ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 20 - ISSUE 1 -2020

COVID-19 Challenges

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Vasoactive Agent Management for Haemoydnamic Support in COVID-19 Patients - The Surviving Sepsis Guidelines

An overview of the Surviving Sepsis Guidelines for the vasoactive agent management of COVID-19 patients with septic shock and the use of arginine vasopressin in this patient population.

The SARS-CoV-2 has caused a global health crisis. Thousands of people across the globe have been affected by COVID-19. Clinicians are in urgent need of guidance and recommendations to treat patients and improve outcomes. The Surviving Sepsis Campaign COVID-19 panel has issued 54 statements, which include four best practice statements, nine strong recommendations, and 35 weak recommendations.

Guidelines on the management of critically ill adults with coronavirus disease also include recommendations for vasoactive agent management and haemodynamic support in COVID-19 patients with septic shock. As per the WHO categorisation of clinical symptoms associated with COVID-19 in adults, septic shock is defined as patients with a clinical construct of sepsis with persisting hypotension despite adequate volume resuscitation, and vasopressors are needed to maintain MAP ≥ 65 mmHg, and serum lactate level > 2 mmol/L (WHO Interim Guidance 2020).

According to the Surviving Sepsis Guidelines, the following recommendations should be followed for vasoactive agent management of COVID-19 patients with septic shock (Alhazzani et al. 2020):

1. Norepinephrine should be used as the first-line vasoactive agent in adults with COVID-19 and septic shock (SSC Guidelines Recommendation 16).

2. If norepinephrine is not present, vasopressin or epinephrine should be used, and preference should be given to these drugs over other vasoactive agents. Both agents have been assessed in RCTs without any clear evidence of harm. The choice between the two should be based on availability and contraindications to the two agents. With vasopressin, digital ischaemia may be a concern while with epinephrine, tachycardia and excess lactate production may occur (SSC Guidelines Recommendation 17).

> **"early combination of arginine vasopressin helps reduce norepinephrine dose and may lessen risk of further increase in catecholamine induced pulmonary artery hypertension"**

3. Dopamine should not be used in COVID-19 patients with shock if norepinephrine is not available (SSC Guidelines Recommendation 18).

4. Vasopressin should be added as a second-line agent instead of over-titrating norepinephrine dose if mean arterial pressure (MAP) cannot be achieved by norepinephrine alone. In a recent clinical practice guideline, the use of vasopressin and vasopressin analogs in critically ill adults with distributive shock was assessed and high certainty of a reduction in atrial fibrillation and moderate certainty of an increased risk of digital ischaemia with the addition of vasopressin or its analogs to catecholamines was observed (SSC Guidelines Recommendation 19).

5. Vasoactive agents should be titrated to a MAP of 60-65 mmHg. Anything higher is not recommended in COVID-19 patients with shock (SSC Guidelines Recommendation 20).

6. If there is a presence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation with norepinephrine, dobutamine should be used instead of an increased dose of norepinephrine (SSC Guidelines Recommendation 21).

7. In the case of refractory shock, low-dose corticosteroid therapy should be used instead of no corticosteroid therapy (SSC Guidelines Recommendation 22).

Use of Arginine Vasopressin in COVID-19 Patients

Arginine vasopressin, also known as vasopressin, argipressin, and anti-diuretic hormone, is a naturally produced human hormone used for raising blood pressure and inducing water retention. The vasoconstrictor effects of arginine vasopressin are due to the activation of V1a receptors This is different to catecholamines, which activate adrenergic receptors with possible

pro-inflammatory and pro-arrhythmogenic potential. The difference in mode of action justifies addition of arginine vasopressin, when increasing mean arterial pressure with norepinephrine alone is not possible, a condition known as catecholamine refractory septic shock. Arginine vasopressin's mode of action also offers a norepinephrine sparing effect.

Norepinephrine increases pulmonary artery pressure and pulmonary vascular resistance, a possible disadvantage for patients with underlying lung disorders such as pulmonary arterial hypertension, (Annane et al. 2018). Early combination of arginine vasopressin helps reduce norepinephrine dose (Russell 2011) and may lessen risk of further increase in catecholamine induced pulmonary artery hypertension. Current experimental evidence indicates that arginine vasopressin does not seem to constrict pulmonary arteries (Currigan et al. 2014; Chan et al. 2015; Holmes et al. 2004).

For mechanically ventilated patients, cumulative dose of norepinephrine is associated with the development of ICU-acquired weakness (ICU-AW). For every 1 µg/kg/d dose of norepinephrine a patient received, the odds of developing ICU-AW increased by 1%. This relationship was not seen with arginine vasopressin (Wolfe et al. 2018) and with the norepinephrine sparing effect of arginine vasopressin, ICU-AW maybe reduced (Russell 2011).

In addition to that, early combination of arginine vasopressin can reduce the incidence of atrial fibrillation and ventricular tachycardia (Dünser 2003; McIntyre et al. 2018; Reardon et al. 2010). In patients with septic shock who are at an increased risk of renal failure (1.5x serum creatine based on the RIFLE criteria), additive treatment with arginine vasopressin can reduce the progression to renal failure and the need for renal replacement therapy by 55% (Gordon et al. 2010).

AMOMED Pharma is the only company in the European Union that has approval for marketing and distributing arginine vasopressin for catecholamine refractory hypotension in septic shock to raise mean arterial blood pressure. The use of arginine vasopressin in the treatment of COVID-19 in septic shock has now been included in the Surviving Sepsis Guidelines.

Arginine vasopressin is marketed by AMOMED under the following brand names: Empressin®, Embesin®, Embesyn®, Empesin®, Empressine® and ReverPleg®. For more information regarding the product, please visit amomed.com. ■

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World Health Organization (WHO) Interim guidance: Clinical Management of Sever Acute Respiratory Infection (SARI) when COVID-19 disease is suspected (13.03.2020)

Surviving Sepsis Campaign:

Guidelines on the Vasoactive Management of Adult COVID-19 Patients with Septic Shock Recommend: Add arginine vasopressin as a second-line agent over titrating norepinephrine dose, if target mean arterial pressure (MAP) cannot be achieved by norepinephrine alone, or use it as first-line vasopressor, if norepinephrine is not available.[1]

EMPRESSIN®
ARGIPRESSIN

Benefits of Empressin® for COVID-19 Septic Shock Patients

Empressin® is the only arginine vasopressin (AVP) in Europe labeled and approved for the treatment of catecholamine refractory (resistant) hypotension following septic shock in patients older than 18.[2]

- Increase mean arterial pressure[3]
- Decrease norepinephrine dose[4]

1. Alhazzani, W., Møller, M.H., Arabi, Y.M. et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med (2020). https://doi.org/10.1007/s00134-020-06022-5
2. Summary of Product Characteristics, current version
3 Dünser M.W.: Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study; Circulation. 2003 May 13;107(18):2313-9.
4. Russell JA: Bench-to-bedside review: Vasopressin in the management of septic shock. Crit Care. 2011; 15(226):1-19

NAME OF THE MEDICINAL PRODUCT: Empressin 40 I.U./2 ml concentrate for solution for infusion. QUALITATIVE AND QUANTITATIVE COMPOSITION: One ampoule with 2 ml concentrate for solution for infusion contains argipressin acetate corresponding to 40 I.U. argipressin (equating 133 microgram). 1 ml concentrate for solution for infusion contains argipressin acetate corresponding to 20 I.U. argipressin (equating 66.5 microgram). Excipients with known effect: Each ml contains less than 23 mg of sodium. List of excipients: Sodium chloride, glacial acetic acid or pH adjustment, water for injections.
Therapeutic indications: Empressin is indicated for the treatment of catecholamine refractory hypotension following septic shock in patients older than 18 years. A catecholamine refractory hypotension is present if the mean arterial blood pressure cannot be stabilised to target despite adequate volume substitution and application of catecholamines (see section 5.1 of the published SmPC). Pharmacotherapeutic group: Vasopressin and analogues, ATC code: H01BA01
Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the published SmPC. Nature and contents of container: Clear glass ampoules (Type I, with a broken ring on the narrow part of the ampoule) with 2 ml concentrate for solution for infusion. Pack sizes: 5 and 10 ampoules. Not all pack-sizes may be marketed. MARKETING AUTHORISATION HOLDER: Orpha-Devel Handels und Vertriebs GmbH, Wintergasse 85/1B, 3002 Purkersdorf, Austria DATE OF REVISION OF THE TEXT: 02 / 2018 Prescription status/ Delivery by pharmacies: Prescription only medicine/ Pharmacy-only.
For information on undesirable effects, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, use in pregnancy and lactation and impact on fertility please refer to the published SmPC.

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