Fluids and vasopressors in septic shock: basic knowledge for a first approach in the emergency department

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Abstract

Much research, both pathophysiological and clinical, has been produced on septic shock during the last 20 years. Nevertheless, many aspects of treatment are still controversial, among these the approach to the administration of fluids and vasopressors. Moreover, most clinical research on septic shock was produced in the ICU setting on mechanically ventilated and invasively monitored patients, a situation hardly comparable to that of most emergency rooms throughout the world. In this non-systematic review, the basic pathophysiological concepts and the most important messages from clinical studies will be summarized, with the aim to identify the baseline skills and knowledge necessary for a first approach to septic shock patients in the emergency room.

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Introduction

Knowledge of pathophysiology and clinical trials are the landmarks of modern medical practice.

Unfortunately, pathophysiological knowledge is often incomplete, and the results of clinical trials may be at odds with each other. The practicing physician must therefore strive to critically use the information derived from these two branches of research to respond as well as possible to each patient's needs.

Many important studies, both pathophysiological and clinical, have been conducted over the past twenty years. Consequently, the approach to patients in septic shock has improved and mortality has fallen,[1] yet controversies are still open as many important questions need answers and additional research.[2] Moreover, most clinical research on septic shock was produced in the ICU setting on mechanically ventilated and invasively monitored patients, a situation hardly comparable to that of most Emergency Departments (ED) throughout the world. This article summarizes the most important aspects of the administration of fluids and vasopressors, based on a personal selection from the endless literature on the topic, to propose as a conclusion some operational suggestions for daily medical practice in the ED.

Macro and microcirculation in septic shock

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. From the perspective of macrocirculation, septic shock is a distributive shock characterized by increased venous capacitance and decreased Systemic Vascular Resistance (SVR). The reduction in parietal tone and increased capacitance of the venous circulation has the most significant hemodynamic effect,[3,4] because about 75% of the blood volume circulates in the veins. As the disease advances, almost half the patients with septic shock develop a cardiomyopathy[5,6] which can significantly impair ventricular function, affecting the Cardiac Output (CO).

Turning to microcirculation, a complex interaction between pro and anti-inflammatory and coagulative phenomena[7] produces endothelial dysfunction, glycocalyx degradation, altered blood cell rheology, and imbalance between the levels of vasodilating and vasoconstricting substances, altering the matching of blood flow to tissue demand.[8] It has been demonstrated that sepsis is associated with reduced microvascular density, an increased number of non-perfused small vessels, and heterogeneity among microcirculatory areas. The direction, extent, and duration of these reactions are determined by factors related to the host (genetics, age, co-pathology, immunodepression) and the pathogen (microbial load and virulence).

Macrocirculatory status can be assessed by the direct or indirect measurement of parameters such as Stroke Volume (SV), Central Venous Pressure (CVP), and Blood Pressure (BP).[9] However, CVP and BP have only a low to moderate predictive

power in assessing response to treatment, being reliable only for very significant variations of their values.[10,11] Although SV is a much better indicator, its measurement requires expertise, and its accuracy in predicting response to treatment is higher for sedated and mechanically ventilated patients for whom hemodynamic and respiratory parameters can be more precisely evaluated. Microcirculatory alterations are more difficult to assess because their assessment relies on semiquantitative measurements that are difficult to apply in emergency, such like the direct visualization of the sublingual capillary network.[12] Because an improvement in macrocirculation does not necessarily correspond to an improvement in microcirculation and peripheral perfusion, the most useful parameters for guiding therapy remain, despite some controversy,[13-15] those that assess tissue oxygenation trends (lactate, $ScvO_2$, veno-arterial PCO_2 gradient)[16] in addition to clinical parameters (level of consciousness, urinary output, and capillary refill time - CRT).[17-18] In a recent trial, patients randomized to CRT-guided resuscitation fared as well or better compared with patients randomized to lactate-guided therapy.[19]

In conclusion, no single measurement best identifies the severity of the shock, nor how an individual patient will respond to fluid administration and other treatments. A combination of clinical signs, hemodynamic parameters, and laboratory tests will continue to be used by physicians according to their level of expertise and the availability of diagnostic instruments.

The determinants of cardiac output

Cardiac output is determined by preload, inotropism, and afterload. Inotropism and preload are directly related to CO, while afterload has an inverse relation. Therefore, when BP falls in front of no change (or an increase) in CO, the primary problem must be a decrease in SVR. On the contrary, when BP falls and CO falls too, the primary problem stays with CO and the next question is whether CO fell because of a decrease in inotropism or in venous return.[3,20] It is unanimously agreed that the administration of fluids and vasopressors has the main clinical goal of enhancing CO through an increase of preload. When this is not the case, they are at best useless and can be detrimental.

The return of systemic venous blood to the heart is determined by the difference between Mean Venous Filling Pressure (MSFP) and Central Venous Pressure (CVP).[3,12] MSFP is the pressure that would be measured at each point in the circulatory system (excluding the heart and pulmonary circulation) if the heart stopped and blood was redistributed instantaneously so that the pressure was the same at each point. Mean venous filling pressure tends to remain constant even for large changes in CO, is not clinically measurable, and is estimated to be between 7 and 12 mmHg in humans.[3]

MSFP is determined by intravascular volume and venous tone. Intravascular volume can be considered as consisting of two parts. The first one, which represents about 85% of the total volume (Vt) exerts no pressure on the vascular walls and theoretically represents the volume that corresponds to an MSFP=0. For this reason, it is referred to as the *unstressed volume* (Vu). The second one, representing the remaining 15% of Vt, exerts the hydrostatic pressure responsible for MSFP and is consequently referred to as the *stressed volume* (Vs).[21] As we will see later, fluids increase Vs replenishing the venous circulation, while vasopressors act on Vs inducing venous constriction.

The role of blood pressure and peripheral resistance

BP plays an important role in determining organ blood flow and therefore it is often used as a surrogate index of tissue perfusion, although this cannot be considered a reliable practice.[22] Blood pressure is the product of CO and systemic vascular resistances, but it is the vascular resistances of each specific organ that determine regional flows. Thus, the distribution of local arterial resistances is the major determinant of where blood goes. If the distribution of vascular resistances changes, blood flow will perfuse the different organs proportionally to the dilation of their arteriolar circulation. The use of vasopressors to induce constriction in the arterioles is based on the assumption that resistance will increase less in vital organs, such as the brain, kidney, and heart, because of the play of local neuronal and hormonal signals, thus favouring the flow to these districts.

Unfortunately, however, in septic patients the ability to autoregulate vascular tone is often impaired.[23] Thus, it is difficult to foresee the effects that the administration of adrenergic agents may have on regional flows. Moreover, while systemic resistances can be calculated by invasive methods or derived by SV and CVP, regional vascular resistances cannot be measured nor calculated in the clinical setting.

The physiological and pharmacological basis of treatment with fluids and vasoactive drugs

The generalized vasoplegia that characterizes septic shock causes a reduction in venous tone with an increase in vascular bed capacitance. As a consequence, when physiological compensation mechanisms are inadequate, both stressed volume and preload are reduced. This situation can be managed in one of two ways: increasing intravascular volume with fluids or increasing venous tone with vasopressors. More often, the decision is made to administer both, to balance the positive and undesirable effects of the two interventions.

Fluids

Crystalloids are the fluids of choice because they have a better benefit/risk ratio than colloids.[24] Recent meta-analyses are conflicting as to whether balanced crystalloid solutions are superior to saline, but most authors recommend their use since saline causes hyperchloremic metabolic acidosis when given rapidly or in large volumes and may increase the risk of acute kidney injury.[25-27] The main problem with crystalloids is their limited stay in the intravascular space and rapid passage into the interstitium of more than three-quarters of the administered volume. This is further promoted by sepsis-induced alterations in endothelial permeability.[28] Interstitial edema hampers oxygen transport to the tissues and can be a serious clinical problem because it may affect the lung parenchyma and increase intra-abdominal pressure. Finally, fluid administration may be ineffective in patients with left ventricular failure who reach the plateau phase of the Frank-Starling curve very early (Figure 1). In this case, the effect of preload on stroke volume may be little or absent, when not counterproductive.

The evaluation of fluid responsiveness, especially outside the ICU, is a much-discussed item that goes beyond the aims of this review.[29] Measuring SV modification after passive leg raising or a fluid bolus administration is the preferred method when instrumentation and expertise are available. Echocardiography is probably the best option to measure SV in the ED setting, since the number

of emergency doctors trained in this technique is growing, while other non-invasive approaches are either too clumsy to use or simply too little diffused. Other measures, like respiratory diameter variation of the inferior vena cava, require confirmatory studies and are reliable in non-ventilated patients only for very significant changes.[30] Yet, most patients in septic shock do show a complete inspiratory collapse of the inferior vena cava, and this can be used as a proxy indicator of fluid responsiveness, or at least of the patient's capability to tolerate a further fluid bolus. Lastly, it is important to point out that being a fluid responder doesn't necessarily mean requiring fluids. Most people who are well and in hemodynamic equilibrium will respond to fluids, but this is not a good reason to treat them.

Vasopressors

The choice generally falls on norepinephrine[31] which has a higher a_1-receptor affinity and safety profile than dopamine and adrenaline.[32,33] Noradrenaline mainly affects CO by reducing the capacitance of the venous circulation, thus increasing stressed volume and venous return. The problem with noradrenaline (especially at the higher doses) is an increase in SVR which could cause an excessive load for a failing heart, despite the positive inotropic effect of this drug.[34] Lastly, the effect of vasopressors on septic shock is difficult to foresee, considering that an altered response to adrenergic stimulation is often encountered in patients with overwhelming bacterial infections.[35]

Inotropes

Administration of dobutamine has a sound pathophysiological basis and is employed in patients with septic shock that persists after adequate fluid loading and administration of noradrenaline, because of its important inotropic effect.[36] Undesirable effects of dobutamine include increased myocardial O2 consumption and its action on the AV node that can increase heart rate in patients with AF.[37]

Before moving on to clinical studies, it may be helpful to summarize the main messages of this very concise overview on the pathophysiology and pharmacology of septic shock. Data on macrocirculation and hemodynamics corroborate the importance of both fluids and vasopressor drugs in improving preload and CO. However, they also show that the efficacy of fluids on preload decreases approaching the plateau phase of the Frank-Starling curve and that this happens much earlier in patients with left ventricular failure. Because of the risk of pulmonary edema, fluid administration to these patients should be particularly careful. Noradrenaline finds a strong rationale in its positive effects on preload and there are sound reasons to support its use in the early stage of septic shock, following initial fluid replenishment. Lastly, the analysis of microcirculatory changes, which are complex, variable, and not directly measurable, cautions against the illusion that a standardized ("*one fits all"*) treatment can be used, and reminds us of the importance of an individualized therapeutic approach.

Epidemiological data

Epidemiological data clearly show that mortality from sepsis has fallen over the past two decades, although the incidence of this syndrome has not declined.[1] They also show that mortality is related to factors such as the site of infection (e.g., lung more than urinary tract), age (in England, nearly 80% of patients who die from sepsis are over 75 years old), and a state of fragility. An interesting editorial from a few years ago, based on English data, points out that sepsis is often the terminal event of a severe and debilitating chronic disease.[38] However, epidemiological data suffer from important limitations. Firstly, they relate mostly to Western countries with advanced healthcare systems and are based mainly on registers of deaths from the hospital settings. Secondly, following major international initiatives to combat sepsis (e.g., Surviving Sepsis Campaign), attention to the problem has increased and many more patients have been recognized as septic. A higher denominator may therefore be responsible for an apparent reduction in mortality.[39] To better understand the role that fluids and vasopressor drugs have played in improving mortality from septic shock, it is then necessary to examine the results of clinical trials.

Observational studies and controlled clinical trials

Fluids

Most studies on fluids in the treatment of sepsis and septic shock are observational studies and as such suffer from important limitations. The populations studied are often not homogeneous with each other (in terms of age, site of infection, co-pathologies, and the severity of septic picture) and have been enrolled predominantly in intensive care units. Consequently, many studies exclude the large proportion of subjects who, for various reasons, are treated outside the ICU and who account for most cases in daily practice. Analysing these studies in chronological order, one can recognize first of all a long series of papers with historical controls that, referring to the pivotal study by Rivers in 2001 (see below),[40] confirm that patients treated according to the Early Goal-Directed Therapy (EGDT) have lower mortality than patients treated with a "traditional" approach.[41-44] Without going into too much detail, suffice it to say that the EGDT protocol required the administration of fluids until CVP values = 8-12 mmHg were reached and considered the administration of vasopressors only after this step was completed. An adequate central venous saturation was the ultimate

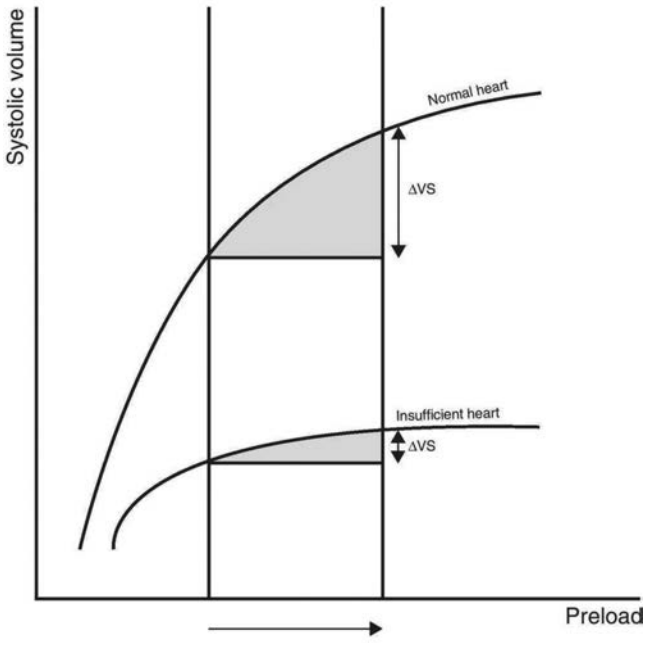

Figure 1. Frank-Starling curve in the normal and insufficient heart.

goal. The EGDT approach was strongly criticized in later years,[45-48] but this did not prevent it from becoming the reference for international guidelines for almost 15 years.[49] In 2017, though, an important paper documented that almost all the benefits shown by the observational studies on EGDT could be attributed to the earlier administration of antibiotic treatment, a likely by-product of the growing attention to speed up all therapeutic interventions.[50]

A second set of observational studies grew out of concern that the EGDT approach could lead to the harmful overuse of fluids. These studies collectively documented that a positive fluid balance at 12-48 hours after diagnosis is associated with increased mortality.[51,52] Other studies showed that a higher cumulative fluid balance was associated with the subsequent development of major adverse kidney events.[53,54] This new awareness stimulated a progressive reversal of fluid administration protocols in septic shock and renewed interest in the early administration of vasopressor drugs.

Among Randomized Clinical Trials (RCT), three large studies which challenged the results of the original EGDT trial should be mentioned, if only for their size. All three studies (ARISE, ProMISe, and ProCESS)[55-57] failed to demonstrate a benefit with EGDT. Nevertheless, their results are difficult to interpret since they were conducted about 15 years after the original study by Rivers, when the general approach to septic patients had already changed profoundly. It is important to notice that in all EGDT studies, patients received more than 2 L of fluids before randomization, and at least 2 L more during the first 6 hours of treatment (Table 1). More interesting, with regard to our topic, are several smaller studies that specifically investigated the amount of fluids to be given in the acute phase of septic shock.[58,59] Most studies that compared a restrictive versus a liberal use of fluids pointed towards a beneficial effect of fluid restriction, but they were not powered to reach statistical significance. In most cases, however, these studies enrolled patients who had already been admitted to the ICU and for whom the quantity of fluids administered before admission was not always clearly reported. Of particular interest is a pilot study that enrolled patients at the time of their arrival at the emergency department. In this study, patients in both groups had received approximately 35/mL/Hg of crystalloids at the time of enrolment and remained in shock, so the difference between the two groups was limited to the hours following randomization. Patients randomized to restrictive treatment received, in the first 24 hours, half the fluids that were administered to controls, with no difference in mortality and with a suggestive reduction (although not statistically significant) in ICU stay and hours of mechanical ventilation and amine administration. It must be emphasized, however, that in this study patients both in the treated and in the control group received much less fluid (respectively 7.8 ± 13.3 and 16.6 ± 23.2 mL/Kg in the first 24 hours) than in each of the four randomized EGDT studies (Table 1). Two recent, randomized studies of adequate numerosity have given a very important contribution to settling the problem since neither demonstrated any clinically significant advantage (or disadvantage) for patients treated with a restrictive fluid approach.[60,61] Considering that in both studies patients had received 1 to 3 L crystalloids before randomization, the message seems to be that after an initial resuscitative bolus, and as far as the first 24 hrs of treatment are concerned, the amount of fluids administered is not such an important determinant of outcome.

The Surviving Sepsis Campaign guidelines recommend initiating 30 mL/kg of IV crystalloids to patients with suspected sepsis within 1-3 hours in case of hypotension or lactate level greater than or equal to 4 μmol/L. Although this is a strong recommendation, it is based upon evidence of low quality. Moreover, specific subpopulations might need different approaches. For instance, patients with hypotension but normal lactate (which should not be considered in septic shock according to the Sepsis 3 definitions) have a better outcome and might need a less aggressive approach.[62] On the other hand, studies aiming to normalize lactate levels in normotensive patients have given conflicting results.[63,64] In clinical practice, determining the optimal amount of fluid to be administered remains a critical issue that might never find a solution appropriate for every case.[64] There is growing agreement that a four-step protocol (Figure 2) should be adopted in most situations, with an aggressive initial approach, followed by optimization and quick reduction in the subsequent hours and days.[65,66]

Vasopressors

Studies on vasopressors are far fewer in number and even less conclusive than those on volemic replenishment. As in the case of fluids, there are no clinical studies comparing patients treated or untreated with vasopressors, but only comparisons between different drugs and timing of treatment.

Noradrenaline is the drug of choice according to the Surviving Sepsis Campaign guidelines and this advice is compatible with available data on the efficacy and side effects of different vasopressors.[67] Vasopressin has also been studied as an adjunctive treatment or first-line therapy, with uneven results. As to the timing of administration, provisional conclusions from the scanty available evidence can be summarized by saying that early treatment with vasopressors (<2h from the onset of shock) seems to be associated with

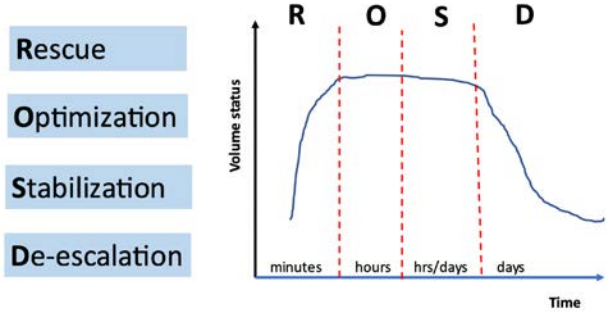

Figure 2. Four-step approach to fluid administration in shock.

Table 1. Fluid administration in the 4 randomized trials on EGDT.

Fluids (mL)	RIVERS (2001)	ARISE (2014)	PROCESS (2014)	PROMISE (2015)
Pre-random	?	2515±1244	2254±1472	1950
0-6h	4981±2984	2226±1363	2805±1957	2000
6-72	8625±5162	4274±3071	4458±3878	3623
Total	13606±8146	8753±5730	9517±7307	7573

a more favorable prognosis.[68,69] An interesting retrospective large study suggests that the best effect of vasoactive amines can be obtained by starting their administration no earlier than 1 hour and no later than 6 hours after the diagnosis and following an initial fluid replenishment of at least 1000 mL.[70] Other studies document that higher doses or a more protracted time of treatment are associated with higher mortality,[71,72] but this evidence is affected by the fact that it is generally the most severe patients who receive the most intense and prolonged drug treatment. Finally, a possible negative immunomodulatory effect of noradrenaline has been discussed.[73] Clinical documentation for dobutamine is also sparse and inconclusive although guidelines continue to recommend it in patients with impaired inotropism and poor response to fluids and noradrenaline. In the large EGDT studies, dobutamine was used in about 1% of patients in the control group and 10-15% of patients in the EGDT group with no difference in mortality. Moreover, several studies seem to document a positive effect of b-blockers in patients with septic shock, making it even more problematic to employ a drug with a strong b-agonist activity.[74]

Sepsis at the end of life

Although sepsis and septic shock can occur at any age, almost 80% of deaths in British hospitals concern patients >75 years of age. The high incidence of frailty and severe comorbidities makes most sepsis-related deaths not directly attributable to sepsis, nor preventable through timely therapeutic interventions. In a point prevalence study in British hospitals including 521 patients with sepsis and 136 deaths, only 40 deaths were directly or possibly attributable to sepsis.[75] Of these, 77.5% were in patients who had substantial frailty, and 70% were in patients who were considered not to resuscitate in the event of cardiac arrest. A US study estimated that only 12% of sepsis deaths were possibly-to-definitely preventable.[76]

Although it is difficult to retrieve data on the percentage of patients with septic shock who are directly admitted from the ED to the ICU, it is a common experience that the very elderly and frailest patients are often admitted to general wards. This limits the monitoring capability as well as the aggressiveness of therapy.

A practical approach to the early therapy of septic shock in the ED

As we have seen, a substantial number of patients with septic shock are not admitted to the ICU because of frailty and severe comorbidities. It is thus of the utmost importance that the chance of a patient being admitted to the ICU is evaluated early. When ICU seems a concrete possibility, the intensivists should be informed and involved from the very early stages of therapy. When ICU admission is not envisaged, the clinical approach must be carried out within the frame of the available monitoring equipment and physicians' expertise. Basic competence in sonography is the minimum standard acceptable for ED physicians called to treat patients in septic shock. Competence in echocardiography to estimate SV would be a welcome addition.

Both the physiology of macrocirculation and microcirculation and the results of clinical trials confirm that fluids and vasopressors are indicated and effective in the treatment of septic shock. As we have seen, the most recent data tend to favour an earlier initiation of vasopressors than previously advised. In evaluating the approach to fluid administration, one must consider that ED physicians face septic patients with hypotension that are not always similar to those treated in clinical trials (that by definition are enrolled only after a first ineffective bolus of crystalloids). As a consequence, although the administration of 30 mL/Kg of crystalloids in the first 3 hours is still recommended by the Surviving Sepsis Campaign guidelines and sounds reasonable as a first approach, it might be appropriate to evaluate the efficacy of volume expansion as early as after the first 1000 mL of crystalloids. Particular attention should be paid to patients with left ventricular failure, in whom volemic expansion has little effect on preload and may cause pulmonary edema. A respiratory collapse >50% of the inferior vena cava is an acceptable sign that the patient will tolerate a further fluid bolus, though not the best way to evaluate fluid responsiveness. Repeated pulmonary ultrasound may help identify the early signs of interstitial edema.

The lack of a consistent correlation between improved hemodynamic values and tissue oxygenation status suggests that macrocirculation-related parameters (PA, CVP, SV when available) be always evaluated in the light of tissue perfusion sensitive parameters (level of consciousness, urinary output, CRT, lactates, SVcO2). CRT is an old, but recently revaluated assessment that is easy to perform, can be repeated frequently, and might be particularly appropriate for the ED setting.

After the first 1000 mL, crystalloids should be preferentially administered in boluses of 250-500 mL followed by the revaluation of the patient's vital parameters and one or more among IVC and pulmonary sonography, SV, CRT. As a rough guide, it could be kept in mind that patients enrolled in the major clinical studies on septic shock received an average of 4 L of crystalloids in the first 6 hours, with a rapid reduction thereafter.

Noradrenaline is the vasopressor of choice and, when necessary, it can be first administered in a peripheral vein.[77] The addition of other vasopressors (adrenaline or vasopressin) is acceptable in patients who do not respond to noradrenaline. The use of inotropic drugs has a rationale in case of left ventricular insufficiency and an inadequate response to fluids and noradrenaline, although it is not supported by appropriate clinical trials. Echocardiography may help identify patients that could better respond to inotropes.[78] This treatment, as well as the administration of adrenaline, should be constantly monitored and reserved for patients followed in an intensive care setting.

Since an early and appropriate antimicrobial treatment has the best correlation with prognosis, ED physicians should pay the utmost attention to identifying and possibly removing the source of infection. Early cultures and initiation of antibiotic treatment are also of paramount importance.

Finally, the very frail patients in whom sepsis is the final event of advanced chronic disease should be spared unnecessary clinical aggressiveness and be started on palliative care early.

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