# Parameters to direct resuscitation in septic patient

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**Abstract**

**Background:** Sepsis and septic shock are common conditions that are associated with unacceptably high mortality and for many of those who survive, long-term morbidity. The world health assembly and WHO made sepsis and septic shock a global priority and adopted a resolution to improve the prevention, diagnosis, and management of sepsis and septic shock. Increased awareness of the septic condition resulting from ongoing campaigns and the evidence arising from research in the past 10 years have increased understanding of this problem among clinicians and have led to improved outcomes. Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes. In septic shock there is an intense inflammatory response leads to marked vasodilation and hypotension. Monitoring of the peripheral circulation can be done noninvasively in contrast to the more traditional invasive systemic haemodynamic monitoring in the intensive care unit. Physical examination of peripheral circulation based on clinical assessment has been well emphasized for its convenience, accessibility, and relation to the prognosis of patients with circulatory shock. Early resuscitation is a key factor to limit progression to multiple organ dysfunction and death in patients with septic shock and this highlights the need to identify the best parameter to be targeted during therapy of shock aiming to achieve maximum benefit to those critical patients.

**Keywords:** Parameters, resuscitation, Septic shock

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## Introduction

Sepsis and septic shock are common conditions that are associated with unacceptably high mortality, and for many of those who survive, long-term morbidity **(1).**

**Definition of Sepsis** is a life-threatening organ dysfunction with a dysregulated host response to infection that assumed to be the result of the host's invasion by pathogenic organisms that then spread in the bloodstream **(2)**.

**Definition of septic shock** is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than in sepsis alone. Septic shock, the most severe complication of sepsis, is a deadly disease. This definition codifies organ dysfunction using the Sequential Organ Failure Assessment score **(3).**

## Incidence

In recent years, the incidence rate of sepsis has increased globally, severely threatening human health and posing a tremendous burden on the economy and society **(4)**.

Sepsis is frequently seen in cases of severe infection, trauma, burns, shock, and major surgery and further develops into multiple organ dysfunction syndrome (MODS), which is the primary cause of death among acute and critically ill patients **(5)**.

Sepsis and septic shock are impacting millions of people around the world each year and killing between one in three and one in six of those it affects **(5)**.

The world health assembly and WHO made sepsis and septic shock a global priority and adopted a resolution to improve the prevention, diagnosis, and management of sepsis and septic shock. Increased awareness of the septic condition resulting from ongoing campaigns and the evidence arising from research in the past 10 years have increased understanding of this problem among clinicians and lay people, and have led to improved outcomes. Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes **(1).**

**Aim**: The time-window for interventions is short, and treatment must promptly control the source of infection and restore hemodynamic homoeostasis.

The Surviving Sepsis Campaign, an international consortium of professional societies involved in critical care, treatment of infectious diseases, and emergency medicine, declared clinical guidelines for the management of severe sepsis and septic shock, these guidelines are intended to reflect best practice and are intended to provide guidance for the clinician caring for adult patients with sepsis or septic shock in the hospital setting **(1)**.

The principles of the initial management are to provide cardiorespiratory resuscitation and mitigate the immediate threats of uncontrolled infection. Resuscitation requires the use of intravenous fluids and vasopressors, with oxygen therapy and mechanical ventilation provided as necessary **(6)**.

The exact components required to optimize resuscitation, such as the choice and amount of fluids, appropriate type and intensity of hemodynamic monitoring, and role of adjunctive vasoactive agents, all remain the subject of ongoing debate and clinical trials **(7)** .

In septic shock there is an intense inflammatory response leads to marked vasodilation and hypotension **(8)**. Regional differences in vascular tone and microcirculatory dysfunction and, in its extreme, microvascular thrombosis can lead to regional hypoperfusion and organ dysfunction (referred to as distributive shock) **(9)**.

It is clear that the persistence of abnormal peripheral circulation is associated with worse patient outcomes **(9)**. Monitoring of the peripheral circulation can be done noninvasively in contrast to the more traditional invasive systemic haemodynamic monitoring in the intensive care unit. Physical examination of peripheral circulation based on clinical assessment has been well emphasized for its convenience, accessibility, and its relation to the prognosis of patients with circulatory shock **(10).**

Conventional haemodynamic parameters must be combined with the clinical assessment of peripheral circulation to continually monitor a critically ill patient as an attempt to optimize resuscitation **(11)**.

Early resuscitation is a key factor to limit progression to multiple organ dysfunction and death in patients with septic shock and this highlights the need to identify the best parameter to be targeted during therapy of shock aiming to achieve maximum benefit to those critical patients. **(1).**

Shock is characterized by increased serum lactate levels, base deficit and signs of tissue hypoperfusion including abnormal peripheral perfusion which can be indicated by capillary refill time( CRT ) **(11)**.

## Capillary refill time

Peripheral perfusion appears as a promising target for resuscitation. The excellent prognosis associated with CRT normalization and the rapid response time to fluid loading , plus its simplicity and availability in resource-limited settings, constitute a solid background to promote studies evaluating capillary refill time usefulness to guide fluid resuscitation **(12).**

It is defined as the duration of time needed for the patient's fingertip to regain color after direct pressure is applied to cause blanching. This concept was first introduced as a component of the international trauma severity score for the rapid and structured cardiopulmonary assessment of trauma patients **(15)**.

In a healthy patient, the CRT should be less than 2 seconds. Skin temperature, ambient room temperature, age, and vasoactive medications can significantly impact CRT and should be considered during each assessment **(16).**

Capillary refill time is the first parameter to be normalized in patients surviving from septic shock **(13)**.

The assessment of CRT in the patient with sepsis may seem counterintuitive because pathophysiologic derangements often lead to peripheral vasodilation resulting in warm, flushed extremities. However, emerging literature suggests CRT may be a valuable bed side tool to assess the adequacy of not only regional, but also global tissue perfusion during the resuscitation phase of septic shock **(14)**.

In the patient with sepsis, assuming the patient's extremities are normothermic, prolonged CRT suggests abnormal microcirculatory flow and need for further intervention **(10).**

Serial assessment of CRT with normalization at 6 hours is independently associated with successful resuscitation when compared against traditional resuscitation targets, such as ScvO2, Pcv-aCO2 gap, and lactate normalization **(13)**.

In critically ill patients, persistent prolonged CRT following initial haemodynamic optimization is associated with more severe organ dysfunction and higher odds for worsening organ failure **(10).**

Taken one step further, **Van Genderen et al.,** explored the effects of peripheral perfusion-guided fluid therapy in patients with septic shock and showed that early peripheral perfusion–targeted fluid resuscitation leads to a trend toward less fluids when compared with a conventional regimen, based on systemic hemodynamic parameters **(14)**.

Peripheral perfusion–targeted resuscitation indicated by capillary refill time was associated with beneficial effects on the SOFA score and mortality in patients with severe organ dysfunction**(10).**

Observational studies have shown that persistent abnormal peripheral perfusion after resuscitation is associated with organ failure and mortality **(12).**

**Serum Lactate**

Peripheral lactate, also referred to as lactic acid, has become one of the most widely used biomarkers to diagnose sepsis-induced organ dysfunction. Measurement of lactate in human blood was first described by Scherer in 1843 when he described a lethal case of fulminant septic shock due to puerperal fever in a young woman **(17)**.

Traditionally, a venous lactate greater than or equal to 4 mmol/L has been used as an initial screen for sepsis-induced organ dysfunction, but more recently, a lactate threshold of 2 mmol/L has been recommended. In a healthy individual at rest, peripheral lactate concentrations are usually ( 0.5 - 2 mmol/L) **(3).**

During periods of physiologic stress, lactate generation often occurs. An elevated lactate in the patient with sepsis has been associated with a significantly increased risk of mortality. Blood lactate concentrations in critically ill adult patients can be used to detect tissue hypoxia at an early stage, assess illness severity, and predict outcome. Serial measurements of blood lactate concentrations are more valuable than a single measurement, not only in providing a more precise assessment of prognosis, but also in evaluating response to treatment **(8)**.

Considering the strong relationship between hyperlactatemia, lactate kinetics, and mortality, the Surviving Sepsis Campaign, proposes to guide hemodynamic resuscitation by repeated measurement of blood lactate levels every 2 to 4 hours until normalization **(1).**

Traditional theory is that increased lactate production occurs in sepsis as a result of global tissue hypoxia, where oxygen supply (DO2) fails to meet oxygen demand (VO2). The resulting DO2/VO2 mismatch leads to increased anaerobic metabolism and a rise in the patient's lactate level **(18).**

Unfortunately, this simplistic explanation for a rise in lactate fails to consider multiple other physiologic and non-physiologic contributors to an elevated lactate **(13)**.

**Causes of elevated lactate level other than global tissue hypoxia**

1. **Aerobic glycolysis**: increased stress response, endogenous catecholamine release, and stimulation of B2 receptors **(19)**.
2. **Mitochondrial dysfunction (limited pyruvate metabolism)** - in septic conditions impaired activity of pyruvate dehydrogenase which is essential for the conversion of pyruvate into acetyl coenzyme A can cause hyperlactatemia **(20)**.
3. **Acute lung injury:** metabolic adaptation to inflammatory mediators **(19)**.
4. **Decreased lactate clearance**
    a. Liver failure or dysfunction
    b. Renal failure or dysfunction **(20)**.
5. **Several drugs and intoxications:** Nucleosidic reverse transcriptase inhibitors used for the treatment of human immunodeficiency virus (by inducing mitochondrial cytopathy), epinephrine (by increased

glycogenolysis, glycolysis, and stimulation of the Na-K-pump), metformin (particularly in the presence of renal insufficiency), Intoxications with methanol, cyanide (by inhibition of oxidative phosphorylation), or ethylene-glycol (by artifactual reaction of lactate electrodes) also significantly elevated lactate levels **(21)**.

6. **Other causes: metabolic alkalosis** because an H-linked carrier mechanism is involved in the transport of lactate across the cell membrane that increases cellular lactate efflux during alkalosis **(19)**.

Lactate reduction during the first 24 hours of ICU stay is useful in septic patients **(19)**. A lactate decrease of at least 20 % in 2 hours for the initial 8 hours of treatment in ICU patients with an initial lactate ≥ 3 mml/l was associated with a lower mortality rate in the lactate-guided therapy in septic patients **(22)**.
Other studies reported that patients randomized to lactate-directed therapy had improved outcomes **(22)**.

**Base deficit( BD )**

Base deficit is one of the important parameter in sepsis and septic shock investigation and management in current days **(25)**.
BD is a common value available at the time of injury to quantify the magnitude of hypoperfusion and is typically closely followed in the resuscitation period **(27).**It is assumed to be the first accurate index of the non-respiratory component of acid-base balance. It has been used as biochemical marker of shock, injury severity and mortality since the 1960s **(23)**.
The base deficit (BD) is defined as the amount of base, in mmol, that is needed to normalize the pH of 1L of whole arterial blood to 7.4, with the sample fully oxygen saturated at $37^{o}_{C}$ with a PaCO2 of 40 mm Hg. Base deficit can also be used as an approximation of global tissue acidosis **(24)**.
Davis JW suggested that base deficit can be used as an indicator of depressed oxygen delivery for those in a state of shock and would be useful in the clinical diagnosis of compensated shock **(23)**.
Measurement of serum base deficit concentrations is another tool used in critically ill adults for assessing tissue perfusion. Base deficit has also been shown to have a strong relationship to indices of tissue oxygen utilization and a reflective of tissue oxygen consumption even in compensated shock **(26).**
The measurement of single lactate value in emergency room has several limitations, like in trauma, diabetic ketoacidosis; liver dysfunction. So base excess value is more important as it isn't much influenced by above factors and gives the proper interpretation value in metabolic acidosis in septic patients **(27)**.
BD is a common value available at the time of injury to quantify the magnitude of hypoperfusion and is typically closely followed in the resuscitation period **(27)**.
The severity of BD is classified to: mild (2–5mmol/l), moderate (6–14mmol/l) or severe (above 15mmol/l).The severity of the deficit directly correlated with the volume of crystalloid replaced within the first 24 h. Failure to normalize the base deficit correlated directly with mortality. A base deficit of 6mmol/l or more has been demonstrated to be a marker of severe injury **(28)**.
The improvement in the base deficit can also access the efficacy of fluid resuscitation. It has been proposed that organ damage in critical illness is due to inadequate oxygen delivery that fails to satisfy metabolic needs **(29)**.
Base deficit was demonstrated as an independent predictor of mortality**.** It can be used as an endpoint for resuscitation but administration of sodium bicarbonate can confound this utility **(30)**.

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