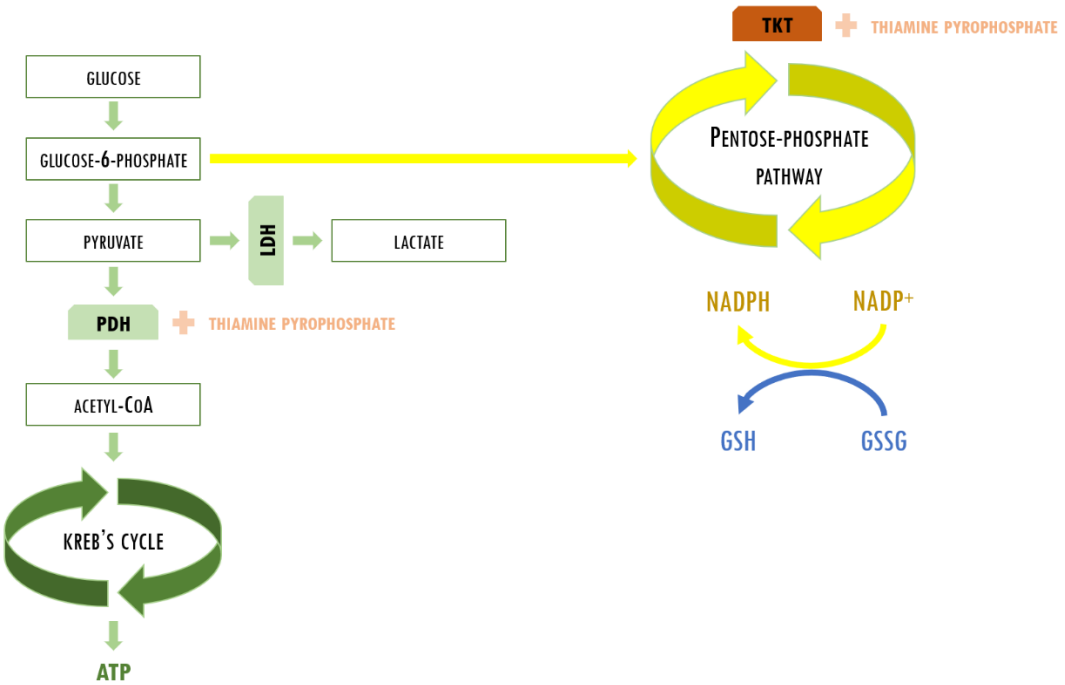

Figure 2. Thiamine role in carbohydrates metabolism and in the pentose-phosphate pathway. GSH: glutathione (reduced state); GSSG: glutathione (oxidized state); LDH: lactate dehydrogenase; PDH: pyruvate dehydrogenase; TKT: transketolase.

Last but not the least, thiamine is also a fundamental cofactor of the enzyme transketolase, part of the pentose-phosphate pathway, essential in generating reduced nicotinamide adenine dinucleotide phosphate (NADPH) and, therefore, regenerating glutathione, an important intracellular antioxidant[33–35].

Thiamine deficiency is common in sepsis patients[36], probably as a result of the associated hypercatabolic state, poor nutritional intake and the presence of multiple comorbidities, predicting a higher mortality[35,37,38]. Although several RCT are now taking place evaluating thiamine supplementation (always in combination with vitamin C and/or hydrocortisone) in septic shock patients, there are few published studies assessing the role of its supplementation alone in this population. The first and only one of such RCT to address this topic demonstrated that thiamine supplementation significantly reduced serum lactate levels at 24 hours, albeit only in septic shock patients with a deficit of this vitamin[37]. A subsequent analysis of this clinical trial has showed that thiamine reduced progression of acute kidney injury, perceived as a reduction in the number of patients requiring renal replacement therapy[39]. Additionally, a last retrospective study has demonstrated that time to lactate clearance was significantly reduced in the group of septic shock patients that received thiamine supplementation and showed a mortality benefit at 28 days with this intervention[40].

Of note, potentially favoring a high reward low risk intervention, thiamine supplementation, even at high doses, is not associated to major side effects[41].

Opposed to the recent interest in thiamine in sepsis, hydrocortisone is already a known and viable therapeutic approach in this syndrome, incorporated for the first time in 2004 on the international guidelines of the Surviving Sepsis Campaign[42] and still recommended on the most recent version of these guidelines in septic shock patients hemodynamically unstable even after adequate fluid resuscitation and vasopressor support (refractory septic shock)[5]. Theoretically, there are several benefits arising from hydrocortisone use in septic shock, traditionally linked to a reversion of diminished peripheral vascular resistance: on the vascular smooth muscle, glucocorticoids prevent induction of nitric oxide synthase, an enzyme leading to smooth muscle relaxation through nitric oxide production and, consequently, to vasodilation[43]. Additionally, glucocorticoids potentiate catecholamine effect on these cells[44]. At the endothelial level, these hormones directly inhibit production of a vast number of vasodilator substances, such as nitric oxide and prostacyclin[43]. Finally, on a broader view, given its anti-inflammatory action, glucocorticoids mitigate the hyperinflammatory state of sepsis[45,46].

Studies with hydrocortisone in sepsis have since the beginning generated contradictory and inconsistent evidence. However, two different and independent RCT have recently shown the benefit of its use on the mortality in these patients[47,48].

The combination of thiamine and hydrocortisone might have a synergistic effect. In sepsis, the hydrocortisone's receptor is down-regulated owing to the large amounts of reactive oxygen species[49]. Bearing in mind one of the aforementioned functions of thiamine, that of a fundamental cofactor in the pentose-phosphate pathway, important in generating antioxidant species to combat oxidative stress, one can hypothesize that the supplementation with thiamine in septic shock patients restores hydrocortisone's receptor function, enhancing hydrocortisone's actions on endothelial and smooth muscle cells, augmenting its role in shock reversion and its systemic anti-inflammatory effect. Additionally, with thiamine supplementation, aerobic respiration would be restored and production of intracellular lactate would fall, raising intracellular pH and enabling catecholamine effects on smooth muscle cells, an effect also potentiated by glucocorticoids, promoting once again shock reversion. Thus, the combination of thiamine and hydrocortisone is expected to act on both the macrocirculatory and the metabolic pathways of septic shock, opposed to most available therapies targeting a specific mechanism.

Although the combination of thiamine, hydrocortisone and vitamin C on sepsis (commonly referred to as "the vitamin C protocol") has been taking the spotlight with a RCT showing promising results[50] and many others taking place, the combination of thiamine and hydrocortisone alone is one that has never been investigated. Therefore, this study will generate novel scientific data and evidence on a much-needed area of sepsis where mortality remains unacceptably high despite many promising interventions which, in the end, all came short of its objective.

OBJECTIVES

Considering the above, the objectives of this study are:

1. To analyze the effect of thiamine on the mortality of septic shock patients.
2. To analyze the effect of thiamine and hydrocortisone on the mortality of septic shock patients.
3. To analyze the effect of hydrocortisone on the mortality of septic shock patients.

METHODS

This study was a retrospective, single-center cohort study conducted at Hospital de Santa Maria, an academic teaching hospital in Lisbon that serves as a regional referral center for the district and surrounding areas. This research included only retrospective data and all the data was maintained anonymous.

The electronic health record (EHR) was queried between January 2018 and January 2019 for patients admitted to the Intensive Care United (ICU) with a diagnosis of septic shock. Inclusion criteria consisted in being at least 18 years old and having a septic shock diagnosis at admission to the ICU. Exclusion criteria at this stage included age less than 18 years old. The medical records of all included patients were consulted to validate the diagnosis of septic shock according to the Sepsis-3 criteria[4], specifically a peak lactate greater than 18 mg/dL and need for vasopressor therapy. Patients not meeting these criteria or patients with missing baseline data were excluded from this study.

The patients' clinical and demographic data were extracted from the medical records, including age, sex, admitting diagnosis, comorbidities, SAPS (simplified acute physiology score) II score, SOFA (sequential organ failure assessment) score at admission and at discharge, need for mechanical ventilation and its duration, need for renal replacement therapy and its duration, isolation of etiologic agent, antibiotherapy used (and adequacy of it according to susceptibility testing), systolic blood pressure (SBP), mean blood pressure (MBP) and heart rate at admission, weight, use of vasopressors (including initial dosage, maximum dosage, total daily dosage for the first seven days and total of days with vasopressor support), serum lactate levels (in the first five days), fluid balance (in the first five days), use of hydrocortisone and use of thiamine (and its dosage).

The main outcome of this study was ICU mortality.

DATA ANALYSIS

Categorical variables are presented as numbers and percentages and were analyzed using chi-square. Continuous variables are presented as means and standard deviations and were analyzed using Student's T-test. To adjust for possible confounders, we performed multiple logistic regression. Statistical significance was defined as a p-value of 0.05 or less.

RESULTS

Upon validation with the Sepsis-3 criteria, our cohort yielded 173 patients. Of these 173 unmatched patients, 73 received no additional therapy besides the standard therapy for septic shock (in accordance with the 2016 Surviving Sepsis Campaign[5]), 24 additionally received thiamine alone, 50 additionally received hydrocortisone only and 26 additionally received a combination of thiamine and hydrocortisone, thus forming the four groups of interest in this study.

These patients were analyzed and clinically and demographically characterized (**table 1**). Patients were mainly male, with a higher preponderance of females in the standard therapy and in the hydrocortisone only groups. The median age was slightly lower in patients receiving thiamine, either alone or in combination with hydrocortisone (median of 64 and 64,5 years, respectively). Patients in the standard therapy and in the thiamine groups had a lower median SAPS II and SOFA score and a higher median mean arterial blood pressure on ICU admission. In contrast, patients receiving hydrocortisone, either alone or in combination with thiamine, appeared to represent a more severely ill population than patients in the other groups, with higher SAPS II and SOFA score and lower systolic and mean blood pressures on ICU admission. Additionally, the percentage of patients that required mechanical ventilation was higher in these two last groups (92% of patients receiving hydrocortisone only and 96% of patients receiving thiamine and hydrocortisone).

The most common site of infection in all groups was the gastrointestinal tract and biliary system, with the second most common site of infection differing between the four groups. Other sources of infection incorporated a variety of conditions, including, but not limited to, meningitis, osteomyelitis and cellulitis.

In order to further evaluate the severity of clinical condition, we characterized patients in the four groups according to the initial dose of vasopressors (noradrenaline), its maximum dose during ICU stay, time (in hours) on maximum dose of vasopressors and dose of vasopressors when starting thiamine and hydrocortisone (**table 2**). The mean initial dose of vasopressors received by patients in all groups studied was above 0,5 mcg/kg/min, the value commonly used to define refractory septic shock. Patients treated with thiamine alone received lower mean maximum doses of noradrenaline (0,86 ± 0,72 mcg/kg/min) and spent less time on its maximum doses (4,33 hours). On the contrary, patients treated with hydrocortisone, either alone or in combination with thiamine,

received higher mean initial doses of noradrenaline (1,29 ± 1,35 and 1,27 ± 1,19 mcg/kg/min, respectively), were submitted to substantially higher mean maximum doses of noradrenaline (2,93 ± 1,64 and 3,15 ± 1,71 mcg/kg/min, respectively) and received maximum doses of noradrenaline for a longer period of time (5,11 hours and 5,41 hours, respectively). In the group of patients treated with thiamine and hydrocortisone, these two drugs were started, on average, when patients were receiving substantially high doses of vasopressors (1,6 ± 1,4 mcg/kg/min of noradrenaline at thiamine initiation and 1,94 ± 1,68 mcg/kg/min of noradrenaline at hydrocortisone initiation).

Regarding the main outcome of this study, the unadjusted hospital mortality (**table 3**) was significantly lower with thiamine treatment (p-value of 0,025) and significantly higher with the use of hydrocortisone, either alone or in combination with thiamine (p-value of 0,005 and 0,003, respectively). These findings remained true when mortality was adjusted to the SAPS II (**table 4**). Finally, when mortality was adjusted to the SAPS II and to the maximum dose of vasopressors used (**table 5**), treatment with thiamine only continued to be associated with a lower ICU mortality (p-value of 0,043). However, there no longer seemed to be a significant correlation between treatment with hydrocortisone and mortality (p-values of 0,127 and 0,881 for patients treated with hydrocortisone alone and patients treated with a combination of thiamine plus hydrocortisone, respectively).

Table 1. Baseline demographics of the study population.

Variables	No additional therapy (n = 73)	Thiamine (n = 24)	Hydrocortisone (n = 50)	Thiamine and hydrocortisone (n = 26)
Age (years), median (IQR)	69 (60-79)	64 (58-73,5)	70,5 (62-78)	64,5 (58-74)
Sex (male), n (%)	45 (61.6)	19 (79.1)	32 (64)	20 (76.9)
SAPS II, median (IQR)	54 (43-75)	51 (36-63)	68 (56-77)	74 (51-83)
SOFA score on ICU admission, median (IQR)	10 (7-13)	9 (7-11)	11 (8-14)	12 (11-15)
SBP (mmHg) on ICU admission, median (IQR)	100 (88-115)	98 (87-123)	97 (86-112)	96 (86-101)
MAP (mmHg) on ICU admission, median (IQR)	67 (62-75)	71 (60-80)	65 (60-69)	66 (60-68)
HR (bpm) on ICU admission, median (IQR)	96 (82-109)	97 (89-119)	103 (89-116)	101 (82-117)
Mechanical ventilation, n (%)	52 (71)	20 (83)	46 (92)	25 (96)
Days on mechanical ventilation, median (IQR)	2 (0-3)	2 (1-4)	2 (1-5)	3 (2-5)
Infection source, n (%)				
GI/IA	32 (44)	12 (50)	24 (48)	11 (42)
Pneumonia	11 (15)	3 (13)	8 (16)	8 (31)
Urosepsis	14 (19)	1 (4)	2 (4)	3 (11)
Bacteremia of unknown source	5 (7)	4 (17)	8 (16)	2 (8)
Other	11 (15)	4 (16)	8 (16)	2 (8)

GI = gastrointestinal; IA = intra-abdominal; ICU = intensive care unit; IQR = interquartile range; SAPS = simplified acute physiology score; SOFA = sequential organ failure assessment.

Table 2. Characterization of the vasopressor support (noradrenaline) of the study population.

Variables	No additional therapy (n = 73)	Thiamine (n = 24)	Hydrocortisone (n = 50)	Thiamine and hydrocortisone (n = 26)
Initial dose of NA (mcg/kg/min), mean ± SD	0.52 ± 0.47	0.59 ± 0.63	1.29 ± 1.35	1.27 ± 1.19
Maximum dose of NA (mcg/kg/min), mean ± SD	1,03 ± 1,02	0,86 ± 0,72	2,93 ± 1,64	3,15 ± 1,71
Time spent (hours) on maximum dose of NA, mean ± SD	4,57 ± 4,15	4,33 ± 3,63	5,11 ± 3,35	5,41 ± 3,43
Dose of NA (mcg/kg/h) at the beginning of thiamine, mean ± SD	N/A	0.57 ± 0.57	N/A	1.6 ± 1.4
Dose of NA (mcg/kg/h) at the beginning of hydrocortisone, mean ± SD	N/A	N/A	1.79 ± 1.24	1.94 ± 1.68

NA = noradrenaline; N/A = not applicable; SD = standard deviation.

Table 3. Unadjusted hospital mortality of the study population.

Variables	Odds ratio	95% CI	P value
No additional therapy (n = 73)			
Thiamine (n = 24)	0,18	0,04-0,80	0.025
Hydrocortisone (n = 50)	2,88	1,37-6,06	0,005
Thiamine and hydrocortisone (n = 26)	4.3	1,65-11,32	0,003

Table 4. Hospital mortality of the study population adjusted for the SAPS II.

Variables	Odds ratio	95% CI	P value
No additional therapy (n = 73)			
Thiamine (n = 24)	0,21	0,04-0.99	0.049
Hydrocortisone (n = 50)	2,25	1,02-4,95	0,044
Thiamine and hydrocortisone (n = 26)	3,11	1,11-8,72	0,031

Table 5. Hospital mortality of the study population adjusted for the SAPS II and maximum dose of noradrenaline.

Variables	Odds ratio	95% CI	P value
No additional therapy (n = 73)			
Thiamine (n = 24)	0,18	0,35-0,95	0,043
Hydrocortisone (n = 50)	0,41	0,13-1,29	0,127
Thiamine and hydrocortisone (n = 26)	0,86	0,26-2,91	0,810

DISCUSSION

The results of this study are in line with what has been recently observed regarding the use of thiamine[40] and the vitamin C protocol[51,52] on septic shock patients: treatment with thiamine alone appears to be associated with significant mortality benefits, whilst combination therapy (without vitamin C) does not seem to have a significant effect on the mortality of these patients.

Adjuvant therapy with thiamine alone is associated with a significant reduction in the mortality of septic shock patients.

Although one might try to justify its mortality benefits with the apparent better clinical condition of patients receiving thiamine, who indeed had lower median SAPS II and SOFA score on ICU admission and lower maximum doses of noradrenaline needed (and lower time on it) (table 1 and 2), it is important to note that this association remained significant even after adjusting mortality to severity of illness (tables 4 and 5). This group, however, comprised a small number of patients (24), representing only 14% of the total sample.

In spite of the above, there did seem to be a tendency to use thiamine in patients with lower severity of illness. Bearing this in mind, we can hypothesize that thiamine might not have been prescribed directly for septic shock in these patients, but for a suspect of alcoholism and an inherent deficit of this vitamin. Indeed patients with a history of chronic alcoholism are at higher risk for thiamine deficiency, given their inadequate dietary consumption and alcoholic-induced impaired intestinal absorption, and supplementation with this vitamin is often given to these patients in order to prevent the devastating Wernicke-Korsakoff syndrome[53]. Interestingly, the major source of infection in the study population was the gastrointestinal tract and biliary system, and this was even more pronounced in the group of patients receiving thiamine alone, with 50% of these patients having an intraabdominal source of infection. This was a surprising finding that might support the initial hypothesis of thiamine supplementation for a suspicion of chronic alcoholism. Based on a large-scale multi-country work[54], one expected for the lungs to be the primary source of infection, only then followed by the abdomen. The abdomen as a source of infection included a diversity of pathologies, such as ruptured viscera, cholangitis and intestinal occlusion, but also spontaneous bacterial peritonitis and variceal bleeding, making it plausible to think that the physician responsible for such

patients might have suspected of a chronic alcohol disorder as the cause for the hypothetic chronic liver disease or cirrhosis of such patients and decided to initiate thiamine supplementation.

In line with the aforementioned, a fundamental question regarding thiamine supplementation and its effect on the mortality of septic shock patients comes to mind: are the baseline levels of thiamine important to take into consideration, in the sense that only those who are thiamine depleted benefit from its supplementation or is thiamine therapy advantageous for all patients in septic shock? The answer to this question is still not known, with confounding results existing. In one hand, there has been evidence showing that thiamine supplementation is only beneficial in those patients with baseline thiamine deficiency, resulting in significantly lower lactate levels at 24 hours and a possible decrease in mortality over time[37]; on the other hand, a recent retrospective study concluded that thiamine administration within 24 hours of admission in patients presenting with septic shock was associated with improved lactate clearance and a reduction in 28-day mortality, not taking into consideration thiamine baseline levels[40]. However, it is important to note the different design of the studies, with one of them being an RCT and the other one a retrospective matched cohort study, with inherent different methodology; importantly, the doses of thiamine and time of initiation were not the same. This is a fundamental question and, in our opinion, one that must be answered in definitive since it is not common to test for thiamine deficiency due to lack of availability and long turnaround times. It would be of great valor if more studies could assess the baseline thiamine levels in septic shock patients and thus elucidate the prevalence of thiamine deficiency in this population and the benefit of its supplementation (selectively or indiscriminately). This could lead to a change in clinical practice, with more interest being put in screening for thiamine deficiency on ICU admission, but this might be delayed until reliable, rapidly available testing for thiamine deficiency is at one's disposal.

Contrary to hydrocortisone, where optimal dosing has been well studied and is somewhat well defined, the dosing strategy for thiamine in septic shock patients and its duration needs to be further established. Different studies have been using different thiamine regimens, with the greatest benefit being observed with higher doses (500 mg IV every 8 hours for 72 hours), theoretically offering the advantage of improved passive absorption into the central nervous system and compensating for its rapid elimination from the serum into the urine[40]. However, on the bright side, thiamine is a particularly safe, non-toxic, inexpensive therapy, albeit rare hypersensitivity reactions to repeated

parenteral administration have been reported[55]. Larger prospective studies need to be performed to establish optimal thiamine dosing and overall treatment strategy in septic shock patients.

Hydrocortisone and combination therapy in septic shock are not associated with significant mortality benefits.

In contrast to thiamine, the use of hydrocortisone besides standard therapy, either alone or in combination with thiamine (table 3), appeared to be associated with a higher mortality. However, when we adjusted the mortality for severity of disease, using the SAPS II and the maximum dose of noradrenaline received by patients (tables 4 and 5), the apparent nefarious effect of hydrocortisone on mortality faded away, suggesting that patients treated with hydrocortisone were already in a worse clinical condition. The aforementioned is further supported by the fact that these patients displayed higher median SAPS II and SOFA score and a lower systolic and mean blood pressure on ICU admission (table 1) and needed higher mean maximum doses of noradrenaline, receiving said doses during a higher mean of time (table 2). Thus, it is reasonable to attribute the higher mortality observed in patients receiving hydrocortisone to a more severe illness when compared to patients in the other groups.

This pattern of use of hydrocortisone as a last resource medicine, reserved for patients with a more severe illness, is consistent with the recommendations of the 2016 Surviving Sepsis Campaign guidelines[5], advocating the use of this therapy only in patients that remain hemodynamically unstable despite appropriate fluid resuscitation and vasopressor support. In fact, as previously stated, the use of corticosteroids in sepsis has been a matter of discussion since early, with the first clinical trials failing to demonstrate a benefit on survival with corticosteroid usage and showing severe side effects of this therapy. Be that as it may, it is important to acknowledge that the rationale at the time behind this therapeutic concept was to suppress the initial hyper-inflammation of sepsis, culminating in the use of high doses of steroids, largely above physiological concentrations[56]. Steroid therapy in sepsis was abandoned following these results but eventually made his way back onto to the spotlight with the rising of a new pathophysiological concept, “CIRCI” (critical illness related corticosteroid insufficiency), stating that in severe disease states, although the organism is able to increase corticosteroid production, even maximally increased production of this hormone may be insufficient to preserve clinical stability[57,58]. Indeed, the current rationale behind

corticosteroid usage in this syndrome is to compensate for a lack of endogenous cortisol activity in situations of severe stress, rather than to maximally suppress the immune system with supra-physiological doses of steroids. This resurgence of steroid therapy in sepsis was accompanied by several clinical trials demonstrating several positive effects of this therapy on this disease[47,59,60], culminating in its inclusion on the already mentioned 2016 Surviving Sepsis Campaign guidelines[5]. Recently, two large-scale RCT of hydrocortisone in patients with septic shock were published and helped to settle the debate, with one of them demonstrating a reduction in the mortality of these patients with steroid therapy[48] and the other one, albeit not showing a significant benefit on mortality with the use of hydrocortisone, documenting remarkable improvements in the morbidity of patients treated with steroids, such as shorter time on vasopressor support and mechanical ventilation and shorter length of stay in the ICU[61]. These two studies also shed some light on the safety of hydrocortisone and its feared side effects, such as superinfection and neuromuscular dysfunction and myopathy, reporting higher side effects with steroid therapy, such has hypertension, hyperglycemia and hypernatremia, but no significant risk of serious adverse events.

Our findings regarding hydrocortisone might differ from the aforementioned studies since the adjuvant treatment with steroids, as it is the case for thiamine, is not protocolized at our hospital and, given the retrospective nature of this work, the decision to initiate and the timing of discontinuation of these drugs was mainly based upon physician's judgment, making it hard to exclude that different criteria for initiation of therapy, different regimens and doses and different treatment durations were used.

Theoretical benefits and practical observations with combination therapy.

Although a seemingly theoretical benefit exists with the combination of thiamine and hydrocortisone, that is, considering a metabolic resuscitation approach to sepsis, these results do not unequivocally establish metabolic dysfunction as a fundamental force driving organ failure in septic shock since combination therapy failed to show significant effects on the mortality of these patients. This might be essentially for three, not mutually exclusive, different reasons:

a) firstly, the obvious reason is that this theory might be incorrect or, at least, metabolic dysfunction might not be a central and causal element in the pathogenesis of organic failure in septic shock. In line with this view, a recent RCT demonstrated no

benefits on mortality or vasopressor-free days in sepsis with the combination of thiamine, vitamin C and hydrocortisone when compared to standard therapy plus hydrocortisone[51]. However, in our study, thiamine supplementation alone was indeed associated with a significant mortality benefit in these patients. Nonetheless, we cannot assume this finding to be proof of the central role of metabolic dysfunction in the pathogenesis of sepsis as this could simply be due to the fact that these patients had baseline thiamine deficiency from the start, which is associated with higher mortality[35,37,38].

b) secondly, a recurring question in sepsis comes to mind: are we too late with these therapies? This question has time and time again proved to be fundamental in sepsis related treatments and one of the most important factors when assessing for their impact on mortality of these patients. It is fundamental to antibiotic efficacy, where antibiotic delay can impact mortality[62], and it is still today a matter of discussion with steroid therapy, with the latest Surviving Sepsis Campaign guidelines recommending its use only in refractory septic shock, a practice that might change in the future owing to the previously mentioned works of Annane *et al.*[48] and Venkatesh *et al*[61]. In refractory septic shock, organ dysfunction is unresponsive to fluid resuscitation and the conventional doses of vasopressors, perhaps reflecting irreversible loss of a critical number of specialized cells in several organs culminating in its failure[63]. Therefore, targeting the mitochondria, trying to turn on the engines of cellular energy production, may not be of benefit since cells may already be in an irreversible state of cellular dysfunction as a result of the prolonged insult they sustained. Combination therapy might be beneficial at an earlier stage of sepsis before generalized cell injury occurs or even during the low energy expenditure hibernation-like state that cells might go through before irreversible damage occurs, as previously described[16]. The work of Marik *et al.* actually hints for a maximal benefit of the Vitamin C protocol when this combination is started within 24 hours of sepsis diagnosis or ICU admission[50]. Thus, it would be interesting to conduct larger studies in order to assess the best timing for initiation of adjunctive metabolic therapy in sepsis (at least with thiamine, given its excellent safety profile, even with high doses) instead of immediately assuming its lack of effect based on its supplementation in severely ill patients with a deteriorating clinical condition;

c) thirdly, and probably the most important, the limitations of this study. Besides the already mentioned limitations regarding the small sample size and a lack of protocols for hydrocortisone and thiamine administration in sepsis at our institution, with differences in dosages and treatment duration between patients, it is also important to note

that this was a retrospective study with data limited to that available in the electronic medical records. Additionally, we observed a significant heterogeneity among the different groups, which fundamentally limits the conclusions that can be drawn from this work. One important consideration regarding homogeneity of populations in sepsis is that this syndrome is not defined by a singular pathophysiological mechanism and septic patients have several clinical and biological differences between each other, making it possible, in a way, to create different subgroups of patients with sepsis (e.g. not every septic shock patient has baseline thiamine deficiency). In fact, this consideration might be important when analyzing our very own data: in the group of patients treated with thiamine, either isolated or in combination with hydrocortisone, there is the possibility that some of them were in fact thiamine depleted and thiamine supplementation actually had an impact on their survival; on the other hand, other patients might have had adequate baseline thiamine levels and thus supplementation with this vitamin had no effect on their prognosis. Therapies are often blindly used in critical care medicine as if the population is homogeneous when that is not the case. It is only rational to design subsequent studies on this and other subjects based on precision medicine and the so called predictive enrichment, selecting subgroups of patients based on individual traits and on a variety of clinical and biological data, minimizing the number of patients that are treated without effect, subject only to the side effects of those treatments, and augmenting the number of patients that are effectively treated[64,65].

Final considerations.

In conclusion, our study supports the use of adjuvant therapy with thiamine in septic shock as its use is associated with a significant reduction on the mortality of these patients. In contrast, there was no significant benefit with the combination of thiamine and hydrocortisone in septic shock patients. Although some important limitations of this work must be taken into consideration when analyzing these results, they are in line with recent studies of the metabolic approach to septic shock. Further randomized controlled clinical trials are warranted to evaluate these therapies, ideally considering the different baseline biological and clinical characteristics of patients with sepsis in order to obtain a sample as homogenously as possible.

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