Research Article

# Fluids, Vasopressors and Inotropes to Restore Heart-Vessels Coupling in Sepsis: Treatment Options and Perspectives

**Francesca Innocenti[1], Vittorio Palmieri[2], Guido Grossi[1], Lucia Maddaluni[1], Alessandra Scardia[1], Riccardo Pini[3]**

1. High-Dependency Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliero Universitaria Careggi, Florence, Italy; 2. Cardiosurgery Unit, Cardiovascular Department, Azienda Ospedaliera Sant'Anna e San Sebastiano di Caserta, Caserta, Italy; 3. Azienda Ospedaliero Universitaria Careggi, Florence, Italy

**Sepsis is a complex syndrome with heterogeneous clinical presentation and outcome, characterized by an abnormal inflammatory response as central pathophysiological process potentially leading to multiorgan damage and hemodynamic instability. Early resuscitation with fluids and the timely control of the source of sepsis are key treatment targets in septic patients. Recommendations on time to treat with vasopressors and inotropes are mostly empirical and anecdotal, remaining therefore a topic of debate.**

**This narrative review has been developed proposing cases to present and discuss typical pathophysiologic problems in the early management of hemodynamic derangement induced by sepsis. We will present the latest findings about the treatments currently used for hemodynamic support in patients with septic shock and their relationship with sepsis-related myocardial dysfunction and outcome.**

**Corresponding author:** Francesca Innocenti, innocenti.fra66@gmail.com

## Introduction

Sepsis is caused by a dysregulated response of the organism to the infection, which may determine multi-organ damage and increased mortality [1]. Despite different symptoms, signs and, even,

prognosis, two elements are common in all septic patients: the beginning of the disease, which always consists in the abnormal activation of an inflammatory response, and the modalities of early treatments. Unfortunately, we don't have the "chest pain" or the "troponin" for sepsis and the lack of specific symptoms and early biomarkers to rely on frequently determines a relevant diagnostic delay.

Inflammation represents a stereotyped response of the organism to a variety of stimuli perceived as dangerous, such as the presence of pathogens or the alteration of the homeostasis (for example, changes in temperature, oxygen level, acid-base balance or levels of electrolytes). The recruitment of cellular lines normally absent in specific sites begins, in order to limit the damage and to prepare the process of healing [2][3]. When the complex interplay between the host and pathogen generates a disproportionate inflammatory reaction with a cytokine storm, we are in the presence of sepsis (Figure 1).

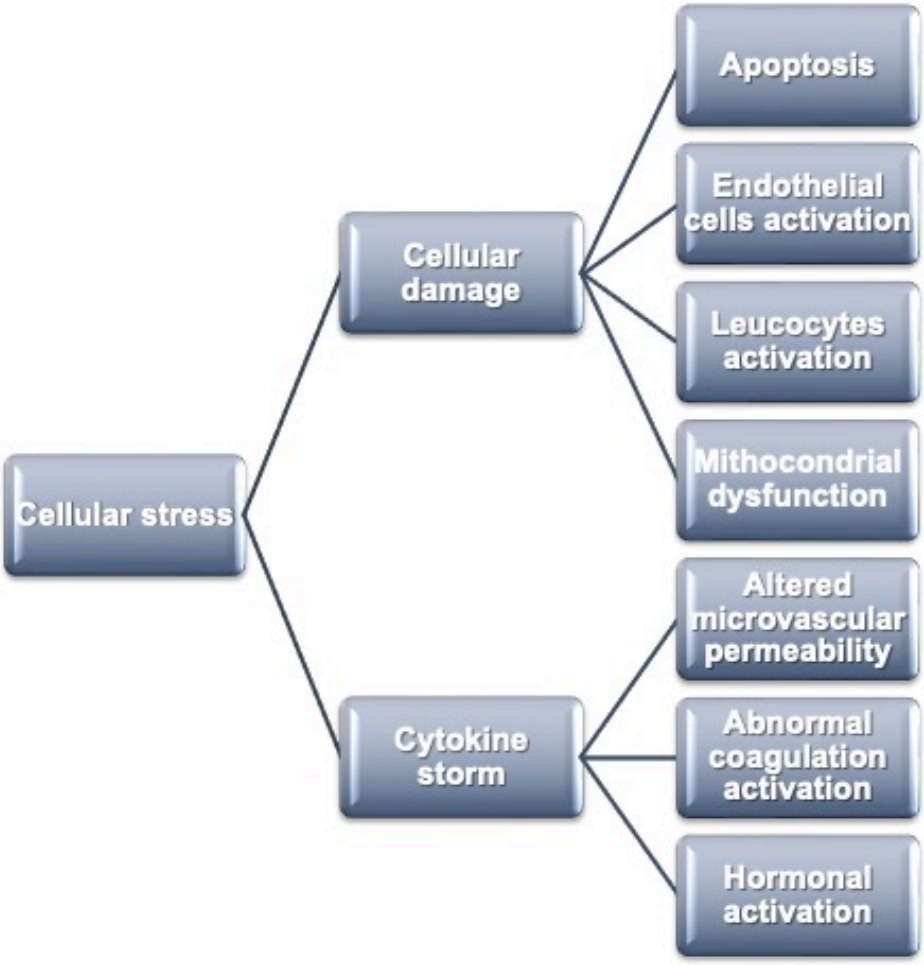


**Figure 1.** Main mechanisms of organ damage during sepsis.

The possibility to intervene directly on the inflammatory reaction has been repeatedly tested in past years by the use of inhibitors of specific pathways activated during inflammation. Promising results obtained in experimental conditions were never replicated in human beings. In fact, the complexity of the involved pathways and their different timing of activation dampened the possibility to modify the course and the entity of the inflammatory response. During sepsis, we always begin our care in front of the full-blown disease. The ways the infection process and the inflammatory activation affect the function of different target organs and systems depends on the presence of previous medical conditions, the involved pathogen and the immune status of the patient.

At the moment of the presentation, early antibiotic therapy aimed at controlling the pathogen widespread and the haemodynamic stabilization are the cornerstone of the treatment in all septic patients, with several point that still represent topic of debate.

We summarize in two different typical clinical scenarios how to embed different treatments in order to improve patients' outcome according to current literature and knowledge, also highlighting gaps in evidences and limitations of practice based on current recommendations.

### *Case 1: When fluids cannot be the only option*

A 77-year old man of 58 kg for 160 centimeters of height with myelodysplastic syndrome with excess blasts (MDS-EB) on chemotherapy and blood transfusion presented to the Emergency Room with hypotension and fever (40°C). Referred cough in previous days. The patient also had a history of type II diabetes on oral therapy, pacemaker insertion for advanced atrio-ventricular block, arterial hypertension, carotid artery disease, past alcohol abuse and smoking (50 pack/year). Upon arrival to the ED he was conscious, and showed no remarks on physical examination. A fluid bolus with crystalloids (30 ml/kg) was administered in 2 hours by a peripheral vein and hemodynamic stability was restored. Initial search for the sepsis source by chest and abdomen CT scan was negative; normal urinalysis, no cutaneous infection (Table 1, ER evaluation). Empiric antibiotic treatment was begun with vancomycin and meropenem as soon as the patient arrived in ER. However, fever was persisting and at 24 hours then the patient presented hypotensive despite standard saline infusion (Table 1, T0 and T1 evaluation). In order to establish whether the failure to obtain a stable hemodynamic was determined by an insufficient fluid replacement, and whether different actions were needed to restore the coupling between peripheral resistances and pump function, a dynamic evaluation was performed. The Passive Leg Raising (PLR) test combined with echocardiographic evaluation of the aortic flow was negative for fluid responsiveness and lung ultrasound showed bilateral ubiquitous interstitial syndrome; central venous pressure was only slightly increased. Echocardiography showed an LV systolic function at the lower normal limit (LV EF 50%). Hence, we reconsidered fluid infusion rate at 1 ml/kg/h and started noradrenaline (NE) at a relatively low dosage (0.2 gamma/kg/min). with prompt hemodynamic stabilization. NE infusion was discontinued after 3 days and the patient maintained adequate respiratory gas exchange and parameters of renal function progressively improved. Blood cultures were positive for Pseudomonas aeruginosa and a transesophageal echocardiography showed endocardial vegetations on pace-maker catheter. The antibiotic therapy was updated with cefepime

and amikacin. By day 10, the patient underwent removal of infected catheters and placement of epicardial electrodes. The case, therefore, illustrated the issue of the correct fluid rate and total fluid infusion to be used, for how long, when vasopressors may be introduced and why, and when it should be withdrawn according to specific parameters describing the evolution of the clinical condition.

| | Normal values | ER | T0 | T1 |
|---|---|---|---|---|
| **HR (b/min)** | 60-100 | 90 | 130 | 100 |
| **PA (mmHg)** | 90-120 | 90/50 | 75/40 | 100/65 |
| **RR (b/min)** | 9-19 | 20 | 25 | 19 |
| **$SpO_2$ (%)** | 94-98 | 94 | 91 | 95 |
| **BT (°C)** | 35,2-36,9 | 39 | 39 | 37,4 |
| **MAP (mmHg)** | >65 | 64 | 53 | 65 |
| **GCS** | 15 | 15 | 15 | 15 |
| **pH** | 7,35-7,45 | 7,46 | 7,42 | 7.43 |
| **pO2 (mmHg)** | 83-108 | 82 | 73 | 86 |
| **HCO3- (mMol/L)** | 21-28 | 28 | 28 | 28 |
| **Lactate (mMol/L)** | 0,5-1,6 | 0.6 | 0,7 | 0.7 |
| **CVP (mmHg)** | 0-2 | | 4 | 4 |
| **ScVO2 (%)** | >70 | | 61 | 68 |
| **ΔpCO2** | <6 | | 2 | 3 |
| **WBC (x 109/L)** | 4,00 - 10,00 | 0,69 | 0,42 | 0.42 |
| **Hb (g/dL)** | 14,0 - 18,0 | 9,2 | 7 | 7 |
| **Plt (x 109/L)** | 140 - 440 | 23 | 30 | 30 |
| **Fibrinogen (mg/dL)** | 200-400 | 393 | 437 | 579 |
| **Creatinine (mg/dL)** | 0,16-0,39 | 1,47 | 1,34 | 1,07 |
| **Total bilirubin (mg/dL)** | 0,2-1 | 1,0 | 1.1 | 1,1 |
| **PCT (ng/mL)** | <0,5 | 4,22 | 30.4 | 17,30 |
| **PCR (mg/dL)** | <5 | 57 | 130 | 73 |
| **TrT hs (pg/mL)** | <14 | 45 | 48 | 41 |

**Table 1.** Vitals, hemodynamic and labs parameters of Case 1.

*Abbreviations: MAP: mean arterial pressure; CVP: central venous pressure; ScVO2: central venous oxygen saturation; ⊿pCO2: venous-arterial pCO2 gradient; WBC: white blood cell count; RBC: red blood cell count; Hb: hemoglobin; Htc: hematocrit; MCV: mean corpuscular volume; MCH: mean hemoglobin concentration; MCHC: mean corpuscular hemoglobin concentration; RDW-CV: red blood cells distribution width; Ptl: platelet count; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; GOT: glutamic-oxaloacetic transaminase; GPT: glutamate pyruvate transaminase; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; PCT: procalcitonine; CRP: C-reactive protein; hs-cTnT: high sensibility cardiac troponin.*

## *Case 2: Recruiting the heat to restore the coupling with peripheral resistances*

An 80-year-old man was brought to the ED for high fever with profound asthenia in the last 15 days, unresponsive to paracetamol and antibiotics prescribed by his primary care physician. His past medical history showed a previous anterior STEMI, treated with primary percutaneous angioplasty. A cardiac defibrillator (ICD) was implanted in primary prevention, in the presence of moderate LV dysfunction, with an improvement of his LV systolic function in following years. At the first evaluation in the Emergency Room, the patient presented mild abdominal pain and asthenia, on auscultation basal left lung crackles, at abdominal examination pain at the palpation in the right upper quadrant; the patient was alert, no neurologic deficit. The ABG showed compensated lactic acidosis, while labs showed severe acute renal failure and increased markers of myocardial damage (Table 2, ER evaluation).

We begin fluid resuscitation with crystalloids, but after a fluid bolus weight-targeted of 30 ml/kg fluids in one hour, hypotension persisted (Table 2, T0 evaluation); we began infusion of NE at low dosage (0.2 mcg/kg/min) and we reached a MAP > 65 mmHg. Hemodynamic monitoring by means of a central venous line showed increased central venous pressure, decreased central venous saturation and normal delta pCO2 (Table 2); no fluid-responsiveness was evidenced by echocardiographic monitoring of aortic flow during passive leg raising. Respiratory exchange tended to worsen and echocardiography showed severe LV systolic dysfunction (LV EF 20%), altogether with RV systolic dysfunction (TAPSE 14 mm) and moderate mitral regurgitation. A new onset or a worsening of left or

right ventricular systolic dysfunction during sepsis is a common event, with obvious consequences on the treatment plan, and, presumably, even on prognosis. In the presence of a pre-existing ischemic heart disease, the diagnosis could be challenging. However, the absence of chest pain, new onset of ECG ischemia-related alterations and a significant troponin curve (first point of TnT 121 pg/ml, second 128 pg/dl), alongside the bi ventricular dysfunction with a non-segmental pattern, made the diagnosis of Acute Coronary Syndrome unlikely. We further increased the dosage of NE up to 0.4 mcg/kg/min and introduced low-dose (2 mcg/kg/min) dobutamine. A chest- abdomen CT scan documented left pararenal abscess. Antibiotic therapy with meropenem was begun and a percutaneous drainage of the abscess was performed. Within 72 hours we were able to suspend vasopressor and inotropic treatment, with restoration of a stable hemodynamic and adequate diuresis, as well as an improvement of LF EF. We presented this case to show that noradrenaline, eventually coupled with dobutamine, is effective even in the presence of left ventricular dysfunction, as it may improve contractility by increasing preload and coronary perfusion, with a concomitant increase in contractility by dobutamine. This therapeutic association could have a role in coping with the ventriculo-arterial uncoupling, frequently present in septic shock, and could restore an adequate correspondence between LV performance and the load opposed by the arterial circulation.

| | Normal values | ER | T0 | T1 |
|---|---|---|---|---|
| **HR (b/min)** | 60-100 | 110 | 108 | 105 |
| **PA (mmHg)** | 90-120 | 80/50 | 80/50 | 90/55 |
| **RR (b/min)** | 9-19 | 28 | 26 | 24 |
| **$SpO_2$ (%)** | 94-98 | 90% | 95% | 95% |
| **BT (°C)** | 35,2-36,9 | 38,7 | 37,5 | 36,7 |
| **MAP (mmHg)** | >65 | 60 | 60 | 75 |
| **GCS** | 15 | 15 | 15 | 15 |
| **pH** | 7,35-7,45 | 7,47 | 7,41 | 7,43 |
| **pO2 (mmHg)** | 83-108 | 69,9 | 92 | 85 |
| **HCO3- (mMol/L)** | 21-28 | 25 | 21 | 22 |
| **Lactate (mMol/L)** | 0,5-1,6 | 2,5 | 1,9 | 1,4 |
| **CVP (mmHg)** | 0-2 | | 13 | 11 |
| **ScVO2 (%)** | >70 | | 50% | 65% |
| **ΔpCO2** | <6 | | 4 | 4 |
| **WBC (x 109/L)** | 4,00 - 10,00 | 20,8 | | 15,0 |
| **Hb (g/dL)** | 14,0 - 18,0 | 10,2 | | 10,1 |
| **Plt (x 109/L)** | 140 - 440 | 118 | | 121 |
| **Fibrinogen (mg/dL)** | 200-400 | 510 | | 121 |
| **Creatinine (mg/dL)** | 0,16-0,39 | 3,71 | | 2,21 |
| **Total bilirubin (mg/dL)** | 0,2-1 | 0.8 | | 0,8 |
| **PCT (ng/mL)** | <0,5 | 3,4 | | 1,48 |
| **PCR (mg/dL)** | <5 | 312 | | 268 |
| **TrT hs (pg/mL)** | <14 | 121 | | 128 |

**Table 2.** Vitals, hemodynamic and labs parameters of Case 2.

*Abbreviations: see previous Table*

# Discussion

## *Fluids in sepsis: are septic patients really empty?*

Recommendations on fluid administration in the early resuscitation of septic patients significantly changed in recent years. The first version of the Early Goal Directed Therapy prescribed to discontinue fluid administration only after the achievement of an "adequate" filling pressure, whatever the necessary amount of infused fluids [4]. In following years, several authors reported the negative prognostic effect of an excessive fluid administration, with increased mortality in patients in the highest quartiles of central venous pressure [5]. In fact, inappropriate fluid administration induces vasodilation and tissue oedema, with consequent worse perfusion and oxygenation.

## *The first bolus: which supporting evidences?*

In 2012, SSC recommended beginning the early resuscitation in septic patients with a fluid bolus of 30 ml/kg in the first 3 hours after the diagnosis; the evidences supporting this advice were reportedly low, but this became the standard of care [6]. In following years, several authors questioned this approach, due to the absence of robust data supporting them [7][8]. However, no trial was conceived to evaluate the real advantages or damages of this practice and all the trials that evaluated fluid administration in the early phases of sepsis took for granted the first bolus. On the other side, a recent retrospective analysis by Kuttab and coll. [9] demonstrated that the failure to complete the first bolus was associated with increased in-hospital mortality, irrespective of comorbidities. Therefore, in actuality, we do not have evidence to support the administration of the first bolus, but it may represent a reasonable compromise to prevent both fluid overload and the risk to begin vasopressors in a fluid-depleted circulation, with high risk of ischemia, especially in the splanchnic district.

## *Fluid replacement after early resuscitation*

The situation is different as regards to the administration of fluids after the first bolus. As shown in the clinical cases we reported before, a consistent proportion of patients are not fluid-responders after the first bolus and, in the event of persistent hypotension, further administration of fluids will not be beneficial. After the first fluid bolus, SCC recommends employing dynamic tests to ascertain the persistence of fluid-responsiveness, because only in that case further fluid administration is useful for hemodynamic stabilization [10]. In patients who reach the hemodynamic stability, fluid replacement may be considered adequate in the absence of signs of hypoperfusion, like lactate levels or urine output. In the presence of persistent hypotension, treating physicians have to choose between administering further fluids or vasopressors.

In Table 3, we reported an overview of the main studies published after 2020 about the possibility to protocolize the fluid regimen after the first fluid bolus. The FRESH study was the only one which included an evaluation of the fluid-responsiveness as a criterion for the randomization process [11]. The size of the FRESH population was limited and it failed to demonstrate a positive effect of this strategy on the patients' prognosis. Further studies, also including large populations, reached similar conclusions [12][13][14]. A recent meta-analysis confirmed these results [15].

| | Year | Study population | Design | Protocol | End-points | Main results |
|---|---|---|---|---|---|---|
| **FRESH study** Fluid Response Evaluation in Sepsis Hypotension and Shock | 2020 | Patients admitted to the ED for sepsis, already treated with the first fluid bolus, with anticipated ICU admission: 83 patients in the intervention arm and 41 with usual care | Prospective, multicenter, randomized clinical trial | **Intervention arm**: assessment for fluid responsiveness before clinically driven fluid bolus or increase in vasopressors. **Control arm**: usual care. | Primary endpoint: the difference between the two treatment groups mean fluid balance at 72 hours or ICU discharge | Lower fluid balance at 72 hours or ICU discharge (-1.37 l) Reduced need of renal replacement therapy (5% vs 18%) or mechanical ventilation (18% vs 34%); |
| **CLOVERS study**: Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension | 2023 | 1563 patients: 782 assigned to the restrictive fluid group and 781 to the liberal fluid group | Multicenter, randomized, unblinded superiority trial | **Restrictive fluid strategy**: prioritizing vasopressors and lower intravenous fluid volumes. **Liberal fluid strategy**: prioritizing higher volumes of intravenous fluids before vasopressor use. | Primary outcome: all-cause mortality before discharge home by day 90. | Less fluids administered in the Group assigned to the restrictive strategy. No difference in the mortality rate and occurrence of serious adverse events. |
| **REFACED study**: Restrictive | 2022 | Sepsis patients without shock: 123 patients, with 61 in | Multicenter, randomized | **Fluid restriction**: fluid boluses | Primary outcome: total IV crystalloid | At 24 , significantly less fluids |


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| | Year | Study population | Design | Protocol | End-points | Main results |
|---|---|---|---|---|---|---|
| fluids versus standard care in adults with sepsis in the emergency department | | the Fluid restriction group and 62 assigned to standard care. | feasibility trial | only permitted if predefined criteria for hypoperfusion occurred. **Standard care**: at the discretion of the treating team. | fluid volumes at 24 after randomization | administrered in the Fluid restriction group (mean difference –801l). No differences between groups in adverse events, use of mechanical ventilation or vasopressors, acute kidney failure, length of stay, or mortality |
| **CLASSIC trial**: Restriction of Intravenous Fluid in ICU Patients with Septic Shock | 2022 | Patients with septic shock in the ICU: 1554 patients; 770 in the restrictive-fluid group and 784 in the standard-fluid group | International, randomized trial | **Restrictive-fluid group**: intravenous fluid (1L) could only be given under pre-specified-conditions. **Standard fluid group**: no upper limit for the amount of intravenous fluids | Primary outcome: all-cause mortality by day 90. | Restrictive fluid group: median of 1798 ml of intravenous fluids vs 3811 ml the standard-fluid group No difference in the mortality rate or incidence of serious adverse events. |

**Table 3**. Recent papers comparing different fluid regimens in septic patients: an overview.

We would have some considerations in front of these findings. Firstly, none of these trails included an evaluation of fluid tolerance and only the FRESH study considered the presence of fluid responsiveness. The administration of fluids is a meaningful therapy in fluid -responder patients, that means those, whose cardiocirculatory system is on the ascending phase of the Frank-Starling curve and who will increase their cardiac output with fluid replacement. In the absence of this picture, fluids will not influence cardiovascular performance, while, in those non-fluid tolerant, will be detrimental by increasing tissue edema and organ dysfunction. A simple tool like lung ultrasound allow clinicians to ascertain the presence of lung fluid overload at the bedside, and could probably improve the stratification of patients, when deciding the most appropriate fluid regimen. Moreover, we are used to speaking about sepsis, as a homogeneous entity, but a septic shock caused by pneumonia or infectious colitis are significantly different from many points of view, and the amount of fluids for the resuscitation is one of the most relevant. Randomizing patients to different fluid regimens, without considering the real advantages of administering further fluids and the sepsis source may determine the assignment of several patients to the inappropriate strategy and hamper the advantages of having a protocolized fluid regimen.

On the other side, we have to consider that septic patients receive fluids in several ways, including maintenance treatment and fluid necessary for the administration of other treatments. Considering all these modalities is quite troublesome, but the global fluid count can significantly hamper the true difference between different regimens of fluid administration. Finally, the mortality rate in septic patients is conditioned by many factors, including comorbidities, type and source of the infection, possible secondary infections due the immunosuppression developed after the acute phase and irreversible organ failure, and this is especially true when considering 30- or 90-day mortality. The choice of a shorter follow-up could allow to obtain a meaningful picture of the real prognostic weight of early fluid resuscitation.

In the actuality, we do not have robust results to support a change of ongoing clinical practice, without reliable criteria to assign patients to a fluid regimen tailored on their needs: the “one size fits all” strategy does not seem to function in this choice. The actual recommendation of a cautious

administration of fluids based on the evaluation of fluid-responsiveness should be completed by a concomitant evaluation of fluid tolerance, in order to avoid both overload and inadequate resuscitation.

### *From sepsis to septic shock: vasopressors for the regulation of peripheral resistance*

The SSC recommends considering vasopressors after the first fluid bolus, when an adequate mean arterial pressure is not achieved by fluid resuscitation [10], with the aim to reverse arterial dilation and to improve tissue perfusion. The rationale beyond this recommendation is the possibility to prevent prolonged or severe hypotension, both linked to an unfavorable prognosis of patients with septic shock [16][17]. NE is the first-choice vasopressor in septic shock. In fact, it combines a strong α-adrenergic activity that causes vasoconstriction both in the arterial and venous tree, without a significant positive chronotropic effect. Vasopressin and its analogues are considered second-line vasopressors, as recent evidence suggests no benefit with their early administration. In the presence of refractory hypotension, NE can be increased up to doses ≥1 μg/kg/min, but the current suggestion is to combine NE with other vasopressors such as vasopressin, with the intent to achieving the MAP target without using very high dosages of NE.

### *Which is the correct moment to begin vasopressors?*

The issue of NE timing is strictly linked to the controversies regarding the possible benefits of a restricted fluid regimen, as there is a point in the resuscitation phase, when we have to decide which of these treatments is best for that specific patient. One more time, sepsis is not a homogeneous disease, as how much the presence of hypotension is due to volume depletion for increased loses or to vasoplegia caused by the cytokine storm should be assessed, and the therapy should be tailored to address the prevailing mechanism. Several authors reported the advantages of the early NE administration[18][19][20]. In a large group of patients with distributive shock, Vincent and coll. demonstrated that the longer the duration of hypotension, the higher the ICU mortality, independent to SOFA score, lactate level and several other parameters of disease severity [17]. In Table 4, we reported an overview of the most recent study about the effects of an early administration of NE. Results were contradictory and they do not support a change of recommendations.

| | Year | Study population | Design | Protocol | End-points | Main results |
|---|---|---|---|---|---|---|
| **Early Use of Norepinephrine Improves Survival in Septic Shock: Earlier than Early** | 2019 | 101 patients admitted to the emergency department with septic shock, 57 in the Early group and 44 in the Late group | Randomized multicenter study | **Early group**: early NEP simultaneously with IV fluids **Late group**: after failed fluids trial | Primary outcome: in-hospital survival | The Early group showed: • Shorter time to achieve MAP>65 mmHg • Reduced mortality rate (46% vs 72%) |
| **CENSER study**: Early Use of Norepinephrine in Septic Shock Resuscitation | 2019 | 310 adults diagnosed with sepsis with hypotension, 155 in each subgroup. | Single-center, randomized, double-blind, placebo-controlled clinical trial | **Early norepinephrine**: low-dose NE together with fluid resuscitation **Standard treatment** | Primary outcome: shock control rate by 6 hours after diagnosis | In the Early group, • shock control rate by 6 hours achieved in 76% vs 48%; • 28-day mortality rate not different, • lower incidences of cardiogenic pulmonary edema and new-onset arrhythmia |
| **Effects of very early start of** | 2020 | Patients with sepsis requiring VP | Propensity score based | Veryearly (VE-VPs) or delayed | Primary outcome: | In the VE-VPs group: |

| | Year | Study population | Design | Protocol | End-points | Main results |
|---|---|---|---|---|---|---|
| **norepinephrine in patients with septic shock: a propensity score-based analysis** | | support for at least 6 h selected from a prospectively collected database and classified into VeryEarly NE (VE-VPs, n = 93) or Delayed (D-VPs, n = 93) | analysis | vasopressor start (D-VPs) categories according to whether norepinephrine was initiated or not within/before the next hour of the first resuscitative fluid load. | all-cause mortality by day 30 | • significant lower net fluid balances 8 and 24 h after VPs<br>• significant reduction in the risk of death compared to D-VPs |
| **Vasopressor Initiation Within 1 Hour of Fluid Loading Is Associated With Increased Mortality in Septic Shock Patients: Analysis of National Registry Data** | 2022 | Patients with septic shock, classified into Early (*n* = 149), propensity matched to Late (*n* = 149) patients. | Prospective, multicenter, observational study | **Early patients**: VP initiated within 1 hour of the first resuscitative fluid load.<br>**Late patients**: VP initiated more than 1 hour of the first resuscitative fluid load. | Primary outcome: all-cause mortality by day 28 | In the Early group, compared to the late group:<br>• SOFA score and lactate level higher at day-3 of ICU stay<br>• Significantly higher mortality rate |

**Table 4.** Timing of the use of noradrenaline in sepsis: an overview of most recent papers

Recently, Roberts and coll. explored the relationship between the dosing intensity of NE in the first 24

hours and in-hospital mortality [21]. They demonstrated that increasing dosage of vasopressors during the first 24 hours after the diagnosis was associated with increased mortality risk, but increasing volumes of administered fluids in the first 6 hours attenuated this relationship. On the other hand, early high exposure to vasopressors was associated with lower mortality compared to later and sustained exposure. Therefore, early aggressive vasopressor titration appears to be safer than a slow titration to high doses, but an early adequate fluid resuscitation is needed to avoid potential deleterious effects of high-dose vasopressors. In other words, the early administration of NE must be associated with a complete fluid resuscitation, to prevent ischemic damage.

## *Vasopressors and sepsis-induced myocardial dysfunction*

The treatment with NE may impact the management and prognosis also in the presence of sepsis induced myocardial dysfunction, for its ability to increase cardiac output by different mechanisms [20] [22]. In fact, through its α-adrenergic-mediated reduction of venous capacitance, it increases the cardiac preload, with consequent increase in cardiac index [18]. Contemporarily, it may reduce preload-dependency. Monnet and coll. showed that in patients with a positive passive leg raising test, the adjunct of NE reduced the response of cardiac index after a second test conducted a few minutes after the beginning of vasopressors [19]. The authors interpreted these data as a demonstration that in the presence of improved contractility, myocardial function was less sensitive to the preload. Moreover, Hamzaoui and coll. evidenced that early NE administration increased LV EF and other indices of left and right systolic function [22]. This was possible thanks to the improvement in the coronary perfusion pressure through an increase in the diastolic arterial pressure (DAP), and to β1-adrenergic stimulation of the cardiomyocytes. In a small series of patients with septic shock, we demonstrated that NE infusion, administered when indicated based on current guidelines, improved LV systolic function, evaluated by means of a load-independent parameter of contractility, like LV Global Longitudinal Strain. This effect was confirmed in patients with baseline normal and reduced systolic function, confirming that this effect is mainly mediated by a direct action on contractility alongside an increase in preload more than in afterload [23].

## *The role of vasopressin*

Another hot topic is the indication to add a second vasopressor in case of persistent shock during NE infusion, which can happen especially in the presence of an inadequate source control. Vasopressin is

the treatment of choice, as during shock states a relative deficiency may develop. It has potent vasoconstrictive activity, without the negative effects linked to the sympathetic overstimulation especially on heart function and rhythm. The timing and NE dosage to begin vasopressin remains a topic of debate. In a retrospective study, Sacha and coll. demonstrated that beginning vasopressin reduced in-hospital mortality rate, when initiated at lower rather than higher NE dosages, as well as in the presence of lower lactate levels [24]. These results have to be interpreted cautiously, as these characteristics could also identify patients with well resuscitated shock, but they represent a further confirmation that avoiding high NE dosage and restoring promptly an adequate perfusion have a definite positive prognostic effect. In actuality, the way to obtain these results has to be tailored on every patient, considering their usual pressure values, their cardiac function and possibly, in a hopeful near future, the guidance of new biomarkers, like copeptin, which partially reflects vasopressin levels [25].

## *Inotropes in septic shock: recruiting the heart in the fight!*

### *The use of inotropes: the role of dobutamine*

Surviving Sepsis Campaign suggests the use of dobutamine in the presence of myocardial dysfunction, indicated by elevated cardiac filling pressures and low cardiac output or ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and mean arterial pressure [10].

Dobutamine used in clinical practice is a racemic mixture of (+) and (−) enantiomers. The (−) enantiomer has a prevalent α-1 agonist activity, with strong effects on arterial pressure, while the (+)-enantiomer is a potent β-1 and β-2 agonist, with minimal agonist activity on the alpha counterpart. The final effect is an increased cardiac output due to the positive inotropic stimulus, with variable and usually mild effects on peripheral vascular resistance and mean arterial pressure, due to the mutual compensation of the vascular effects of each isomer [26]. Surprisingly, the favorable effects of low doses of dobutamine on microcirculatory blood flow seem to be independent from macro hemodynamics [27][28]. In this sense, dobutamine could exert a favorable effect on microvascular blood flow distribution, and consequently, on the cellular oxygen consumption capabilities. No randomized controlled trials have compared the effects of dobutamine versus placebo on clinical outcomes, but several studies had investigated the action of this inotrope in resuscitation protocols. All. The studies, which included the administration of dobutamine in their protocol for the early

resuscitation of septic patients (EGDT, ProCESS, ProMISe and ARISE trial) did not perform any specific analysis on how the use of dobutamine impacted prognosis [4][29][30][31]. In a cohort of patients with septic shock, Wilkman and coll. reported a higher 90-day mortality (43% vs. 24%, P<0.001) and hospital mortality (19% vs. 34%, P<0.001) in patients who received inotropes than those who did not [24], alongside a higher age and APACHE II score. However, those who received inotropes were more ill than the rest of the group, as shown by their higher CVP, lactate levels and dosage of vasoactive medications. The authors themselves recognized the need of further prospective studies to assess the real prognostic weight of the treatment with inotrope medications. A recent meta-analysis, which investigated the prognostic effect of several vasoactive medications, demonstrated that the combination of NE and dobutamine was associated with a reduction in 28-day mortality in patients with septic shock, especially in those with low cardiac output [32].

Most of the aforementioned studies regarding the use of dobutamine in septic shock have been conducted more than ten years ago, when the awareness about the specific features of sepsis induced cardiomyopathy was less than now. In fact, we demonstrated that the classical echocardiographic indices of myocardial function failed to diagnose the presence of myocardial dysfunction in a relevant proportion of septic patients [33][34]. In the presence of reduced peripheral resistances, the heart can show a normal chamber function, mirrored by a normal ejection fraction, despite a reduced myocardial contractility. The employment of new indices of contractility, like Global Longitudinal Strain, showed that sepsis-induced myocardial dysfunction is present in most of septic patients, up to 60-80% of them, and its presence exerts a relevant prognostic effect [35][36]. Whether the use of dobutamine could improve the myocardial performance and the prognosis of septic patients remains actually undefined. The need of an appropriate selection of patients to treat with inotropes has clearly emerged, in terms of hemodynamic profile and entity of myocardial dysfunction, alongside a better definition of the timing and dosing of the inotropes. Several trials are actually ongoing, in order to clarify these relevant and intriguing issues [37][38].

## *The use of inotropes: the role of medications independent to adrenergic system*

Cardiac myocyte $Ca^{++}$ homeostasis is commonly altered during sepsis and lipopolysaccharide exposure, with serious alterations in cardiac muscle contractility. Nevertheless, it is not clear whether this phenomenon is the product of an abnormal rapid calcium cycling [39], a decreased myofilament sensitivity to calcium [40] or an inadequate intracellular calcium handling.

Levosimendan is a Calcium ($Ca^{++}$) sensitizer that augments myocardial contractility by inducing conformational changes in troponin-C (TnC), thus enhancing its sensitivity to $Ca^{++}$. The extent of actin–myosin interaction increases, independent to the concentration of intracellular $Ca^{++}$, in the absence of a relevant increase in myocardial oxygen consumption [41]. This increased $Ca^{++}$ sensitivity can exert a negative effect on the relaxation phase ("negative lusitropic effect"), with a potential worsening of the diastolic dysfunction already present in several septic patients. However, levosimendan also has a potent inhibitory effect on PDE-3, which determines a positive lusitropic effect and antagonizes the consequences of $Ca^{++}$ sensitization [42][43]. In the peripheral circulation, levosimendan activates ATP-sensitive $K^{+}$channels, leading to systemic vasodilation [44]. A recent meta-analysis by Feng and coll. explored the effectiveness of levosimendan in septic patients and it showed that this medication improved cardiac function and reduced lactate levels, without significant effects on the mortality rate. Once again, the selection criteria probably played a crucial role, as the inclusion of an unknown proportion of patients with normal systolic function could have influenced these results [45].

Milrinone is a phosphodiesterase inhibitor that can be considered as an inotropic agent and, at the same time, a vasodilator, capable of inhibiting intracellular degradation of cyclic AMP. It is able to increase myocardial contractility, without leading to an increase in myocardial oxygen consumption [46][47] and its hemodynamic effects consist in the increase of the cardiac index and in the reduction of pulmonary artery pressure and wedge pressure [48]. Data about efficacy and safety of its use in sepsis are scarce and, in actuality, mostly derived from experimental studies. A recent subgroup analysis of a big-data, real world study showed that, compared to dobutamine, milrinone did not decrease in-hospital mortality, but it increased the use of renal replacement therapy and the hospital length of stay.

Cardiovascular failure during sepsis is caused by a complex interplay of cardiac and vascular factors, which compromise both macro- and microcirculation, and finally result in reduced organ perfusion and multisystem failure. We try to manage this complex pathophysiology with medications that act both on heart and vessels, but their effects are sometimes detrimental: dobutamine is used for the positive inotropic effect, but its positive chronotropic effect or the vasodilation may be deleterious in septic patients. This is probably the reason why the data on the effectiveness of these treatments are disappointing. A careful selection of patients based on hemodynamic monitoring and

echocardiographic assessment or left and right systolic and diastolic performance will be probably the key to offer the right medication to the right patient, in the most appropriate moment of its disease.

## Conclusions

In summary, fluids administration and early employment of NE in septic shock unresponsive to fluids are gaining more precise support in literature, and should be considered by the next guidelines, alongside with the "dark sides" of most inotropes. This manuscript was not intended to add something to existing literature, but to present an overview of the hot topics regarding the early resuscitation of septic patients. Clinicians could be helped by this presentation in applying correctly current guidelines, without inappropriate adoption of new uncertain therapeutic approaches, but able to consider weaknesses and drawbacks of several usual treatments. In actuality, we do not have clear answers, but we can be aware of areas of uncertainty, in order to apply them cautiously and, why not, evaluate new selection criteria and treatment options by rigorous studies.

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