

# Oxygen Therapy

**Oxygen Therapy in Intensive Care Medicine,**  
*J. Grensemann, S. Sakka*

**Oxygen: Too Much is Bad,** *B. Pastene, M. Leone*

**Oxygen Therapy in COVID-19 Patients: The Role of HFNC and CPAP,** *S. Ferrari, A. Isirdi, E. Taddei et al.*

**Apnoeic Oxygenation for Intubation - Where is the Evidence?** *A. De Jong, C. Monet, S. Jaber*

**Major Adverse Peri-intubation Events in Critically Ill Patients - Update on the INTUBE Study,**  
*V. Russotto, S. Myatra, J. Laffey et al.*

**New Applications of Pulse Oximetry,** *F. Michard*

**Practical Strategies in Mechanical Ventilation for Patients With Acute Respiratory Failure Due to COVID-19,** *O. Pérez-Nieto, E. Zamarron-Lopez, J. Meade-Aguilar et al.*

**Airway Management in Critically Ill Patients - Striving to Improve Outcomes,** *K. Karamchandani, A. Khanna, S. Myatra*

**Hyperoxia - A Journey to the Centre of the Cell,**  
*J. Poole*

**Diaphragm Ultrasonography in ICU: Why, How, and When to Use It?** *Y. Aarab, A. De Jong, S. Jaber*




**Jacob C. Jentzer**

Director of Cardiac ICU  
Research  
Assistant Professor  
of Medicine  
Department of  
Cardiovascular Medicine  
Mayo Clinic  
Rochester  
Minnesota, USA

jentzer.jacob@mayo.edu


**Arthur R.H. van Zanten**

Internist-Intensivist  
Head of ICU Research  
Gelderse Valley Hospital  
Ede, The Netherlands

Division Nutrition Health  
Wageningen University  
& Research  
The Netherlands

zantena@zgv.nl

# Vasopressor Management in Septic Shock: General Overview and Personalised Approaches

This article summarises the proceedings of an ESICM webinar in which two experts discuss vasopressor therapy and its fundamental role in the treatment of septic shock-induced hypotension. They provide an overview of severe septic shock, the benefits of second-line vasopressors and their use in COVID-19 patients.

## Vasopressors in Severe Septic Shock - An Overview

(Jacob C. Jentzer)

Vasopressors are classified as drugs that are designed to increase arterial pressure by peripheral vasoconstriction. There are two types of vasopressors: pure vasoconstrictors and catecholamines. Pure vasoconstrictors only affect the peripheral vessels and do not have direct cardiac inotropic effects. Examples include phenylephrine which is a pure alpha-1 agonist, as well as vasopressin and angiotensin-II. These drugs have an important advantage as they have no direct cardiac toxicity (Jentzer 2015).

Catecholamines are more commonly used as inoconstrictors since, in addition to causing peripheral vasoconstriction, they exert inotropic effects by activating beta receptors. These beta ionotropic effects increase cardiac output and heart rate, which might be beneficial but also increase the risk of cardiac toxicity, especially at higher doses. Drugs such as epinephrine and dopamine have much stronger beta inotropic effects than norepinephrine, which predominantly has beta inotropic effects at higher doses (Jentzer 2015).

In patients who do not respond adequately to vasopressors, two dominant mechanisms

may be involved. The first is related to metabolic abnormalities that can interact to cause alpha one receptor desensitisation through a number of mechanisms. Examples include the systemic inflammatory response, acidemia or lactic acidosis. These can cause dysregulation of nitric oxide metabolism and accumulation of reactive oxygen species, both of which can act through a number of mechanisms to impair the vascular responsiveness to catecholamines. The other mechanism is related to absolute or relative deficiencies in vasopressin, angiotensin-II and corticosteroids. It is important to remember these different mechanisms, since potential treatments are available for patients with refractory shock (Jentzer 2018).

Vasopressors have a better safety profile at lower doses. As higher doses are given, the potential for toxicity increases. In patients who require high doses of catecholamines, there is a risk of off-target cardiac toxicity due to beta receptor activation. Therefore, the best approach would be to use drugs with different mechanisms at lower doses to maximise both safety and efficacy. This approach is often referred to as the vasopressor toolbox approach. In patients who do not respond well to or do not

tolerate an initial catecholamine, it is recommended that a second agent should be added - predominantly a catecholamine-sparing drug - to improve the clinical status (Levy 2010).

Vasopressor requirements are used as a simple metric of shock severity. Burstein et al. (2021) show that patients requiring more than 0.3 µg/kg/min of norepinephrine are at a very high risk of death. Once a level of 0.5 µg/kg/min or above is reached, the outcome will be fatal in the majority of patients. Therefore, this has been used as a threshold to define refractory shock (Burstein 2021).

Norepinephrine is the first-line vasopressor drug not only for septic shock but for most forms of shock, including cardiogenic shock. The Surviving Sepsis Campaign guidelines recommend norepinephrine as the first-line vasopressor for septic shock, and there is sufficient evidence to support this recommendation (SSC Guidelines; Rhodes ICM 2017).

In a secondary analysis of the VASST study (Russell et al. 2008), it was observed that adding on vasopressin to reduce norepinephrine requirements was associated with lower mortality in patients who had less severe shock at baseline and those who

also received corticosteroids. Vasopressin was also associated with a lower risk of acute kidney injury (AKI). Vasopressin may be a better choice when given as a second vasopressor to reduce catecholamine doses.

When using vasopressors in septic shock, severity should be the deciding factor. For patients with mild septic shock, defined as a norepinephrine requirement  $<0.1 \mu\text{g}/\text{kg}/\text{min}$ , norepinephrine is sufficient, and there is no need for secondary vasopressors in these patients as long as they are managed with adequate antibiotic source control and fluid resuscitation.

In patients not responding to low doses of norepinephrine and who may need higher doses up to  $0.2 \mu\text{g}/\text{kg}/\text{min}$ , it is important to determine why they are not responding. It must be ensured that the patients do not have concomitant cardiac dysfunction, which could possibly result in a mixed cardiogenic septic shock state. It is also important to address reversible metabolic abnormalities before starting a second vasopressor. In patients with a more severe septic shock where they require a dose of  $0.2 \mu\text{g}/\text{kg}/\text{min}$  of norepinephrine or higher, it might be beneficial to add a second vasopressor. A second vasopressor should be added before patients develop resistant or refractory septic shock, defined as a norepinephrine requirement of  $>0.3 \mu\text{g}/\text{kg}/\text{min}$  or  $>0.5 \mu\text{g}/\text{kg}/\text{min}$ .

Adding dopamine or phenylephrine when a patient is refractory despite significant doses of norepinephrine is not a recommended strategy as the response is often poor. Because of its strong beta inotropic effects, epinephrine can increase cardiac output, which can be advantageous for patients with low heart rate, cardiac output or venous oxygen saturation. However, it is associated with significant cardiac toxicity with myocardial ischaemia, arrhythmias, and tachycardia. It can also cause increases in lactate and glucose levels. In contrast, vasopressin and angiotensin-II have similar haemodynamic effects and are free from major cardiac toxicity. They do not cause

off-target metabolic abnormalities and may be associated with better outcomes when added on to catecholamines. Vasopressin can be useful when the arterial pH is low, and catecholamine receptors are not effective.

In another analysis, researchers investigated the cost-effectiveness of second-line vasopressors. They compared escalating norepinephrine doses with the use of norepinephrine plus adjunctive vasopressin or angiotensin II for septic shock. Adjunctive vasopressin demonstrated to be the most cost-effective therapy and resulted in a higher ICU survival rate at less cost (Lam 2020).

When individualising second-line therapies, it is recommended to use epinephrine in patients with inappropriately low cardiac output, a low  $\text{SvO}_2$  or inappropriately low heart rate. Many patients with sepsis either have pre-existing cardiomyopathy, septic cardiomyopathy

## the Surviving Sepsis Campaign guidelines recommend norepinephrine as the first-line vasopressor for septic shock

or cor pulmonale lung disease and may require inotropic support. In these cases, dobutamine can be used, but can cause excessive vasodilation, aggravating the problem. Still, in patients with severe lactic acidosis or uncontrolled hyperglycaemia with diabetic ketoacidosis, epinephrine is not recommended, and the default drug should be vasopressin.

If catecholamine doses are rising rapidly, it is important to confirm that the patient is suffering from septic shock and to ensure source control and appropriate antibiotics. It is also important to identify treatable and reversible metabolic abnormalities. Rapidly rising catecholamine doses suggest that catecholamines are not effective. This should prompt consideration of an additional

catecholamine-sparing vasopressor and a corticosteroid. It is important to note that catecholamine-sparing vasopressors may not be effective if the patient is not deficient in these signalling molecules.

Overall, with early septic shock, it is important to identify and treat the underlying aetiology. Appropriate fluid resuscitation guided by optimal measures of fluid responsiveness should be used. Norepinephrine should be the drug of choice as long as high doses are not needed ( $<0.2 \mu\text{g}/\text{kg}/\text{min}$ ). In patients with severe septic shock requiring  $>0.2 \mu\text{g}/\text{kg}/\text{min}$  of norepinephrine, secondary contributing factors must be identified to ensure the patient is not hypovolaemic, acidaemic or hypocalcaemic. Vasopressin should be added to norepinephrine. If a patient has borderline or low cardiac output, epinephrine is a reasonable alternative. If one or both of those drugs do not work, angiotensin-II can be used, especially if the patient requires  $>0.3 \mu\text{g}/\text{kg}/\text{min}$  of norepinephrine after vasopressin has been added.

## Second-line Vasopressor: Benefits and COVID-19 Cases

(Arthur R.H. van Zanten)

Patients on high levels of vasopressors have high mortality rates. This is primarily due to the severity of illness. However, there is sufficient clinical evidence on the harmful effects of catecholamines. They can be injurious to the myocardial cells, induce oxidative stress and have immunomodulating effects. Recent studies show that high-dose norepinephrine may dysregulate the innate immune system. In late phase recovery of sepsis, sepsis-induced immunoparalysis may occur, which can further induce secondary infections. All these factors can have a significant impact on clinical outcomes (Stolk 2016).

However, vasopressin does not have this effect. In the late phase of septic shock, there may be vasopressin deficiency. Vasopressin not only has an effect on vasoconstriction

but can also address vasopressin deficiency (Landry et al. 2017). Vasopressin is a vasoconstrictor hormone that is naturally produced for raising blood pressure and inducing water retention. There are three receptors involved. The v1 receptor induces vasoconstriction; the v2 receptor induces water retention in the kidney, and the v3 or v1b receptor leads to the release of ACTH from endocrine cells, which stimulate cortisol release from the adrenal gland. This is very important during septic shock. At higher levels, v1 activation and the vasoconstrictive properties of vasopressin are predominant, but at low plasma levels of vasopressin (10 pmol/l), arginine vasopressin's v2 receptors anti-diuretic actions predominate.

While definitions for refractory shock, septic shock, or vasodilatory shock are lacking, a threshold of 0.5 µg/kg/min is generally accepted. However, at Gelderse Valley Hospital, 0.25 µg/kg/min is considered to indicate refractory shock because, after that point, mortality increases rapidly. Adding a second vasopressor may be helpful in these patients, along with optimal fluid resuscitation, and cardiac output should also be closely monitored.

The VAAST trial compared norepinephrine with norepinephrine plus vasopressin. While the study did not show a significant reduction in mortality rates with the vasopressin group (baseline mean arterial pressure (MAP) of patients were NE. Group 73±10 and Vaso. group 72±9), the effect of adding vasopressin had a marked norepinephrine sparing effect (Russell et al. 2008).

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In a post-hoc analysis of the VAAST trial, patients were separated into groups according to APACHE-II scores. In patients with lower APACHE-II scores (and NE ≤15µg/min) there was a significant reduction in mortality when vasopressin was added to the catecholamines. These findings suggest that in patients with refractory shock, it might be a good idea to add vasopressin earlier (Russell et al. 2011; Wacharasint 2012).

Findings from McIntyre et al. (2018) show that the incidence of new-onset atrial fibrillation distributive shock is about 23% less when catecholamines are combined with vasopressin. An 11% lower mortality was observed when the drugs were combined. There was also a trend towards less use of renal replacement therapy (RRT) in septic shock. More ischaemia was observed in patients treated with vasopressin, especially digital ischaemia. The risk is higher when the use of vasopressin is increased without optimal fluid status and optimal cardiac output (McIntyre 2018).

In another recent meta-analysis that compared vasopressin with catecholamines versus catecholamines alone and with a focus on renal outcomes, the incidence of AKI and renal failure and the need for RRT was lower with the use of the combination with vasopressin (Nedel 2019). The Surviving Sepsis Campaign Guidelines also recommend adding vasopressin up to a dose of 0.03 IU/min if there is a need to raise the mean arterial pressure and reduce the dose of norepinephrine (Martin et al. 2015).

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In a patient with refractory shock, where MAP is still insufficient, despite norepinephrine 0.25 µg/kg/min, adequate fluid resuscitation, and adequate to high cardiac output, vasopressin can be started with 0.01IU/min and gradually increased to 0.03IU/min in steps of 20 minutes. When the desired blood pressure level is achieved and maintained sufficiently, norepinephrine should be gradually decreased to 0.1 µg/kg/min, after which vasopressin should be tapered to 0.01IU/min every 60 minutes, providing that MAP is stable. Once vasopressin infusion stops, then noradrenaline should be tapered. Tapering norepinephrine first, then vasopressin has less risk of rebound hypotension (Duclos et al 2019). This is the tapering protocol being used in the vasopressin registry in the Netherlands (Netherlands ICU Sepsis Protocol).

Overall, high-dose norepinephrine or noradrenaline monotherapy may not be the best approach. Catecholamine sparing effects can be achieved by treating the patient with vasopressin. This also helps vasopressin deficiency in sepsis and may reduce atrial fibrillation, AKI incidence and the need for RRT. ■

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