

When sepsis affects the heart: A case report and literature review

Giuseppe Clemente, Antonino Tuttolomondo, Daniela Colomba, Rosaria Pecoraro, Chiara Renda, Vittoriano Della Corte, Carlo Maida, Irene Simonetta, Antonio Pinto

Giuseppe Clemente, Antonino Tuttolomondo, Daniela Colomba, Rosaria Pecoraro, Chiara Renda, Vittoriano Della Corte, Carlo Maida, Irene Simonetta, Antonio Pinto, U.O.C. di Medicina Interna e Cardioangiologia, University of Palermo, 90127 Palermo, Italy

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Correspondence to: Antonino Tuttolomondo, MD, U.O.C. di Medicina Interna e Cardioangiologia, University of Palermo, P.zza delle Cliniche, n.2, 90127 Palermo, Italy. bruno.tuttolomondo@unipa.it
 Telephone: +39-91-6552128
 Fax: +39-91-6552142

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Abstract

A 59-year-old nursing home patient with Down syndrome was brought to the internal medicine department of our hospital due to fever, cough without expectorate, and dyspnea. A thoracic computed tomography revealed the presence of bilateral basal parenchymal opacities. Her condition deteriorated after admission and troponin reached a peak serum concentration of 16.9 ng/mL. The patient was in cardiogenic shock. In addition to fluid resuscitation, vaso-active amine infusion was administered to achieve hemodynamic stabilization. The differential diagnosis investigated possible pulmonary embolism, myocardial infarction, and myocarditis. Furthermore, a second transthoracic echocardiogram suggested Tako-Tsubo syndrome. This is a septic patient. The purpose of this manuscript is to review studies which formerly examined the possible association between high levels of troponin and mortality to see if it can be considered a positive predictive factor of fatal prognosis as the case of thrombocytopenia, already a positive independent predictive factor of multiple organ failure syndrome, and generally to characterize risk profile in a septic patient.

Key words: Sepsis; Shock; Hypotension; Troponin; Myocardial dysfunction

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Core tip: The importance of cardiac involvement during sepsis, when occurs, worsens prognosis. However, as myocardial dysfunction is reversible, an early diagnosis and treatment to improve the survival. The awareness of risk profile to develop a severe myocardial dysfunction in a septic patient would be suitable in order to enforce careful resources in this subset of patients. Moreover, other research are needful to perform the best therapeutic strategy of haemodynamic stay which,

sometimes, (*e.g.*, when Tako-Tsubo syndrome occurs) can call for intra-aortic balloon pump counter pulsation.

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INTRODUCTION

Sepsis is a syndrome caused by the inefficiency of the mechanisms of control and containment of the infection. It is characterized by symptoms and signs of systemic inflammatory reaction to infection and manifestations of organ dysfunction resulting from alterations in the microcirculation.

It is the second most common cause of death in non-coronary intensive units, and the tenth in high-income countries, with a mortality rate between 15% and 50%. Approximately 150000 deaths per year are caused by sepsis in Europe. The number of cases is expected to increase at a rate of 1.5% per year from the current prevalence of 3 cases for every 1000 inhabitants^[1].

The most common pathogenic Gram positives (whose incidence is progressively increasing) are *Staphylococcus aureus* and *Streptococcus pneumoniae*, whereas among the most frequent Gram negatives it is possible to include *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa*^[2].

In a smaller percentage of cases, sepsis can be caused by mycobacteria, mycetes, protozoa (*Plasmodium falciparum*) and viruses^[1].

CASE REPORT

A 59-year-old nursing home patient with Down syndrome had high fever unresponsive to paracetamol, and unproductive cough for 4 d. Accordingly, ceftriaxone was administered with some improvement (defervescence and reduction of cough). After the reappearance of fever associated with dyspnea, acrocyanosis, and her deteriorating condition, she was brought to the emergency room, and on initial evaluation she was admitted to the internal medicine department of our hospital. She had a ventricular (pacing), ventricular (sensing), inhibition (response) (and) rate-adaptive holder pacemaker because of a third degree atrioventricular block. Furthermore, her past medical history included chronic cerebrovascular disease due to previous ischemic strokes complicated by vascular dementia and epilepsy. The latter was possibly due to Alzheimer-like disease as is often seen in down syndrome patients.

On arrival in the internal medicine department the patient was drowsy, tachypneic, tachycardic, low blood pressure (80/50 mmHg) and hypoxemic (PaO₂

57 mmHg). The thoracic computed tomography (CT) revealed the presence of bilateral basal parenchymal opacities. The patient was treated empirically with piperacillin/tazobactam, levofloxacin, and vancomycin according to protocol for health care-associated pneumonia. An initial bed-side echocardiogram evaluation revealed severe left ventricular dysfunction with an ejection fraction of 36%, and dilatation of the right ventricle with medium-apical akinesis. In addition to fluid resuscitation, dopamine, dobutamin, and norepinephrine infusion were administered. At times simultaneous administration of two vaso-active amines was necessary to achieve hemodynamic stabilization and adequate diuresis. The first electrocardiogram showed regular activation of the pacemaker and subsequent evaluations revealed repolarization abnormalities of probable hypoxic nature in the inferior wall only (Figure 1).

The results of blood tests are shown in Table 1, reporting thrombocytopenia (80000 10³/μL) and the peak serum concentration of troponin I (16.9 ng/mL - reference range < 0.012 ng/mL). Blood and urine cultures showed no growth.

A second transthoracic echocardiogram showed akinesis of medium-apical segments of both ventricles with moderate systolic dysfunction (E.F. 45%). This evidence does not rule out an acute ischemic event, but could be seen as suggesting Tako-Tsubo syndrome.

The differential diagnosis also concerned pulmonary embolism, myocardial infarction and myocarditis. The former was excluded through execution of CT angiography. In relation to myocardial infarction and myocarditis, it was not possible to perform coronary angiography or a myocardial biopsy. However, the absence of persistent regional abnormalities ruled out acute coronary syndrome. The third transthoracic echocardiogram showed complete remission of the regional abnormalities (E.F. 50%). The patient was discharged after gradual weaning from vaso-active amines in adequate clinical condition. Therefore, our patient had survived, in spite of severe cardiac involvement and possible Tako-Tsubo syndrome.

DISCUSSION

In our case there was a significant cardiac involvement associated with sepsis due to pneumonia, up to heart failure which presented itself as an out-and-out cardiogenic shock. The "fluid resuscitation", the administration of vasoactive amines and early antibiotic therapy were needed to restore the hemodynamic stability, until the complete recovery of cardiac function, as indeed typically happens in Tako-Tsubo syndrome. The latter, in our patient, was induced by septic injury and characterized initially by hypokinesia of intermediate and apical segments of left ventricle and at a later stage by akinesis of the same with hyperkinesia of basal segment that typically characterizes the disease.

Nevertheless, the absence of head trauma, cerebral hemorrhage, pheochromocytoma, hypertrophic cardiomyopathy made the diagnosis of Tako-Tsubo syndrome

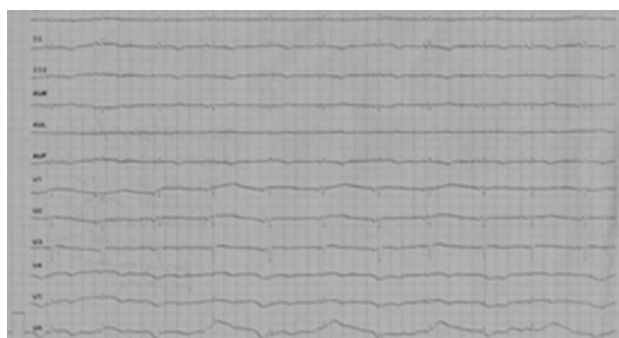


Figure 1 Electrocardiogram at the third day from presentation (showed repolarization abnormalities of probable hypoxic nature in the inferior wall).

plausible. Instead, it was ruled out obstructive atherosclerosis of coronary epicardial artery, since coronary angiography has not been carried out within 48 h, as suggested by Mayo Clinic's diagnostic criteria^[3]. However, the disappearance of the alterations of the segmental kinesis at echocardiographic final assessment, allowed us to exclude this diagnosis. Endomyocardial biopsy would have been necessary for ruling out a myocarditis, in which the predominant involvement of right ventricle is quite, as it has been at any rate^[4] initially in our case. The clinical presentation, at last, was not suggestive of Guillain-Barré syndrome^[5] nor electrocardiographic monitoring of recurrent ventricular tachycardia^[6], conditions in which cases of reversible left ventricular dysfunction have been observed^[7]. Therefore, differential diagnosis about Tako-Tsubo syndrome has been ruled out after analyzing anamnesis and clinical presentation. The latter (hypotension, tachycardia, hypoxiemia) also was suggestive of pulmonary embolism, excluded by CT angiography.

The principal cardiovascular manifestation of severe sepsis and septic shock is hypotension and myocardial dysfunction is often associated with them. Myocardial dysfunction does not seem to be caused by myocardial hypoperfusion^[8,9] (coronary circulation is maintained or even intensified, although to observe disfunctions in the microcirculation is probable)^[10] but rather by the action of depressant factors such as alpha tumor necrosis factor and beta interleukin 1 and does persist despite fluid resuscitation, as Court *et al.*^[11] have already shown. In addition to the effects of host's immuno-inflammatory responses (*e.g.*, cytokines and mechanisms related to nitric oxide)^[12] circulating substances released by pathogens (*e.g.*, endotoxins) also seem to play an important role in provoking myocardial depression. In this sense, the first-line therapy is causal and consists of antibiotic therapy associate with the possible surgical excision of the infectious focus^[13]. However, the restoration of hemodynamic stability is an important goal for the survival of the patient. Fluids remain a first-step therapy in clinical management of the cardiovascular failure in sepsis but it is arguable which of them would be the gold standard. Recent results indicate that

Table 1 Results of blood tests on admission and discharge

	Admission	Discharge	Reference range
Aspartate aminotransferase (U/L)	94	17	< 37
Alanine aminotransferase (U/L)	66	37	< 41
Calcaemia (mg/dL)	7.5	7.4	8.4-10.2
Gamma-glutamyltranspeptidase (U/L)	155	171	8-61
C-reactive protein (mg/dL)	14.6	3.2	0-0.5
Alkaline phosphatase (U/L)	163	47	40-129
Lactate dehydrogenase (UI/L)	755	511	240-480
Ferritin (ng/mL)	2440		15-150
D-dimer (ng/mL)	478	338	10-250
RB count ($\times 10^6/\mu\text{L}$)	3.72	3.53	4.5-5.5
Hemoglobin (g/dL)	12.5	11.7	12-18
Platelet count ($\times 10^3/\mu\text{L}$)	92	217	150-450
Myoglobin (ng/mL)	1031	99	0-62
Troponin I (ng/mL)	6.43	1.36	0-0.034

albumin also might be used with advantage in some specific subgroups of patients pending for the results of the ongoing trials on new generation starches^[14]. Furthermore, thanks to its electrostatics properties, albumin reduces the endothelial permeability (sealing effect)^[15-20]. Its efficacy is still now matter of debate. In patients with severe sepsis, treated with albumin and crystalloids compared with ones treated with crystalloids only, an increase in survival to 28 and 90 d was not observed^[21]. As regards the methods of liquids' administration, according to Surviving Sepsis Campaign 2012, an initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, up to achieve ≥ 30 mL of crystalloids per kilogram of body weight. It would be needed to continue with the fluid-challenge technique until an actual hemodynamic improvement. Yet, a particular attention in balancing the fluids is necessary, inasmuch a positive fluid balance and elevated central venous pressure are associated with increased mortality^[22,23].

With ongoing sepsis, advantageous effects, especially as for cardiac output, could be gained with administration of hypertonic saline solutions, as Oliveira *et al.*^[24] already suggested in their review. For the first time, this kind of therapy was employed in the treatment of hemorrhagic and traumatic shock, with quick restoration of central and peripheral blood flow^[25]. Intravenous infusion of hypertonic saline solution summons fluids into vascular compartment and determines a redistribution of blood flow which, as for that matter our team has shown, in refractory heart failure enhances myocardial performance^[26]. The proposed mechanism to explain these effects suggests a direct action on myocardial functionality and a decreased sympathetic tone^[27]. Hence, infusion of hypertonic saline could be an alternative to early volume resuscitation of a patient with sepsis^[28].

Furthermore, in a multicentric trial conducted in a tertiary care setting, protocol-based resuscitation of patients with septic shock diagnosed in the emergency

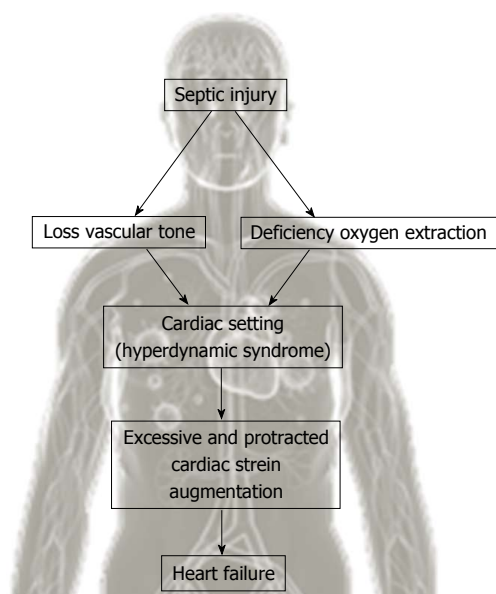


Figure 2 Synopsis of heart failure pathogenesis sepsis.

department, does not improve the outcomes^[29].

Even more complex is the pathogenesis of heart failure that could occur during sepsis and which can provoke a significant increase of troponin.

The increase of troponin in sepsis is an event to be rationally expected. Its dosage, therefore, should not be taken for granted. Considering the heart's fundamental cardiovascular adaptation role in sepsis, a significant metabolic-inflammatory impairment can occur with high levels of troponin, associated with severe myocardial dysfunction. Moreover, a meta-analysis in "Intensive Care Medicine" a year ago evaluated the prognostic role of troponin in sepsis, showing that its elevated serum concentration was associated with a subset of patients at higher risk of death. Nonetheless, further studies are needed to determine an optimal troponin cut-off value^[30]. B-type natriuretic peptides could also have a role in alerting clinicians to myocardial dysfunction. Their low serum values could exclude severe myocardial impairment. Yet echocardiography is the gold standard method to reveal cardiac dysfunction. Heart rate has also been proposed in the prognostic evaluation of septic patients. A rate of < 106 bpm on presentation suggested a favorable prognosis^[31]. Concerning the latter, it is still debatable whether the use of β -blockers in septic tachycardial patients improves the survival. It has been observed that patients being in chronic treatment with β -blockers and later developed sepsis, and were admitted to the intensive care unit (ICU), could have advantages in terms of survival. However, physicians' doubts about using β -blockers in early stages of sepsis are licit^[32]. Among other things, it is not still clear enough if in septic shock the increased cardiac rate is pathological or simply an expression of sympathetic hyperactivation. Instead, tachycardia is associated with a worse prognosis. In a prospective observational study in an ICU, esmolol's titrated administration for 24

h, maintaining a cardiac rate between 80 and 94 bpm in selected adult patients in septic shock after 24 h of hemodynamic stabilization, was able to maintain the microvascular blood flow and reduced the demand for epinephrine. However, patients with severe myocardial dysfunction had been excluded from the study^[33]. Recent results suggest that β -blockers' effects on metabolism, glucidic homeostasis, inflammatory feedback and cardiac function might be advantageous for septic patients^[34,35]. In regard to the anti-inflammatory, antioxidant, immunomodulatory and anti-apoptotic actions, statins also might fall within preventing and treating patients with severe sepsis and septic shock^[36,37].

However, beyond the value of troponin, B-type natriuretic peptides, and heart rate, the presence of myocardial dysfunction in sepsis is associated with higher mortality. It has been shown that cardiovascular disablement increased mortality from 70% to 90%, compared to 20% in septic patients without myocardial impairment^[38].

Therefore, cardiac dysfunction in sepsis has prognostic value and coincides with its severity. Hence it's mandatory to know the pathophysiology of cardiovascular disease in sepsis. Microcirculatory disfunctions and mitochondrial derangement occurring in septic shock reduce the cellular energetic production^[39]. Septic injury triggers a reaction in the cardiovascular setting that aims to increase the peripheral availability of oxygen and reduce the cellular effects of oxygen deficiency^[40]. The cellular deficiency of oxygen and reduction in systemic vascular resistance give rise to hyperdynamic syndrome (increased stroke volume, heart rate, usage of oxygen)^[41] (Figure 2). Alteration of cellular energetic production following to mitochondrial imbalances might be of great relevance in determining tissue injury and sepsis-associated multi organ failure. Future studies should focus on mitochondrial disfunction in order to comprehend the pathophysiological mechanisms of apoptosis and cellular protection to achieve a increasingly accurate treatment^[42].

Such a hyperdynamic reaction, favoring adrenergic stimulation, can be hidden by hypovolemia due to insufficient fluid contribution or a mechanism of myocardial impairment^[43] (Figure 3). The most frequent occurrence is heart failure with high cardiac index, which is in a phase of unbalance, but it is insufficient to increase metabolic requirements. Hyperdynamic syndrome endows an organism with the possibility to reduce septic injury and survival derives largely from that^[44]. Hence the usefulness of administering inotropic positive drugs and to correct hypovolemia because a possible condition of circulatory failure, in the presence of increased oxygen requirements, is linked to a fatal prognosis^[45].

The management of myocardial dysfunction sepsis-induced encompasses fluids's administration until the optimization of preload and, among positive inotropic agents, norepinephrine is the first choice^[39]. The administration of dopamine should be reserved to carefully selected patients (those with a low risk of

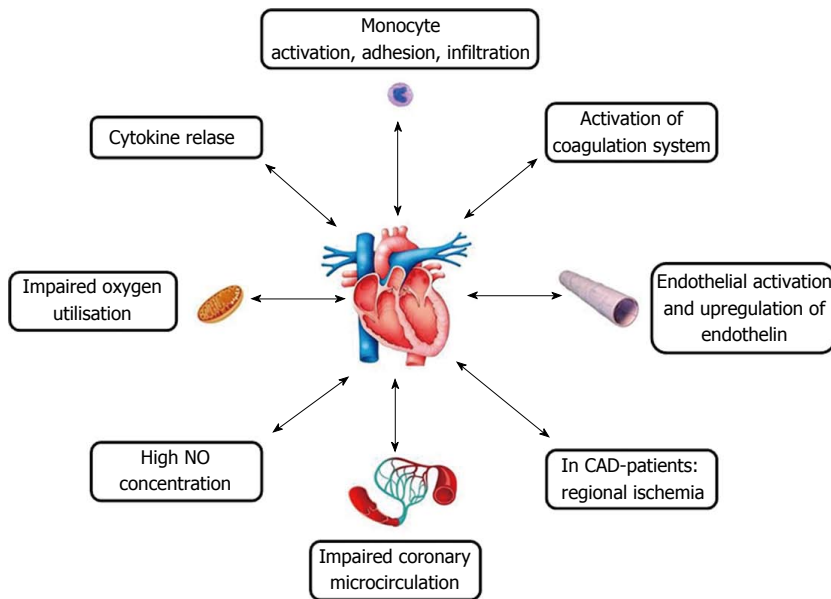


Figure 3 Possible mechanisms of myocardial impairment^[43].

arrhythmias and either known grave left ventricular systolic dysfunction or low heart rate). The Surviving Sepsis Campaign guidelines 2012 promote either norepinephrine or dopamine as the first-choice vasopressor agent to maintain adequate perfusion tissue in septic shock^[46,47]. Dobutamine also can be used in the early stages of sepsis in order to increase cardiac output. It has a certain selectivity for β_1 -receptors^[48]. Anyway, β_1 -agonists can be less effective in case of septic shock. It has been shown that its infusion improves the left ventricular ejection fraction more than 10% in 35% of patients affected by septic shock^[49]. Its use requires careful clinical and instrumental monitoring for risk of tachycardia or arrhythmias and hypotension through β_2 -adrenergic receptors activation^[50]. However, dobutamine is endorsed as the care's fundamental element of sepsis-related cardiovascular failure in international guidelines. Furthermore, it has been demonstrated that dobutamine enhances liver function and hepatic perfusion after experimental hemorrhagic shock^[51]. Since one of the mechanisms of sepsis-induced myocardial dysfunction is the alteration of intracellular transport of calcium, a possibility of therapy might be represented by levosimendan^[52], inotrope and peripheral vasodilator which is employed in acute congestive heart failure^[53]. Levosimendan, acting with a mechanism of calcium-sensibilization in randomized studies comparing it with dobutamine in patients with severe heart failure with low cardiac output, has been observed as emodynamically more effective than dobutamine^[54-56].

Another kind of heart failure associated with sepsis is Tako-Tsubo syndrome. For this reason it has been supposed that sepsis-induced systemic inflammation could have a role in starting the pathogenesis of the syndrome^[57-59]. Myocardial dysfunction in sepsis could be a consequence of the direct action of different

mediators of flogosis (catecholamines responsible for hyperdynamic syndrome included) and of products of microbial derivation^[13]. On the other hand, another pathogenic hypothesis for Tako-Tsubo syndrome is cardiac catecholamine toxicity, as it could occur in sepsis, which would constitute the trigger^[60].

Our case shows that exogenous support of vasoactive amines can be essential in facilitating hyperdynamic syndrome which characterizes sepsis in the pre-clinical phase. As for Tako-Tsubo syndrome, even though β -agonist agents have often been used, the results are conflicting^[7], so intra-aortic balloon pump counter pulsation remains the first-line treatment if, after medical therapy (dopamine) and volume resuscitation, hypotension endures^[61]. However, the disappearance of segmental kinesis's alterations and complete resolution of myocardial dysfunction, as in our case, if Tako-Tsubo syndrome is actually diagnosed, offer new perspectives that could improve our understanding of the physiopathology of this illness. Randomized clinical trials could demonstrate the possible efficacy of the treatment.

COMMENTS

Case characteristics

A 59-year-old nursing home patient with down syndrome presented fever, cough and dyspnea.

Clinical diagnosis

Main clinical findings were tachypnea, tachycardia and hypotension.

Differential diagnosis

Computed tomography (CT) angiography, thoracic CT, transthoracic echocardiogram were executed and differential diagnosis concerned pulmonary embolism, myocardial infarction, myocarditis, Tako-Tsubo syndrome and sepsis with severe myocardial involvement.

Laboratory diagnosis

The results of blood tests showed alterations of liver function (aspartate aminotransferase: 94 U/L; alanine aminotransferase: 66 U/L; gamma-glutamyl-transpeptidase: 155 U/L; alkaline phosphatase: 163 U/L); ferritin: 2240 ng/mL; myoglobin: 1031 ng/mL; C-reactive protein: 14.6 mg/dL; lactate dehydrogenase: 755 U/L; calcaemia: 75 mg/dL; D-Dimer: 478 ng/mL; thrombocytopenia ($92000 \times 10^3/\mu\text{L}$); myoglobin: 1031 ng/mL; troponin: I 643 with peak serum concentration of 169 ng/mL.

Imaging diagnosis

Echocardiogram revealed severe left ventricular dysfunction with an ejection fraction of 36% and dilatation of the right ventricle with medium-apical akinesis.

Pathological diagnosis

The thoracic CT showed the presence of bilateral basal parenchymal opacities but blood cultures showed no growth.

Treatment

The patient was treated with piperacillin/tazobactam, levofloxacin, and vancomycin according to protocol for health care-associated pneumonia in add to fluid resuscitation and infusion of dopamine, dobutamin and norepinephrine.

Related reports

The sepsis-induced systemic inflammatory response syndrome can produce myocardial dysfunction that sometimes defines Tako-Tsubo syndrome.

Term explanation

The dosage of troponin and B-type natriuretic peptides, the monitoring cardiac rate can be helpful to identify setting risk of myocardial dysfunction during sepsis.

Experiences and lessons

This article points out the importance of early haemodynamic support with fluid resuscitation, vaso-active amine and catecholamines in sepsis-induced myocardial dysfunction, trying at the same time to define a risk profile of a septic patient with cardiac involvement whose mortality is high.

Peer-review

In spite of richness of literature about the cardiac involvement during sepsis and management of sepsis-induced myocardial dysfunction, other research to identify the more suitable therapeutic strategy is necessary.

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