

Vasoactive Drugs for Septic Shock: Where are we now?

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Sepsis develops in about 750,000 people annually and accounts for more than 210,000 deaths per year in the United States [1]. Pediatric severe sepsis is also a burdensome public health problem, with prevalence, morbidity, and mortality rates similar to reports from critically ill adult populations [2]. In sepsis inflammatory mediators lead to circulatory abnormalities including peripheral vasodilatation, reduced mean arterial pressure (MAP), myocardial depression, and intravascular volume depletion [3]. With increased awareness and the use of protocolized care in the emergency department and in the intensive care unit (ICU) the mortality associated with sepsis has decreased significantly in the last decade in some countries [4,5].

Hypovolemic, cardiogenic and obstructive forms of shock are characterized by decreased cardiac output, arterial pressure and profound vasoconstriction in the peripheral circulation. In vasodilatory shock, there is a complex interaction between pathologic vasodilation, relative and absolute hypovolemia, altered blood flow distribution, and myocardial depression [3]. Vasoactive drugs are the mainstay of hemodynamic management of vasodilatory shock when fluids fail to restore hemodynamics or to improve regional perfusion. It seems that an optimal goal of MAP is 65 to 75 mm Hg in patients with septic shock, but a higher MAP (75 to 85 mm Hg) may be preferable in patients with chronic arterial hypertension [6].

The Surviving Sepsis Campaign (SSC) launched in 2002 consists of management guidelines and performance improvement programs for adults with severe sepsis [7]. The second revision of the guidelines, published in 2012, is sponsored by 30 international scientific organizations [8]. According to the SSC recommendations, vasopressor agents should be initiated to raise the MAP to 65 mm Hg if fluid resuscitation of 30 mL/kg fails to achieve that goal.

Adrenergic agonists are the first-line vasopressors because of their rapid onset of action, high potency, and short half-life, which allows easy dose adjustment [9]. The SSC guidelines recommend norepinephrine as the first-choice vasopressor [8]. Norepinephrine is a potent α -adrenergic agonist, and with modest β -adrenergic effects that help to maintain cardiac output. Administration of doses of 0.1 to 2.0 μ g per kilogram of body weight per minute generally results in a clinically significant increase in MAP, with little change in heart rate or cardiac output [9]. The delayed norepinephrine administration was found independently associated with hospital mortality in patients with septic shock in a recent report [10].

Dopamine, the immediate precursor of norepinephrine and epinephrine, is a less potent vasopressor with dose varying receptor binding [11]. The results of a meta-analysis had previously suggested that dopamine administration as compared with norepinephrine might be related to higher rates of death among patients with septic shock [12]. Indeed in a large, randomized, controlled, double-blind trial, dopamine had no advantage over norepinephrine as the first-line vasopressor agent [13]. In addition, more induced arrhythmias and was associated with increased mortality in patients with cardiogenic shock. Dopamine should be reserved for special situations such as patients with bradycardia and low risk of arrhythmias [8].

Relative vasopressin deficiency may be a contributor factor to

vasodilatory septic shock. The Vasopressin and Septic Shock Trial (VASST) found no mortality benefit when comparing the addition of arginine vasopressin to norepinephrine versus norepinephrine alone [14]. However, post hoc analyses suggest that it may benefit patients with lower norepinephrine doses or those at risk for renal failure [14,15]. Arginine vasopressin 0.03 unit/minute may be added to norepinephrine with the anticipation of an effect equal to higher doses of norepinephrine alone [8]. Vasopressin should be administered only in patients with a high level of cardiac output and should not be used at doses higher than 0.04 U per minute due to adverse effects such as elevated liver enzymes and serum bilirubins, hyponatremia, mesenteric ischemia, skin necrosis and digital ischemia.

Dobutamine is a β -adrenergic agent that remains the 'gold standard' inotropic agent in the treatment of septic shock, regardless of whether norepinephrine is also being given [9]. Doses from 2.5 to 20 micrograms/kg/min substantially increase cardiac output. A dose in excess of 20 μ g per kilogram per minute usually provides little additional benefit. Dobutamine may improve capillary perfusion in patients with septic shock, independent of its systemic effects [16]. Other inotropes such as phosphodiesterase type III inhibitors and levosimendan, a calcium sensitizer have inotropic and vasodilator activities, what limit its use in acute shock states.

Vasoplegia, as well as persistent and irreversible hypotension, is considered as a key factor leading to death due to refractory septic shock. Combination therapy with either epinephrine or vasopressin is used in patients who failed to increase MAP with norepinephrine alone [8]. Addition of epinephrine to norepinephrine in patients with septic shock unresponsive to fluid resuscitation improves hemodynamics, but may increase serum lactate and worse acidosis [17]. Vasopressin can be added to norepinephrine with the intent of achieving the target MAP. Another possible candidate for combination therapy is terlipressin that has selective V1 and V3 receptors action, and can be considered in septic patients with liver failure, portal hypertension and variceal bleeding [18].

Corticosteroid hormones play an important role in the control of vascular smooth muscle tone by potentiating vasoactive responses to catecholamine through glucocorticoid receptors. In addition relative adrenal insufficiency can occur in up to 70% of patients with septic shock [19]. Moderate doses of hydrocortisone improve sublingual capillary perfusion [20]. Hydrocortisone is recommended as an adjunctive therapeutic agent in patients with septic shock if adequate

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fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability at a dose of 200 mg per day.

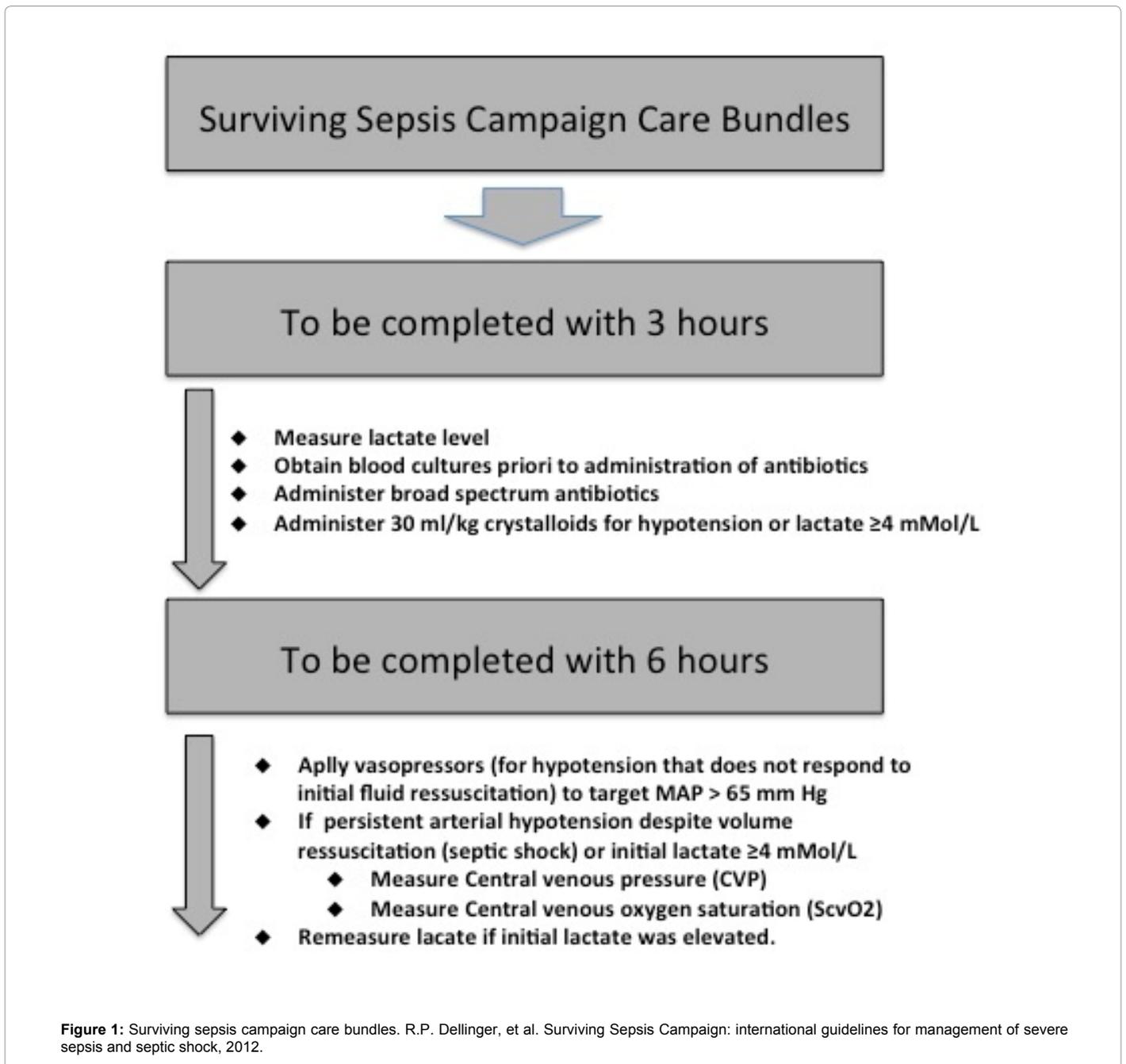
The following sets of care elements ('bundles') are to be completed within 3 and 6 hours from the patient's time of presentation to the emergency department, or within 3 and 6 hours of diagnosis on hospital wards or in the ICU (Figure 1). Adopters of the guidelines and bundles have already reported successful implementation with significant improvement in sepsis-bundle compliance and marked reduction in mortality [5].

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